Transoesophageal echocardiography in cardiogenic embolism : left atrial spontaneous echo contrast and thrombus

Author:
Black, Ian William

Publication Date:
1997

DOI:
https://doi.org/10.26190/unsworks/13003

License:
https://creativecommons.org/licenses/by-nc-nd/3.0/au/
Link to license to see what you are allowed to do with this resource.

UNIVERSITY OF NEW SOUTH WALES
Thesis/Project Report Sheet

Surname or Family name: ....BLACK..........

First name: ....IAN.......... Other name/s: ....WILLIAM..........

Abbreviation for degree as given in the University calendar: ....MD.........

School: PRINCE OF WALES HOSPITAL Faculty: MEDICINE

Title: TRANSOESOPHAGEAL ECHOCARDIOGRAPHY IN CARDIOGENIC EMBOLISM: LEFT ATRIAL SPONTANEOUS ECHO CONTRAST AND THROMBUS

Abstract 350 words maximum: (PLEASE TYPE)

This thesis assessed the role of transoesophageal echocardiography (TEE) in the detection of potential cardiac sources of embolism, particularly left atrial (LA) thrombus and spontaneous echo contrast (SEC). In 400 patients undergoing TEE, LA SEC was associated with conditions causing LA stasis, and with previous thrombus and/or embolism in patients with nonvalvular atrial fibrillation (AF) or with mitral valve disease. In 135 patients with nonvalvular AF, LA SEC correlated with haematocrit and fibrinogen. LA SEC predicted future embolism and increased mortality in 272 patients with nonvalvular AF. LA SEC was shown to produce increased integrated backscatter, and also specific temporal patterns by Fourier analysis. In 88 patients the prevalence of LA SEC reduced after percutaneous mitral valvuloplasty. In 193 patients with LA thrombus, LA cavity thrombi were associated with mitral stenosis or prosthesis and LA dilatation. LA appendage thrombi were associated with nonvalvular AF, previous embolism and left ventricular dysfunction. Mobile LA thrombi were associated with appendage location, previous embolism and nonvalvular AF. A case of embolism of a LA ball thrombus during TEE was described. In 824 patients undergoing TEE after embolic events, ≥ 1 potential source of embolism was detected in 49% of patients, with LA SEC in 26%, LA thrombus in 7%, complex aortic atheroma in 13%, and interatrial septal anomalies in 15%. Abnormal TEE findings after embolism, except for atrial septal abnormalities, were predicted by abnormal transthoracic echocardiography or AF. Exclusion of thrombus by TEE prior to electrical cardioversion of AF did not preclude post-cardioversion embolism in 17 non-anticoagulated patients. Two patients who reverted spontaneously from AF to sinus rhythm during TEE developed atrial stunning. The Assessment of Cardioversion Using Transoesophageal Echocardiography (ACUTE) randomised pilot study of 126 patients demonstrated that TEE-guided management of cardioversion was a safe and feasible alternative to the conventional approach. In summary, this thesis describes the value and limitations of the detection by TEE of LA SEC, LA thrombus and other findings in assessing embolic risk.

CERTIFICATE OF ORIGINALITY

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any other degree or diploma at UNSW or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at UNSW or elsewhere, is explicitly acknowledged in the thesis.

I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

(Signed) ....

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY IN CARDIOGENIC EMBOLISM: LEFT ATRIAL SPONTANEOUS ECHO CONTRAST AND THROMBUS

Ian William Black MBBS FRACP FACC

Thesis submitted for the degree of Doctor of Medicine
University of New South Wales
1997

CONTENTS

2

ABSTRACT

This thesis assessed the role of transoesophageal echocardiography (TEE) in the detection of potential cardiac sources of embolism, particularly left atrial (LA) thrombus and spontaneous echo contrast (SEC). In 400 patients undergoing TEE, LA SEC was associated with conditions causing LA stasis, and with previous thrombus and/or embolism in patients with nonvalvular atrial fibrillation (AF) or with mitral valve disease. In 135 patients with nonvalvular AF, LA SEC correlated with haematocrit and fibrinogen. LA SEC predicted future embolism and increased mortality in 272 patients with nonvalvular AF. LA SEC was shown to produce increased integrated backscatter, and also specific temporal patterns by Fourier analysis. In 88 patients the prevalence of LA SEC reduced after percutaneous mitral valvuloplasty. In 193 patients with LA thrombus, LA cavity thrombi were associated with mitral stenosis or prosthesis and LA dilatation. LA appendage thrombi were associated with nonvalvular AF, previous embolism and left ventricular dysfunction. Mobile LA thrombi were associated with appendage location, previous embolism and nonvalvular AF. A case of embolism of a LA ball thrombus during TEE was described. In 824 patients undergoing TEE after embolic events, ≥1 potential source of embolism was detected in 49% of patients, with LA SEC in 26%, LA thrombus in 7%, complex aortic atheroma in 13%, and interatrial septal anomalies in 15%. Abnormal TEE findings after embolism, except for atrial septal abnormalities, were predicted by abnormal transthoracic echocardiography or AF. Exclusion of thrombus by TEE prior to electrical cardioversion of AF did not preclude post-cardioversion embolism in 17 non-anticoagulated patients. Two patients who reverted spontaneously from AF to sinus rhythm during TEE developed atrial stunning. The Assessment of Cardioversion Using Transoesophageal Echocardiography (ACUTE) randomised pilot study of 126 patients demonstrated that TEE-guided management of cardioversion was a safe and feasible alternative to the conventional approach. In summary, this thesis describes the value and limitations of the detection by TEE of LA SEC, LA thrombus and other findings in assessing embolic risk.

ACKNOWLEDGEMENTS

GENERAL INTRODUCTION AND OVERVIEW

Cardiogenic embolism accounts for at least 15% of all strokes and transient ischaemic attacks (Sherman et al 1995) and is an important cause of systemic arterial embolism. Cardiogenic embolism may also complicate therapeutic procedures, including cardioversion of AF, and percutaneous mitral valvuloplasty.

Cardiac ultrasound has been used to detect LA thrombi since the 1950's (Sjoberg 1954). Until the late 1980's, transthoracic echocardiography (TTE) was the principal imaging modality used to detect of intracardiac thrombi and other potential cardiac sources of embolism. However, it became apparent that with the exception of LV thrombus, TTE had poor sensitivity for most sources of cardiogenic embolism, particularly LA appendage thrombus (Sansoy et al 1995).

The development of TEE is credited to Frazin et al (1976), who obtained M-mode views of the heart with an oesophageal probe, although there were previous reports of Doppler measurements of the aorta from the oesophagus (Tomlin and Duck 1975, Daigle et al 1975, Side and Gosling 1971). In the mid and late 1980's, European and Japanese investigators began describing clinical applications for TEE, with the use of TEE in the United States spreading from anaesthetists to cardiologists. In Australia, TEE had been used in 1985 by Michael Feneley for research, but was introduced for the first time on a clinical basis by Andrew Hopkins in late 1988 at the Prince Henry Hospital, where I was a cardiology registrar.

TEE provides high quality imaging of cardiac anatomy including the LA cavity and appendage, which are in close proximity to the oesophagus, without interference from the chest wall and lungs. TEE also provides excellent visualisation of most of the thoracic aorta. A few early reports (Aschenberg et al 1986, Erbel et al 1986) had suggested the use of TEE to detect cardiac sources of embolism, including

9

LA thrombi and LA spontaneous echo contrast (SEC). The latter term, described by Erbel et al (1986) refers to swirling, smoke-like echoes initially seen in the LA in patients with mitral stenosis (Beppu et al 1985), and was reported to be an independent predictor of thromboembolic risk in patients with mitral valve disease (Daniel et al 1988). Detection of cardiac and aortic sources of embolism has become the major indication for TEE in most centres.

I had become interested in AF as a medical and then cardiology registrar, and was struck by the paucity of knowledge regarding most aspects of this common arrhythmia. When TEE arrived, I was fascinated by the real-time, in vivo, detailed display of cardiac anatomy and function, and in particular by the phenomenon of LA SEC. There was very little in the literature on LA SEC at the time, and I therefore decided to commence the studies which form this thesis.

The studies in this thesis were conducted at the Prince Henry Hospital, Sydney, a teaching hospital of the University of New South Wales, and at the Cleveland Clinic Foundation, USA. The period in Cleveland was approved by the Higher Degree Committee of the University of NSW as external candidature.

The overall objective of these studies was to assess the clinical role of TEE in the detection of potential cardiac sources of embolism, focussing on LA thrombus and SEC. This included the role of TEE in patients following suspected cardiogenic embolism and in patients undergoing procedures with a risk of cardiogenic embolism, including electrical cardioversion of AF and percutaneous mitral valvuloplasty. A particular focus was AF, particularly nonvalvular AF, which had emerged as the commonest form of the arrhythmia after the declining incidence of rheumatic heart disease.

Part 1 of this thesis comprises a literature review, Chapter 1, which addresses AF, thromboembolism and cardioversion. Other aspects of literature review are addressed in the introduction and discussion of the specific studies.

The remaining 12 chapters each represent a single study. Of the 12 studies, all have been published in major peer-reviewed journals, except Chapter 7. These journals comprise *Circulation* (Chapter 11), the *Journal of the American College of Cardiology* (Chapters 2,3,4,5), *Annals of Internal Medicine* (Chapter 13), *Stroke* (Chapter 9), the *American Heart Journal* (Chapters 6,10,12), and the *Journal of the American Society of Echocardiography* (Chapter 8). Chapter 7 was published as an abstract in the *Journal of the American College of Cardiology*. Full details of publications arising from this thesis are shown below.

Part 2 comprises a series of five studies assessing the significance of LA SEC, particularly in nonvalvular AF. Chapter 2 describes the clinical and echocardiographic features of LA SEC in 400 consecutive patients undergoing TEE . This was the first study in the literature to demonstrate an association between LA SEC and thromboembolism in patients with nonvalvular AF, and also demonstrated the importance of mitral regurgitation as a protective factor.

Chapter 3 prospectively analysed the relationship between haematological, clinical and echocardiographic variables in 135 consecutive patients with nonvalvular AF. This study was performed after the completion of the study outlined in Chapter 2 and comprises a separate cohort of patients. This was the first study to demonstrate a relationship between LA SEC and haematological variables, specifically haematocrit and fibrinogen but not platelets, and provided a crucial link between LA SEC and thrombosis, as well as providing strong support for red cell aggregation as the mechanism of LA SEC.

Chapter 4 is a prospective follow-up of 272 patients with nonvalvular AF, examining the relationship between LA SEC and subsequent embolism or death. This study demonstrated for the first time that LA SEC was an independent predictor of subsequent embolism and mortality, overall and in subgroups with and without previous embolism. This was also one of the first studies to show the prognostic significance of any source of embolism detected by TEE.

11

Chapter 5 reports the ability of integrated backscatter to quantify LA SEC, in contrast to the traditional qualitative diagnosis. This represented a novel application of a technique usually employed in contrast echocardiography. Objective diagnosis and quantification of LA SEC may enable more precise assessment of thromboembolic risk.

Chapter 6 describes the prospective TEE follow-up of 88 patients undergoing percutaneous mitral valvuloplasty. Mitral stenosis represents the major risk factor for LA thrombus and SEC other than AF. Percutaneous mitral valvuloplasty is a procedure with a risk of embolism from LA thrombus and also provides insights into the pathogenesis of LA SEC. This study showed a decrease, but not abolition, in the prevalence of LA SEC after percutaneous mitral valvuloplasty.

Part 3 comprises two studies relating to LA thrombus, the most common actual source of embolism in many TEE series. Chapter 7 examined a series of 193 patients with LA thrombus detected by TEE. The location (cavity or appendage) and mobility of LA thrombi were shown to correlated with clinical and echocardiographic variables, with implications for pathophysiology and clinical management. Chapter 8 is a case report of embolism during TEE of a LA ball thrombus. This was the only serious complication of TEE encountered during the entire study period.

Part 4 comprises Chapter 9, which compared TTE and TEE findings in 824 patients undergoing TEE for the evaluation of suspected embolic events. This is the largest such study in the literature. In addition to confirming the superior sensitivity of TEE for a variety of findings, the study demonstrated that TTE findings can predict TEE findings and therefore improve patient selection for TEE, a principal clinical question.

Part 5 comprises four studies regarding the role of TEE in the cardioversion of AF and flutter. This application of TEE was first reported in the literature by this author

in 1991 (Black et al 1991b and Black et al 1991c), and has subsequently become the subject of intense international interest. The studies outline the progress of this application of TEE from an initial case series to an international multicenter randomised trial. An important step in this development was the finding of patients with an adverse outcome after TEE-guided cardioversion, emphasising the importance of a randomised trial.

Chapter 10 describes 40 non-anticoagulated patients undergoing TEE-guided cardioversion, selected from more than 200 patients whose TEE guided cardioversions I supervised or attended. This was the first study to demonstrate de novo thrombosis after cardioversion, and represented a clinical confirmation of the concurrent report from Richard Grimm et al (1993), my colleague in Cleveland, who described an unexpected reduction in LA appendage function, manifested in part by an increase in LA SEC, immediately following cardioversion.

Chapter 11 reports 17 patients from 8 centres in the US, Europe and Australia who suffered embolic events after cardioversion of nonvalvular AF despite exclusion of LA thrombus by TEE. Inadequate anticoagulation in the post-cardioversion period emerged as the common link. There was no clear pre-cardioversion predictor. This influential study led to mandatory inclusion of post-cardioversion anticoagulation in protocols for TEE-guided cardioversion.

Chapter 12 reports two patients who serendipitously reverted spontaneously to sinus rhythm during TEE, in whom an acute reduction in LA appendage function was documented. This suggested that the atrial "stunning" phenomenon was not a function of the method of cardioversion, ie electrical energy, but could be a consequence of AF manifest following reversion to sinus rhythm.

These and other studies led to our group in Cleveland commencing the ACUTE (Assessment of Cardioversion Using Transoesophageal Echocardiography) Study, comparing TEE-guided and conventional approaches to electrical cardioversion.

13

Chapter 13 reports the pilot study of 126 randomised patients, demonstrating the safety and feasibility of the TEE-guided approach. Following this pilot, the ACUTE Randomised Trial was commenced and is currently underway with more than 700 patients enrolled in more than 50 centres around the globe.

PERSONAL PUBLICATIONS RELATED TO THESIS

ORIGINAL ARTICLES AND REVIEWS

Black IW, Fatkin D, Sagar KB, Khandheria BK, Leung DY, Galloway JM, Feneley MP, Walsh WF, Grimm RA, Stollberger C, Verhorst PMJ, Klein AL. Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation: A multicenter study. Circulation 1994;89:2509-2513.

Black IW, Chesterman CN, Hopkins AP, Lee LCL, Chong BH, Walsh WF. Haematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation. Journal of the American College of Cardiology 1993;21:451-7.

Black IW, Hopkins AP, Lee LCL, Walsh WF. Evaluation of transesophageal echocardiography prior to cardioversion of atrial fibrillation and flutter in non-anticoagulated patients. American Heart Journal 1993;126:375-381.

Black IW, Stewart WJ. The role of echocardiography in the evaluation of cardiac source of embolism: Left atrial spontaneous echo contrast. Echocardiography 1993;10:429-439

Black IW. Role of transesophageal echocardiography in cardioversion. ACCEL (American College of Cardiology Extended Learning) September 1993.

Black IW, Cranney GB, Walsh WF, Brender D. Embolization of a left atrial ball thrombus during transesophageal echocardiography. Journal of the American Society of Echocardiography 1992;5:271-3.

15

Black IW, Hopkins AP, Lee LCL, Walsh WF. Left atrial spontaneous echo contrast: A clinical and echocardiographic analysis. Journal of the American College of Cardiology 1991;18:398-404.

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Role of transoesophageal echocardiography in evaluation of cardiogenic embolism. British Heart Journal 1991;66:302-7.

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. The clinical role of transoesophageal echocardiography. Australian and New Zealand Journal of Medicine 1990;20:759-64.

Black IW, Fatkin D, Sagar KB, et al. Unexpected embolism (despite screening) after cardioversion of atrial fibrillation. Cardiology Board Review 1995;12:17-20.

The Steering and Publications Committees of the ACUTE Study, for the ACUTE Investigators. Design of a clinical trial for the Assessment of Cardioversion Using Transesophageal Echocardiography (The ACUTE Multicenter Study). American Journal of Cardiology 1998;81:877-83.

McCredie RM, Allan RM, Black IW, Hill AT. Percutaneous transseptal mitral valvotomy. Australian and New Zealand Journal of Medicine 1998 (in press).

Klein AL, Grimm RA, Black IW, Leung DY, Chung MK, Vaughn SE, Murray RD, Miller DP, Arheart KL. Cardioversion guided by transesophageal echocardiography: The ACUTE Pilot Study. A randomized, controlled trial. Annals of Internal Medicine 1997;126:200-209 .

Klein AL, Murray RD, Black IW, Chandra S, Grimm RA, D'Sa AP, Leung DYC, Miller D, Morehead AJ, Vaughn SE, Thomas JD. Integrated backscatter for quantification of left atrial spontaneous echo contrast. Journal of the American

College of Cardiology 1996;28:222-31.

Grimm RA, Chandra S, Klein AL, Stewart WJ, Black IW, Kidwell GA, Thomas JD. Characterization of left atrial appendage Doppler flow in atrial fibrillation and flutter by Fourier analysis. American Heart Journal 1996;132:286-96.

Leung DYC, Black IW, Cranney GB, Walsh WF, Grimm RA, Stewart WJ, Thomas JD. Selection of patients for transesophageal echocardiography after stroke and systemic embolic events. Role of transthoracic echocardiography. Stroke 1995;26:1820-4.

Grimm RA, Leung DY, Black IW, Thomas JD. Left atrial appendage "stunning" after spontaneous conversion of atrial fibrillation demonstrated by transesophageal Doppler echocardiography. American Heart Journal 1995;130:174-6.

Leung DYC, Black IW, Cranney GB, McCredie RM, Hopkins AP, Walsh WF. Resolution of left atrial spontaneous echocardiographic contrast after percutaneous mitral valvuloplasty: Implications for thromboembolic risk. American Heart Journal 1995;129:65-70.

Klein AL, Murray RD, Grimm RA, Bailey AS, Piedmonte M, Black IW. The effect of technical factors on the quality of pulmonary venous flow from the transverse and longitudinal imaging planes with transesophageal echocardiography. Journal of the American Society of Echocardiography 1995;8:879-87.

Leung DYC, Black IW, Cranney GB, Hopkins AP, Walsh WF. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. Journal of the American College of Cardiology 1994;24:755-62.

Grimm RA, Stewart WJ, Black IW, Thomas JD, Klein AL. Should all patients undergo transesophageal echocardiography before electrical cardioversion of

atrial fibrillation?. Journal of the American College of Cardiology 1994;23:533-41.

Sgarbossa EB, Black IW, Maloney JD. Pacemakers, defibrillators, and direct current cardioversion. Current Opinion in Cardiology 1993;8:27-38.

Klein AL, Grimm RA, Black IW. Transesophageal echo screen for left atrial thrombus prior to cardioversion for atrial fibrillation. MVP Video Journal of Cardiology 1993;VIII;14:00.

Lee LCL, Black IW, Hopkins A, Walsh WF. Transoesophageal echocardiography in heart disease - old technologies, new tricks. Australian and New Zealand Journal of Medicine 1992;22:527-531.

Walsh WF, Black IW (Anonymous). Transoesophageal echocardiography (Editorial). Lancet 1992;339:709-11.

Galvin IF, Black IW, Lee CL, Horton DA. Transoesophageal echocardiography in acute aortic transection. Annals Of Thoracic Surgery 1991;51:310-1.

ABSTRACTS

Black IW, Stewart WJ, Walsh WF, Grimm RA, Leung DYC, Ward MR, Cranney GB, Klein AL, Hopkins AP, Thomas JD. Different aetiology of left atrial appendage vs cavity thrombus assessed by transoesophageal echocardiography. Australian and New Zealand Journal of Medicine 1995;25:610.

Black IW, Stewart WJ, Grimm RA, Klein AL, Thomas JD, Cosgrove DM. Role of direct epivascular echocardiography in intraoperative assessment of aortic atheroma. Australian and New Zealand Journal of Medicine 1994;24:645.

Black IW, Grimm RA, Walsh WF, Leung DY, Cranney GB, Stewart WJ, Thomas JD, Klein AL. Transoesophageal echocardiographic findings and clinical outcome in 223 patients undergoing cardioversion. Australian and New Zealand Journal of Medicine 1994;24:639.

Black IW, Klein AL, Grimm RA, Murray RD, Stewart WJ, Thomas JD. Quantification of left atrial spontaneous echo contrast using integrated backscatter. Australian and New Zealand Journal of Medicine 1994;24:625.

Black IW, Fatkin D, Sagar KB, Leung DY, Galloway JM, Feneley MP, Walsh WF, Grimm RA, Klein AL. Does exclusion of atrial thrombus by transesophageal echocardiography preclude embolism after cardioversion? A multicenter study. Circulation 1993;88(Suppl):314.

Black IW, Stewart WJ, Grimm RA, Savage RM, Klein AL, Thomas JD, Cosgrove DM. Direct epivascular echocardiography is essential for complete intraoperative assessment of aortic atheroma. Circulation 1993;88(Suppl):387.

Black IW, Grimm RA, Walsh WF, Stewart WJ, Hopkins AP, Lee LCL, Thomas JD, Klein AL. Low incidence of stroke after cardioversion in patients screened by transesophageal echocardiography. European Heart Journal 1993;14(Suppl):356.

Black IW, Stewart WJ, Klein AL, Thomas JD, Cosgrove DM. Intraoperative assessment of aortic atheroma: comparison of epivascular and transesophageal echocardiography. European Heart Journal 1993;14(Suppl):358.

Black IW, Grimm RA, Walsh WF, Klein AL, Stewart WJ, Hopkins AP, Lee LCL. Risk factors for atrial thrombus and stroke in 156 patients undergoing electrical cardioversion: a multicenter transesophageal echocardiographic study. Journal of the American College of Cardiology 1993;21(Suppl A):28.

Black IW, Stewart WJ, Walsh WF, Klein AL, Hopkins AP, Duffy CI, Lee LCL, Cohen GI, Lever HM, Salcedo EE. Location of left atrial thrombi (appendage vs cavity) is dependent on underlying cardiac disease. Journal of the American College of Cardiology 1993;21(Suppl A):200.

Black IW, Hopkins AP, Lee LCL, Walsh WF. Haematological factors in left atrial spontaneous echo contrast and thromboembolism. Australian and New Zealand Journal of Medicine 1993;23:106.

Black IW, Hopkins AP, Lee LCL, Walsh WF. Thromboembolic risk of atrial flutter. Journal of the American College of Cardiology 1992;19(Suppl A):314.

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Role of transesophageal echocardiography in the cardioversion of atrial arrhythmias. Circulation 1991;84(Suppl II):694.

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Improved detection of source of peripheral arterial embolism with transesophageal echocardiography. Circulation 1991;84(Suppl II):22.

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Left atrial spontaneous echo contrast and thromboembolic risk in nonvalvular atrial fibrillation. Australian and New Zealand Journal of Medicine 1991;21(Suppl II):521.

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Detection of left atrial thrombi by transoesophageal echocardiography prior to elective cardioversion of atrial arrhythmias. Australian and New Zealand Journal of Medicine 1991;21(Suppl II):521.

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Should all patients with embolic events have transesophageal echocardiography?. Circulation

1990;82(Suppl III):246.

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Cardiac rhythm, mitral valve disease and left atrial spontaneous echo contrast. Circulation 1990;82(Suppl III):31.

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. Diagnosis of aortic disease with transoesophageal echocardiography. Australian and New Zealand Journal of Medicine 1990;20(Suppl I):318.

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. Transoesophageal colour flow mapping of clinically normal prosthetic valves. Australian and New Zealand Journal of Medicine 1990;20(Suppl I):318.

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. The role of transoesophageal echocardiography in the diagnosis of left atrial thrombi. Australian and New Zealand Journal of Medicine 1990;20(Suppl I):317.

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. The clinical value of transoesophageal echocardiography. Proceedings, Australian Society for Ultrasound in Medicine 19th Annual Scientific Meeting, Melbourne, 1989:68.

Murray RD, Gupta R, Scalia G, Grimm RA, Leung DY, Black IW, Vaughn SE, Thomas JD, Klein AL. The quantitative measure of spontaneous echo contrast as a predictor of left atrial mechanical function. Journal of the American College of Cardiology 1997;29(Suppl):440.

Leung DYC, Cranney GB, Black IW, Stewart WJ, Thomas JD, Walsh WF. Patients with suspected embolism can be selected for transesophageal echocardiography based on clinical and transthoracic echo variables: Analysis of 824 cases. Australian and New Zealand Journal of Medicine 1995;25:610.

Murray RD, Klein AL, Chandra S, Grimm RA, Black IW, Morehead A, Stewart WJ, Thomas JD. The "swirling" pattern of atrial spontaneous echo contrast can be characterized by integrated backscatter using Fourier analysis. Journal of the American College of Cardiology 1995;25(Suppl):202.

Leung DY, Cranney GB, Black IW, McCredie RM, Walsh WF. Left atrial spontaneous echo contrast resolves after successful percutaneous mitral valvuloplasty. Australian and New Zealand Journal of Medicine 1994;24:628.

Leung DY, Black IW, Cranney GB, Hopkins AP, Walsh WF. Left atrial spontaneous echo contrast is a risk factor for future thromboembolic events in non valvular atrial fibrillation: Results of a prospective study. Australian and New Zealand Journal of Medicine 1994;24:640.

Klein AL, Grimm RA, Black IW, Stoddard MF, Orsinelli DA, Manning WJ, Leung DY, Miller DP for the ACUTE Investigators. Assessment of cardioversion using transesophageal echocardiography compared to conventional therapy: The ACUTE Randomized Pilot Study. Circulation 1994;90:21.

Leung DY, Black IW, Grimm RA, Klein AL. Multi-lobed left atrial appendage: Visualization by multiplane transesophageal echocardiography. Circulation 1994;90:224.

Leung DY, Black IW, Grimm RA, Cranney GB, Walsh WF. Transesophageal echo findings in patients with suspected embolism can be predicted from clinical and transthoracic variables: Analysis of 800 cases. Circulation 1994;90:237.

Sheldon WS, Vandervoort PM, Black IW, Grimm RA. Aortic intramural hematoma in patients evaluated for aortic dissection: Clinical, echocardiographic, radiographic and pathologic findings. Circulation 1994;90:385.

22

Klein AL, Murray RD, Grimm RA, Morehead AJ, Black IW, Miller D, D'Sa A, Meyer A, Stewart WJ, Thomas JD. The utility of integrated backscatter to quantify left atrial spontaneous echo contrast. Canadian Journal of Cardiology 1994;10(Suppl C):97.

Leung DY, Black IW, Cranney GB, McCredie RM, Walsh WF. Determinants of spontaneous echo contrast after percutaneous mitral valvuloplasty: implications for thromboembolic risk. Journal of the American Society of Echocardiography 1994;7(Suppl):54.

Grimm RA, Klein AL, Stewart WJ, Greenberg N, Kidwell GA, Chung MK, Black IW, Thomas JD. Left atrial appendage function does not predict immediate success of cardioversion for atrial fibrillation and flutter. Journal of the American Society of Echocardiography 1994;7(Suppl):57.

Leung DY, Black IW, Cranney GB, Walsh WF. Left atrial spontaneous echo contrast is a risk factor for future thromboembolic events in non valvular atrial fibrillation: Results of a prospective study. Journal of the American College of Cardiology 1994;23(Suppl):441.

Klein AL, Grimm RA, Black IW, Orsinelli DA, Manning WJ, Stoddard MF, Piedmonte M. Cost effectiveness of TEE-guided cardioversion with anticoagulation compared to conventional therapy in patients with atrial fibrillation. Journal of the American College of Cardiology 1994;23(Suppl):128.

Grimm RA, Klein AL, Stewart WJ, Kidwell GA, Castle LW, Black IW, Underwood DA, Thomas JD. Left atrial appendage function in atrial fibrillation and flutter as a predictor of outcome following cardioversion: A transesophageal echo Doppler study with one year follow-up. Journal of the American College of Cardiology 1994;23(Suppl):281.

Klein AL, Grimm RA, Murray RD, Morehead AJ, Black IW, D'Sa A, Meyer A, Stewart WJ, Thomas JD. Quantification of left atrial spontaneous echo contrast using a new approach of integrated backscatter. Journal of the American College of Cardiology 1994;23(Suppl):77.

Grimm RA, Klein AL, Black IW, Stewart WJ, Pacheco TR, Kidwell GA. Can patients with atrial arrhythmias susceptible to postcardioversion thromboembolism be identified precardioversion by clinical or echocardiographic parameters? Circulation 1993;88(Suppl):313.

Stewart WJ, Ares M, Klas B, Black I, Duffy C, Vandervoort P, Barzilai B, Lytle B. Epicardial 3-dimensional echo using a standard transthoracic transducer: promises and limitations. Circulation 1993;88(Suppl):350.

Klein AL, Grimm RA, Bailey AS, Black IW, Murray RD, Cohen GI, Lever HM, Griffin BP. The longitudinal imaging plane by biplane TEE is required for complete assessment of pulmonary venous flow in patients with heart disease. Circulation 1993;88(Suppl):305.

Klein AL, Grimm RA, Black IW, et al. Return of atrial function postcardioversion: comparison between left atrial appendage and left atrial cavity function by Doppler transesophageal echocardiography. Journal of the American College of Cardiology 1993;21(Suppl A):28.

Klein AL, Grimm RA, Black IW, Bailey AS, McQueen YM, Cohen GI, Pearce GL, Maloney JD, Castle LW. Return of atrial function postcardioversion: comparison between left atrial appendage and left atrial cavity function by Doppler transesophageal echocardiography. Journal of the American College of Cardiology 1993;21(Suppl A):28.

Savage RM, Duffy CI, Thomas JD, Stewart WJ, Black IW, Licina M, James KB,

O'Conner M, McCarthy PM, and the LVAD Study Group. Transesophageal echocardiography is indicated in the placement of the implantable left ventricular assist device. Journal of the American College of Cardiology 1993;21(Suppl A):321.

Grimm RA, Klein AL, Stewart WJ, Maloney JD, Black IW, Thomas JD. Characterization of left atrial appendage flow by Fourier analysis: application to patients with atrial fibrillation and flutter. Journal of the American College of Cardiology 1993;21(Suppl A):29.

Grimm RA, Klein AL, Stewart WJ, Pacheco TR, Black IW, Lever HM, Castle LW. Why are patients with atrial flutter less susceptible to systemic embolization following cardioversion than those with atrial fibrillation?. Circulation 1992;86(Suppl 1):663.

Hopkins AP, Black IW, Lee LCL, Jacobson BM, Walsh WF. Clinical and echocardiographic relationships of left atrial spontaneous contrast detected by transesophageal echocardiography. Proceedings, Australian Society for Ultrasound in Medicine 20th Annual Scientific Meeting, Adelaide, 1990:50.

LETTERS

Grimm RA, Black IW, Klein AL. Transesophageal echocardiography before cardioversion. New England Journal Of Medicine 1993;329:577.

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. Cardiogenic brain embolism: role of anticoagulants. Australian and New Zealand Journal of Medicine 1990;20:630-1.

THE CANDIDATE'S CONTRIBUTION

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning. I also declare that the intellectual content of this thesis is the product of my own work, even though I may have received assistance from others on style presentation and language expression.

My work in this thesis has benefitted from collaboration with others as stated below. The studies in this thesis were conducted at the Prince Henry Hospital, Sydney, and at the Cleveland Clinic Foundation, USA. At Prince Henry Hospital, I was responsible for establishing cardiogenic embolism as an area of research, and had the lead role in the conception, data collection and data analysis of Chapters 2,3,7,8 and 10. I was personally present and/or performed almost all TEE studies, more than 900, performed at Prince Henry in the period 1988-1991. I conceived the study and performed the majority of data collection for Chapter 6, with Dominic Leung completing data collection and analysis. I conceived the study and collected the baseline data collection for Chapter 4, with Dominic Leung performing patient follow-up and the majority of data analysis. Dominic Leung and I shared responsibility for Chapter 9, in which I had a greater role in study conception, a shared role in data collection, and a lesser role in data analysis. At the Cleveland Clinic, I was responsible for the conception, data collection and data analysis of Chapter 11. Richard Grimm, Dominic Leung and I shared equally in Chapter 12. The ACUTE Study, Chapter 13, was also a collaborative effort, with Allan Klein, Richard Grimm and I sharing from the start in all phases of the study. I had a moderate role in conception, data collection and analysis of Chapter 5.

Signed:

Date: 10/11/98

26

ABBREVIATIONS

TEE rather than TOE is used as the abbreviation for transoesophageal echocardiography. TEE is the accepted abbreviation in the majority of the published literature, based on the US spelling without the diphthong. TEE was also, paradoxically, selected as the abbreviation by the Editor of the Australian and New Zealand Journal of Medicine in my publication in that Journal (Black et al 1990).

Arguably another abbreviation is the term "spontaneous echo contrast" rather than "spontaneous echocardiographic contrast". However, the shorter term has become accepted in the literature and was used in the title of several published papers.

Other frequent abbreviations are as follows:

AF = atrial fibrillation

CI=confidence interval

ESR=erythrocyte sedimentation rate

INR=International Normalised Ratio

LA = left atrial or left atrium

LAA = left atrial appendage

LV = left ventricular or left ventricle

NYHA = New York Heart Association

PTMV = percutaneous transeptal mitral valvuloplasty

SD= standard deviation

SEC = spontaneous echo contrast

TEE = transoesophageal (or transesophageal) echocardiography

TTE = transthoracic echocardiography

Values in tables and text are expressed as n (%) or mean ± SD, unless otherwise stated.

PART 1

Literature Review

CHAPTER 1

Literature Review

Atrial Fibrillation and Thromboembolism

Introduction and definitions

Atrial fibrillation (AF) is characterised by irregular, disorganised electrical and mechanical activity of the atria. Although apparently first described in ancient China, AF was described in modern times by William Harvey who in 1628 reported "fibrillation of the auricles" in animals (Flegel 1995, Lip and Beevers 1995). In the present era AF is an electrocardiographic diagnosis based on the absence of visible P waves, or the presence of irregular F waves, associated with irregular ventricular response. Electrophysiologically, AF is considered to arise from multiple wavelets of micro-reentry (Flegel 1995).

AF is found in a wide variety of medical and surgical settings. As shown in the Framingham study, most patients with AF have demonstrable cardiovascular disease, including hypertension, coronary artery disease, congestive heart failure, and rheumatic heart disease (Wolf et al 1978, Kannel et al 1982). These and other studies distinguished AF related to rheumatic heart disease from "non-rheumatic" AF.

More recently, the term "nonvalvular" AF has been used in patient with non-rheumatic AF. Rheumatic heart disease is a pathological diagnosis, and it appears more appropriate to use a term based on clinical and echocardiographic grounds. It is possible to have rheumatic heart disease without significant mitral stenosis, with rheumatic heart disease leading to AF by other mechanisms, including direct rheumatic damage to the atrial myocardium (Thiedemann et al 1977, Virmani et al 1977, Roberts et al 1978, Kuschner et al 1991). The term nonvalvular allows for the exclusion of, for example, patients with mitral valve prostheses secondary to mitral regurgitation from mitral valve prolapse. The term nonvalvular AF is therefore employed in this thesis. Specifically, nonvalvular AF is defined as AF in the absence of echocardiographic mitral stenosis or a mitral valve prosthesis. In certain studies in this thesis, severe mitral regurgitation was

also excluded from the diagnosis of nonvalvular AF after the finding in Chapter 2 that LA SEC is almost never found in patients with severe pure mitral regurgitation.

AF is customarily described as either chronic or paroxysmal, with the latter term describing the presence of periods of sinus rhythm and of AF. However, there is no uniformity in the literature regarding the duration or frequency of AF to distinguish the categories. The reflects the difficulty on clinical grounds in distinguishing the onset of AF, or determining the time of transition between paroxysmal and chronic AF. In this thesis, a distinction is generally made between patients with AF at the time of the index TEE study, regardless of duration, and patients with SR at the time of the study with AF having occurred previously, regardless of duration or remoteness of the previous AF.

Prevalence of AF (Table 1)

The prevalence of AF in an unselected adult population such as the Tecumseh study (Ostrander et al 1965) is approximately 0.4%, with a higher prevalence in males. However, both the prevalence and incidence are strongly dependent on age. The average age at diagnosis of AF in the Framingham study (Kannel et al 1982) was 63 years in men and 65 years in women. In the Australian study (Lake et al 1989), based on the population of Busselton, Western Australia, the prevalence rose from 1.7% in those aged 60-64 to 11.6% in those >75 years. In the 22-year follow-up of the Framingham population (Kannel et al 1982), AF developed in 0.22% of those aged 25-34 at baseline and in 3.8% of those aged 55-64 years. The age-related increase is consistent with the increasing prevalence of cardiovascular disease with age, including age-related changes in atrial structure and function.

Table 1. Prevalence of AF (adapted from Cairns and Connolly 1991).

Study	Reference	Patients (n)	Age (yr)	Prevalence (%)	Population
US Air Force	Hiss and Lamb 1962	122,043	15-50	0.004	USAF personnel
Tecumseh	Ostrander et al 1965	5,129	≥16 >60	0.4 3.3	Community survey
Whitehall	Flegel et al 1987	19,018	40-49 40-69 60-64	0.16 0.4 1.13	Male civil servants
Reykjavik	Onundarson et al 1987	9,067	32-64	0.28	Population sample
CASS	Cameron et al 1988	18,343	All 18-39 40-59 ≥60	0.6 0.2 0.5 1.4	Coronary artery disease
Hill	Hill et al 1987	819	>65	3.7	Asymptomatic patients in general practice
Edinburgh	Kitchin and Milne 1977	487	62-90	5.0	Population sample
Campbell	Campbell et al 1974	2,254	≥65 ≥75	2.0 5.0	Community sample
Australia	Lake et al 1989	1,770	60-64 65-69 70-74 ≥75	1.7 3.0 7.0 11.6	Population sample

Epidemiology of AF

Although AF is found in a wide variety of clinical settings, most patients with sustained AF have co-existing cardiovascular disease. In the Framingham study (Kannel et al 1982), AF was significantly related to cardiac failure, rheumatic heart disease, LV hypertrophy, hypertensive heart disease in men, and diabetes in women. Although hypertension as a risk factor was the most common association, occurring in 59% of men and 61% of women in AF, it was also common in controls. Conversely, heart failure and rheumatic heart disease were uncommon in controls and thus carried higher risk ratios.

Although the association is of clinical importance, coronary artery disease is not an important precursor of AF. In the Framingham study (Kannel et al 1982), "coronary heart disease" was not significantly different between AF patients and controls, while "coronary attacks" were of borderline significance and in men only. In the Coronary Artery Surgery Study registry (Cameron et al 1988) of patients with angiographically proven coronary artery disease, only 0.6% of the sample had AF, and only 2/978 (0.2%) of patients 18-39 years of age. AF in this population was however strongly related to LV dysfunction.

Other disease associated with AF include non-rheumatic mitral valve disease, ethanol abuse, thyrotoxicosis, atrial septal defect and repair, and acute medical and surgical illness, including the post-operative period.

Lone AF

A considerable although variable proportion of patients with AF have no apparent cardiovascular or other associated disease, and have been described as having "lone" AF. Unfortunately, there is no standard definition of the term, leading to considerable confusion in the literature and in clinical practice. These differences are of particular importance due to the varying relationship with thromboembolic risk, as detailed below.

Evans and Swann (1954) used the term "lone auricular fibrillation" to describe AF in the absence of known heart disease or thyrotoxicosis. Hypertension and paroxysmal AF were specifically excluded from their definition. No embolism or other complication was observed in the 20 subjects described, all male, mean age 56 years, with only 2 patients >70 years. The period of observation for embolism was not stated, however two patients were followed for 20 years.

In the Framingham population, Brand et al (1985) defined lone AF as excluding coronary heart disease, congestive heart failure, rheumatic heart disease, and hypertensive cardiovascular disease. There were no age limits, with a mean age of 70, and hypertension per se and diabetes did not exclude the definition of lone AF. This definition comprised 11.6% of all patients with AF, and the incidence of embolism was 2.6%/yr.

In contrast, the definition of Kopecky et al (1987) was highly restrictive and also excluded patients with diabetes and hypertension, valve disease including mitral valve prolapse, chronic lung disease, heart failure or cardiomyopathy, radiologic cardiomegaly, thyroid disease or other medical or surgical precipitant, and potentially life-threatening non-cardiac disease. Both chronic and paroxysmal AF were included. Patients aged >60 were excluded, with the mean age 44 years. Only 97/3623 AF patients (2.7%) met these strict criteria, and the embolism rate was 0.4%/yr.

In the recent pooled analysis of the antithrombotic therapy trials (Atrial Fibrillation Investigators 1994) lone AF was defined to exclude patients with previous stroke or TIA, angina, myocardial infarction, congestive heart failure, hypertension or diabetes. The stroke rate in control patients with lone AF was 1.5% overall; 0% in patients <60 years, 1.6% for age years, 2.1% for age 70-79 years and 3.0% for age >80 years.

It is evident that the term lone AF is plagued by a lack of uniform definition, and the

term is falling out of favour. The antithrombotic trials described below have employed a different and more clinically useful approach, with the specific assessment of varying co-existing risk factors in determining thromboembolic risk.

Prognosis of AF - Mortality

The often clinically quiescent nature of chronic AF, particularly in the elderly, initially led clinicians to consider AF as a relatively benign entity. However, AF is associated with not only a significantly increased risk of thromboembolism but also increased mortality. Multiple studies (Kannel et al 1982, Flegel et al 1987, Onundarson et al 1987, Hill et al 1987, Kitchin and Milne 1977, Cameron et al 1988, Lake et al 1989) have consistently demonstrated an two-fold increase in mortality, attributed to both the increased stroke risk and also associated cardiovascular disease. In the Framingham study (Kannel et al 1982), 98 men and women with AF, from a total group of 5,191 subjects, were followed for up to 22 years. All-cause mortality was increased by a factor of 1.7x in men and 1.8x in women, with cardiovascular mortality increased 2.0x in men and 2.7x in women. The average time to death, after diagnosis of AF at a mean 64 years, was only 6 years. The impact of AF on mortality reflects both the increased stroke risk and the frequently associated cardiovascular disease.

Prognosis of AF - Stroke

The most feared complication of AF, and the basis of much of this thesis, is thromboembolism and in particular stroke. It has long been known that AF associated with rheumatic heart disease carries a greatly increased risk of stroke. The Framingham study (Wolf et al 1978) assessed the risk of stroke on 24-year follow-up stratified according to rheumatic heart disease and normalised for age and blood pressure. Patients with AF and rheumatic heart disease had a 17.56x risk ratio for stroke, while patients with non-rheumatic AF had an increased risk of 5.60x. Notably, given the much younger age of patients with rheumatic AF, the absolute stroke risk per year was similar in the two groups, 4.1% without and 4.5%

with rheumatic heart disease. Table 2 provides the incidence of stroke in other follow-up studies, including the placebo arms of two of the recent randomised antithrombotic therapy studies.

One report from the Framingham study (Wolf et al 1987) examined the relative role of non-rheumatic AF and other risk factors as precursors of stroke. The proportion of strokes associated with AF was 14.7% overall, increasing from 6.7% for ages 50-59 years to 36.2% for ages 80-89 years. In contrast to the impact of heart failure, coronary heart disease and hypertension, which declined with age, AF was a significant contributor to stroke at all ages. These findings suggested that AF was not merely a marker of coexisting cardiovascular disease, but an important independent contributor to stroke.

Table 2. AF and Stroke (adapted from Cairns and Connolly 1991).

Study	Reference	Follow-up (yr)	Patients (n) (n with AF)	Age (yr)	Stroke (%/yr) AF	Stroke (%/yr) no AF	Relative Risk
Framingham	Wolf et al 1978	24	5,184 (98)	30-60	4.1 (non-rheumatic) 4.5 (rheumatic)	0.29	5.6 17.6
Reykjavik	Onundarson et al 1987	14	9,067 (25)	32-64	3.8	0.31	4
Whitehall	Flegel et al 1987	18	19,018 (63)	40-69	1.8		6.9
Montreal	Roy et al 1986	3.3	(254)	18-86	5.5		
AFASAK	Petersen et al 1989	2	(336)	38-91	4.9		
SPAF	SPAF 1990	1.1	(528)	67 (mean)	5.7		

Outcome of stroke in AF

Ischaemic stroke in patients with AF is often clinically devastating or fatal. In the pooled analysis study (Atrial Fibrillation Investigators 1994), 47% of the strokes were either fatal or caused functional impairment 1 to 3 months after the event. A comparable number, 55% of patients from the Framingham series also died following AF-related stroke (Wolf et al 1978). In another report (Fisher 1979), 71% died or had severe permanent neurologic deficit.

Silent cerebral infarction

In addition to the often severe consequences as clinically manifest stroke, AF is also an important cause of silent cerebral infarction. This term applies to cerebral infarction detected by imaging studies, usually cerebral CT scanning, in patients without overt acute stroke.

Several studies (Petersen et al 1987, Kempster et al 1988, Guidotti et al 1990, Feinberg et al 1990) have examined the prevalence of silent cerebral infarction in AF, with a prevalence range of 13-48%, and a significantly increased prevalence compared to controls. A report from the SPINAF investigators (Ezekowitz et al 1995) uniquely assessed both the prevalence and incidence of silent cerebral infarction in nonvalvular AF, by performing CT scans at entry and completion of the study, as well as after new neurologic events. 76 patients (14.7%) had one or more cerebral infarcts at baseline, with 40 patients having large or superficial lesions consistent with an embolic aetiology, and 46 had small and deeply located lesions. 70% of the silent infarcts were in the middle cerebral artery territory. Risk factors for silent infarction were increasing age, hypertension and active angina. Other studies have identified LA enlargement (Feinberg et al 1990) as a risk factor. During follow-up in the SPINAF study, new silent cerebral infarction occurred with an incidence of 1%/year in the placebo arm. Of the patients with symptomatic stroke during the study, 7 of 9 with post-stroke scans had large superficial lesions. Prior silent cerebral infarction was slightly (odds ratio 1.5) but not statistically

significantly more common in patients with symptomatic stroke during follow-up. Silent cerebral infarction may be associated with impaired cognition and neurological deficits (Price et al 1997).

Mechanism of stroke in AF

Most strokes in AF appear to be cardioembolic. In the Framingham study (Wolf et al 1978), patients with stroke were seen by a study neurologist, most had lumbar puncture, brain scan and EEG, and cerebral arteriography was performed in a minority. However, it was noted that it is clinically difficult to distinguish thrombotic from embolic stroke and to identify small cerebral haemorrhages. The difficulty in distinguishing occlusive disease of large arteries and lacunar infarction was also noted. Of 20 strokes associated with AF in this study, 19 were judged to be embolic in nature. The strokes in these 19 patients had abrupt onset with maximal deficit at the onset, absence of preceding TIAs, and often rapid reversal of the signs. Autopsy in 6 patients was consistent with an embolic origin, including 1 patient in whom atrial thrombus was identified. More recent studies (Ezekowitz et al 1995, Weinberger et al 1988, Bogousslavsky et al 1990), with the addition of imaging techniques such as cerebral CT scanning, carotid ultrasonography and TTE, such as the study noted above, have suggested an embolic origin in some 70% of strokes in patients with AF. Bogousslavsky et al (1990) systematically performed these three investigations in 159 patients with nonvalvular AF and anterior circulation stroke. Cardiogenic embolism was diagnosed in 76% of the patients. In 67% of the patients, ipsilateral internal carotid artery disease was present, but with stenoses ≥50% in only 14%.

Perhaps the best evidence for the thromboembolic nature of most strokes in AF, apart from the TEE findings discussed subsequently, arises from the antithrombotic trial results also discussed below. The mean 68% reduction in stroke with warfarin is strong support for the thromboembolic nature of the strokes.

Wolf et al (1978) noted that it is clinically difficult to distinguish thrombotic from embolic stroke and to distinguish occlusive disease of large arteries from lacunar infarction. Other investigators (Humphrey and Harrison 1985, Ramirez-Lassepas et al 1987) have also noted the inaccuracy of clinical assessment of the mechanism of stroke. A consensus report (Mohr et al 1997) stated that diagnosis of ischaemic stroke mechanism, classified as embolism, decreased perfusion, or thrombosis, is based on the presence of risk factors for stroke (preexisting condition or circumstance epidemiologically related to stroke) and aetiologies (disease directly causing the mechanism) that implicate the cause of stroke in a given patient. However, multiple potential mechanisms may be present in a single patient, and lacunar infarction may be caused by all three mechanisms (Mohr et al 1997). The accuracy of diagnosis of stroke mechanism cannot be precisely determined in the absence of a gold standard, and reflecting these difficulties, none of the major antithrombotic trials discussed below attempted to distinguish between cardioembolic and other mechanisms of ischaemic stroke.

In addition to embolic stroke, presumed even prior to the advent of TEE to arise from LA thrombi, stroke in patients with AF may arise from any of the other known mechanisms. Ischaemic stroke is a syndrome with multiple aetiologies, as summarised in Table 3. Atherosclerosis of large and small arteries, including the aorta, is overall the most common cause of stroke (Sherman et al 1995). However, cardiogenic embolism is considered to account for approximately 15% of all strokes, and 20% of ischaemic strokes (Wolf et al 1978, Sherman et al 1995). Cerebral angiography after otherwise unexplained stroke often reveals transient occlusion of intracerebral arteries, suggesting an embolic origin (Sherman et al 1995). The proportion of cardiogenic embolism may therefore be underestimated. The association between AF and various forms of cardiovascular disease also increases the incidence of stroke related to the associated diseases, compared to the normal population. These conditions include atherosclerotic carotid disease and aortic atheroma, and LV dysfunction resulting in LV thrombus.

40

Table 3. Aetiology of Stroke (From Sherman et al 1995).

All stroke:

85% Ischaemic stroke

15% Primary haemorrhage - intraparenchymal, subarachnoid

Ischaemic stroke:

20% Atherosclerotic cerebrovascular disease - hypoperfusion, arteriogenic emboli (including aortic atheroembolism)

25% Penetrating artery disease - Lacunes

20% Cardiogenic embolism - Atrial fibrillation, valve disease, ventricular thrombus, others

30% Cryptogenic stroke

5% Other, unusual causes - prothrombotic states, dissections, arteritis, migraine/vasospasm, drug abuse, others

Risk factors for stroke

Identification of subgroups of AF patients with different stroke risks has long been of interest. Lone AF has been discussed previously, and the increased stroke risk associated with cardioversion and with mitral stenosis or prosthesis will be discussed below, as well as other clinical and echocardiographic markers of risk.

Recent onset AF

Wolf et al (1983) from the Framingham study reported a distinct clustering of stroke events at the time of onset of AF, with AF first diagnosed during admission with stroke in 24% of patients, and with AF of less than 2 years duration in 37%. Petersen and Godtfredsen (1986) also reported clustering of embolic events both at the onset of paroxysmal AF and in the first year after progression to chronic AF. In persisting paroxysmal AF, the incidence of embolism was 6.8% in the first month and 2% per year thereafter. In patients developing chronic AF, the rate of embolism was 13.3% in the first year and 4% per year thereafter. These results are consistent with the higher rate of embolism in the early period after cardioversion, discussed below, and with the concept that freshly formed atrial thrombus carries the highest embolic risk.

Despite the attractiveness of this concept, the relationship between duration of AF and embolic risk was not significant in the pooled analysis of the antithrombotic therapy trials (Atrial Fibrillation Investigators 1994), with a relative risk of 0.9 for onset of AF > 1 year.

Recent embolism

Recent embolism, however, appears to carry a clearly increased risk of recurrent stroke in AF. Kelley et al (1984) reported a 33% recurrence rate over 2.5 months, while Darling et al (1967) reported 20% recurrence in 14 days. In the EAFT (EAFT Study Group 1993) secondary prevention trial of antithrombotic therapy after minor stroke or transient ischaemic attack in AF, the annual rate of stroke was 12% patients receiving placebo, 10% in the aspirin group and 4% in the warfarin group.

The 12% incidence is substantially higher than the typical 5%/year incidence of stroke in AF. This also supports the role of dynamic alterations in haemostasis and flow in the LA, including the formation of atrial thrombus, in the pathogenesis of stroke in AF.

Paroxysmal AF

Several retrospective studies have examined the embolic risk of paroxysmal AF. Petersen and Godtfredsen (1986) followed 426 consecutive hospital derived patients with paroxysmal AF for up to 24 years. One third of the patients developed chronic AF during follow-up, loosely defined as transition into persisting AF without periods of sinus rhythm. Embolism occurred with an incidence of 2.0% during AF and 5.1% during chronic AF. The difference was not explained by age. Their finding of a clustering of embolic events at the onset of both paroxysmal and chronic AF has already been noted. Shimomura et al (1989) assessed 572 patients with either chronic or paroxysmal AF and found embolic rates of 2.8% and 1.5%/year respectively.

Few prospective studies have examined paroxysmal AF. In a report from Framingham (Kannel et al 1983) the annual stroke rate and relative risks compared to controls were respectively 5.4% and 4.7x for chronic AF and 1.3% and 1.0x for paroxysmal AF.

Three of the five major antithrombotic trials (Stroke Prevention in Atrial Fibrillation Investigators 1991, Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990, Connolly et al 1991 (CAFA)) included patients with paroxysmal AF. The pooled analysis of the antithrombotic trials (Atrial Fibrillation Investigators 1994) included 462 patients (of a total 3706 patients) with paroxysmal AF at randomisation, defined as documented SR within 2 months. No significant effect of paroxysmal AF on the stroke rate was apparent, with a risk ratio of 0.9 on univariate analysis, and no significance on multivariate analysis. The stroke rate in paroxysmal AF was 5.7% on warfarin and 1.7% on control. However, the

43

proportion of patients who progressed from paroxysmal to chronic AF during the studies is not known, and the multivariate analysis included clinical but not echocardiographic data. Patients with paroxysmal AF may have lesser cardiac structural abnormalities, such as LA dilatation, than patients with chronic AF. Noting these issues and the disparity between the earlier and recent studies, the relative stroke risk of paroxysmal compared to chronic AF remains unsettled, reflected in clinicians relative lack of enthusiasm for anticoagulation in paroxysmal AF.

Randomised trials of antithrombotic therapy in AF

Between 1989 and 1994 seven randomised trials were published assessing the role of antithrombotic therapy in the prevention of thromboembolism in nonvalvular AF. These studies, all except AFASAK published during or after the studies described in Chapter 2 of this thesis, have had profound effects on the understanding and management of patients with nonvalvular AF and will be discussed in detail.

The first group of five trials compared warfarin, and in two studies aspirin, with placebo in the primary prevention of thromboembolism in nonvalvular AF. These were the Danish AFASAK study (Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation, Petersen et al 1989), the SPAF study (Stroke Prevention in Atrial Fibrillation, 1990 and 1991), the BAATAF trial (Boston Area Anticoagulation Trial for Atrial Fibrillation, 1990), the CAFA study (Canadian Atrial Fibrillation Anticoagulation, Connolly et al 1991), and the SPINAF study (Stroke Prevention in Atrial Fibrillation Study, Ezekowitz et al 1992).

The EAFT study (EAFT Study Group 1993) compared warfarin, aspirin and placebo in patients with nonvalvular AF and recent transient ischaemic attack or minor stroke. In 1994 the SPAF investigators published a second study, known as SPAF-II (Stroke Prevention in Atrial Fibrillation Investigators 1994), with the first SPAF study subsequently known as SPAF-I. SPAF-II directly compared warfarin

44

and aspirin for primary prevention in nonvalvular AF, and included many patients previously enrolled in SPAF-I. This was followed by SPAF-III, comparing low dose warfarin together with aspirin versus moderate intensity warfarin (Stroke Prevention in Atrial Fibrillation Investigators 1996).

The five initial studies differed (Table 4) differed with respect to the blinded administration of warfarin, whether or not paroxysmal AF was included, the measurement of anticoagulant intensity using International Normalised Ratio (INR) or Prothrombin Ratio (PR), the target intensity of anticoagulation, and study length. All of these studies except CAFA were stopped by their independent monitoring committees due to the clear superiority of active treatment, with CAFA stopped due to the publication of the other trials.

In 1994 a pooled analysis was published by the investigators of the five initial trials (Atrial Fibrillation Investigators 1994). The analysis was based on patient-specific data from the individual trials. Only ischaemic stroke as the common endpoint and only clinical but not echocardiographic data were analysed. Several adjustments for variables either not collected or defined differently were required.

Table 4. Randomised Antithrombotic Trials in AF.

Study	AFASAK	SPAF	BAATAF	CAFA	SPINAF
Publication Year	1989	1990	1990	1991	1992
Screened	2546	18376	?	?	7982
Enrolled (n) (% of screened)	1007 (39%)	1330 (7%)	420	378	538 (7%)
Follow-up (yrs)	2	1.3	2.2	1.3	1.7
Primary Endpoints	Stroke, TIA, systemic embolism	Stroke, systemic embolism	Stroke	Stroke, systemic embolism	Stroke
Warfarin Blinded	No	No	No	Yes	Yes
Age (mean, yrs)	74	67	68	68	67
Paroxysmal AF	No	Yes	Yes	Yes	No
INR or PR	INR	PR	PR	INR	PR
Target INR	2.8-4.2	2.0-4.5	1.5-2.7	2.0-3.0	1.4-2.8
Aspirin	75 mg	325 mg	46%	No	No
Primary Endpoint Risk reduction	52% (Warfarin) 16% (Aspirin)	67% (Warfarin) 42% (Aspirin)	86%	37%	79%
Stroke Risk Reduction	58%	67%	86%	42%	79%
Major Bleeding	3.5%	1.7%	0.4%	2.5%	1.0%

Patient selection in the randomised trials

A feature of all trials was the highly selected patient populations. Criteria for exclusion included perceived indications for or contraindications to warfarin, and were detailed in SPAF-1 and SPINAF. Indications for warfarin, in whom placebo may have been unethical, included mitral stenosis or any prosthetic heart valve, severe heart failure, marked LA dilatation, known intracardiac thrombus, idiopathic dilated cardiomyopathy, previous systemic embolism, or recent bypass surgery, percutaneous transluminal coronary angioplasty, myocardial infarction, unstable angina, stroke or TIA, pulmonary embolism or deep venous thrombosis.

Contraindications to warfarin (in one or more of the five studies) included age > 75 years, dementia or psychosis, expected life expectancy < 2 years, chronic renal failure, thrombocytopenia, anaemia, haemostatic disorder, alcoholism, requirement for non-steroidal anti-inflammatory drugs, inadequate follow-up, repeated falls or unstable gait, positive stool test for blood, recent gastrointestinal or genitourinary bleeding, microscopic haematuria, recent peptic ulcer disease or esophageal varices, uncontrolled hypertension, occupational hazards to anticoagulant therapy, atrial tumour, bacterial endocarditis, severe haemorrhage during previous anticoagulant therapy, recurrent syncope or seizure, intrinsically prolonged prothrombin time, previous intracranial haemorrhage, planned surgery or invasive procedure, abnormal liver function tests, and any psychological, social or general condition rendering the patient unsuitable for anticoagulation.

These extensive exclusions led to up to 93% of initially screened patients eventually enrolled (Table 4). This high degree of patient selection is likely to have influenced the rate of bleeding complications compared to an unselected population, and is one factor in the still incomplete application of the trial results to routine clinical practice (Stafford and Singer 1996). Interaction between variables such as advanced age, poor compliance and tendency to haemorrhage may lead a non-linear increase in risk. Conversely, it could be argued that the efficacy results are particularly impressive given that many patients with higher risk

of thromboembolism were excluded.

Efficacy of warfarin

Warfarin produced a marked and consistent reduction in ischaemic stroke in all five trials. Combining the 5 trials (Atrial Fibrillation Investigators 1994), the stroke rate was decreased by 68% (95% CI, 50% to 79%), with an absolute annual reduction of 3.1%, from 4.5% to 1.4%. Systemic embolism was non-significantly reduced from 0.5%/yr to 0.3%/yr. There was also a significant 33% (95% CI 9-51%) reduction in mortality, from 5.4%/yr to 3.6%/yr. The combined endpoint of stroke, systemic embolism or death was reduced by 48% (95% CI 34-60%) from 9.8%/yr to 5.0%/yr. Despite the wide variation in target INR in the studies, there was no apparent relation between anticoagulant intensity and risk reduction. Paradoxically, the two studies with the greatest risk reduction, BAATAF and CAFA, used the lowest target intensity (prothrombin ratio 1.2-1.5). The incidence of major bleeding was however directly related to anticoagulant intensity (Table 4).

Following the publications of these studies, an expert panel (Laupacis et al 1995) recommended that a target INR of 2.0-3.0 be used for warfarin anticoagulation in AF. The SPAF-III trial (Stroke Prevention in Atrial Fibrillation Investigators 1996), discussed below, subsequently confirmed the efficacy and safety of a target INR of 2.0 to 3.0. An observational study (Hylek et al 1996) also demonstrated that an INR of 2.0 or greater was required for effective prophylaxis, although a lesser degree of stroke prevention was provided with an INR of 1.5-2.0.

It is notable that the intention-to-treat approach of these trials may have underestimated the biological effect of warfarin. In the five studies, 8 of the 27 patients with stroke despite randomisation to warfarin were not taking the medication at the time of stroke, and 16 of the 27 had subtherapeutic anticoagulation as defined in the individual studies.

Bleeding

The incidence of major bleeding (intracranial bleeding, bleeding requiring two units of blood, or bleeding requiring hospital admission) in the selected patients in this study was relatively low, occurring in 1.0%/yr in both control and aspirin treated patients and in 1.3%/yr of warfarin treated patients, a 0.3%/yr absolute increase. When defined as bleeding requiring hospitalisation, blood transfusion or surgery (Albers 1994), a rate of 0.9%/yr in control patients and 1.0%/yr in warfarin patients was observed. Patients with intracranial bleeding (0.3%/yr on warfarin, 0.1%/yr in control patients) were older and relatively hypertensive, and usually had an elevated INR at the time of the event.

The SPAF Investigators (1996) specifically examined risk factors for bleeding from the SPAF-2 study. The rate of major haemorrhage in patients on warfarin was 1.7%/year in patients < 75 years and 4.2% per year in older patients (relative risk, 2.6, p = 0.009); rates by age for intracranial bleeding were 0.6% per year and 1.8% per year, respectively (P = .05). Advancing age and more intense anticoagulation were identified as risk factors for major haemorrhage in patients given warfarin for stroke prevention in AF.

Risk factors for stroke

Given the potential bleeding complications, most studies attempted to identify patients with the greatest risk of thromboembolism on control and therefore the greatest potential benefit from warfarin. These risk factors are outlined in Table 5. Two reports from the SPAF-I study (Stroke Prevention in Atrial Fibrillation Investigators 1992a and 1992b) and the pooled analysis (Atrial Fibrillation Investigators 1994) examined such risk factors in detail.

The SPAF investigators (The Stroke Prevention in Atrial Fibrillation Investigators 1992a and 1992b) examined both clinical and TTE predictors of thromboembolism in the placebo group by multivariate analysis. The three clinical predictors were hypertension, history of thromboembolism and recent (within 3 months) heart failure. The thromboembolism rate was 2.5%/yr with no risk factors, 7.2%/yr with

49

one risk factor, and 17.6%/year with 2 or 3 risk factors. Non-diabetic patients without clinical risk factors, comprising 38% of the cohort, had a 1.4%/yr risk of embolism. Patients without clinical risk factors under age 60 had no embolic events. The two echocardiographic predictors were LA dilatation (M-mode diameter > 2.5 cm/m^2) and global LV dysfunction. Patients with neither clinical or echocardiographic risk factors had an embolic rate of 1.0%, and were judged not to require warfarin. The addition of echocardiographic to clinical variables altered embolic risk stratification in 18% of the entire cohort, and in 38% of those without clinical risk factors. The echocardiographic report (The Stroke Prevention in Atrial Fibrillation Investigators 1992b) also noted the potential role of TEE, referencing the publication included as Chapter 2 of this thesis (Black et al 1991a).

The original pooled analysis (Atrial Fibrillation Investigators 1994, Table 6) only examined clinical variables, as echocardiographic variables were not available in all trials. The significant independent risk factors for stroke in multivariate analysis were increasing age, previous stroke or TIA, hypertension and diabetes. Warfarin reduced the risk of stroke in all risk factor subgroups except patients < 65 years with no risk factors, in whom the stroke rate was 1.0% year with or without warfarin. A subsequent analysis of transthoracic echocardiographic variables, based on 1066 patients from 3 of the trials, found that left ventricular systolic dysfunction predicted stroke, and was of particular discriminating value in clinically low risk patients (Atrial Fibrillation Investigators 1998).

Table 5. Risk Factors for Thromboembolism From the Randomised Trials.

These univariate or multivariate risk factors were stated in the initial publications, except for SPINAF where the risks factors were only reported in the pooled analysis (Atrial Fibrillation Investigators 1994).

AFASAK	Clinical	Previous myocardial infarction
BAATAF	Clinical	Age
		Angina
		Clinical heart disease
	Echo	Mitral annular calcification
SPAF-1	Clinical	Recent congestive heart failure
		Hypertension
		Previous thromboembolism
		Diabetes
	Echo	LV systolic dysfunction
		LA enlargement
SPINAF	Clinical	Angina
		Not currently smoking
POOLED ANALYSIS	Clinical	Hypertension
		Previous thromboembolism
		Diabetes
		Age >65 years
	Echo	LV systolic dysfunction

51

Table 6. Predictors of Stroke in Control Patients in the Pooled Analysis (Atrial Fibrillation Investigators 1994).

Variable	n or %	Relative Risk		Stroke Rate (%/yr)	
		Univariate	Multivariate	Control	Warfarin
Prior stroke/TIA	101	3.1	2.5	11.7	5.1
Hypertension	750	1.9	1.6	5.6	1.9
Age (decades)	-	1.4	1.4	-	-
Diabetes	250	2.0	1.7	8.6	2.8
Congestive heart failure	349	1.7	1.4	6.8	1.6
Clinical heart disease	657	1.6	1.0	6.1	1.6
Myocardial infarction	217	1.7	1.2	8.2	3.3
Angina	363	1.5	-	6.7	0.9
Current smoker	158	0.4	-	2.5	1.3
Intermittent AF	207	0.9	-	5.7	1.7
AF onset > 1 yr	1087	0.9	-	4.4	1.5
Female	439	1.3	-	5.8	0.9
PVD	99	1.4	-	6.0	1.8
Systolic BP	-	1.0	-	-	-
Diastolic BP	-	1.0	-	-	-
Age <65, no risks	16%			1.0	1.0
Age <65, ≥1 risk	17%			4.9	1.7
Age 65-75, no risks	20%			4.3	1.1
Age 65-75, ≥1 risk	27%			5.7	1.7
Age >75, no risks	11%			3.5	1.7
Age >75, ≥1 risk	9%			8.1	1.2

Risks are defined as history of prior stroke, transient ischaemic attack, diabetes or hypertension. Clinical heart disease is defined as history of angina, myocardial infarction or congestive heart failure. BP= blood pressure, PVD=peripheral vascular disease.

SPAF II

The second study from the Stroke Prevention in Atrial Fibrillation Investigators (1994) was designed to address the relative efficacy of aspirin and warfarin. An unusual and controversial aspect of the study design was the inclusion and continued follow up of 416 patients who had been randomised to aspirin or warfarin in SPAF-I. In addition, a group of 265 patients originally assigned to placebo were re-randomised. An additional 419 patients were enrolled, including patients with age over 75 years, which was an exclusion criteria for most of the enrollment period of SPAF-1 due to concern regarding bleeding. This age restriction had been removed during the course of enrollment for SPAF-1 based on their early experience and the AFASAK results. Two parallel studies were performed, comprising 715 patients ≤75 years (mean 64 years) and 385 patients >75 years (mean 80 years). As a result of this design, the younger group were followed for 3.1 years compared to only 2.0 years for the older patients. Relatively high doses of both agents were used, warfarin target INR 2.0-4.5 and aspirin 325 mg/day.

In the combined age groups, warfarin was more effective than aspirin in reducing ischaemic stroke, with a non-significant 32% relative risk reduction (95% CI -13-59%). However, 12 of the 28 patients randomised to warfarin were not taking the medication at the time of stroke. "On-treatment" analysis, confined to patients actually taking the prescribed medication (Albers 1994) demonstrates a 54% risk reduction in patients ≤75 years receiving warfarin and a 53% reduction in patients >75 years. The reasons for patients not taking warfarin were not stated, and may have comprised intercurrent illness or operation. However, the benefits of warfarin were largely offset by increased intracranial haemorrhage, particularly in the older group, so that the combined rate of ischaemic and haemorrhagic stroke was non-significantly reduced by 10% in younger patients and 9% in older patients.

These results indicated that the relative safety of warfarin in the relatively younger patients in other studies, including the mean age of 74 years in AFASAK, may not

apply to the very elderly at high INR. The mean anticoagulant intensity at the time of intracranial haemorrhage in 13 patients in SPAF-II (Albers et al 1994) was a prothrombin ratio of 1.7, equivalent to an INR of approximately 3.5, in excess of the target intensity generally recommended.

The SPAF-II study also identified a low risk group with an embolic event rate of only 0.5%/year on aspirin, comprising patients ≤75 years without hypertension, recent congestive heart failure or previous thromboembolism.

SPAF III

This trial (Stroke Prevention in Atrial Fibrillation Investigators 1996) arose from the safety concerns in SPAF-II. 1044 patients with AF and at least one other thromboembolic risk factor were randomised to either a combination of low-intensity, fixed-dose warfarin (target INR 1·2-1·5, mean achieved 1.3) and aspirin (325 mg/day), or adjusted-dose warfarin (target INR 2·0-3·0, mean achieved 2.4). The trial was stopped after an interim analysis at a mean follow-up of 1·1 years. The primary endpoint, ischaemic stroke or systemic embolism, was 7·9% per year in patients on combination therapy and 1·9% per year on adjusted-dose warfarin (p<0·0001), an absolute reduction of 6·0% per year (95% CI 3·4, 8·6) by adjusted-dose warfarin. The annual rates of disabling stroke (5·6% vs 1·7%, p=0·0007) and of primary event or vascular death (11·8% vs 6·4%, p=0·002), were also higher with combination therapy. The rates of major bleeding were similar in both treatment groups. It was concluded that the low-intensity, fixed-dose warfarin plus aspirin regimen was insufficient for stroke prevention in patients with nonvalvular AF at high risk for thromboembolism. In contrast, adjusted-dose warfarin (target INR 2·0-3·0) effectively reduced the rate of stroke. A similar advantage for adjusted dose warfarin compared to low dose warfarin, or low dose warfarin and aspirin in combination, was recently reported in the AFASAK 2 Study (Gullov et al 1988).

In addition, the SPAF III Writing Committee for the Stroke Prevention in Atrial

Fibrillation Investigators (1998) reported a prospective cohort study of 892 low risk patients, with a mean age of 67 years. Patients were defined as low risk in the absence of heart failure, left ventricular systolic dysfunction, systolic blood pressure greater than 160 mm HG, or females older than 75 years. All patients received 325 g aspirin per day. The rates of embolism and disabling ischaemic stroke was 2.2% per year and 0.8% per year respectively, with a rate of disabling ischaemic stroke of 0.5% per year in the group without hypertension.

EAFT

This secondary prevention study from the European Atrial Fibrillation Trial Study Group (1993) compared anticoagulation (INR 2.5-4.0), aspirin (300 mg/day) and placebo in patients with AF and recent (<3 months) stroke or transient ischaemic attack. Various anticoagulants were used, mostly coumarin derivatives. There were 1007 patients followed for a mean 2.3 years. Similar to AFASAK, EAFT provided a comparison of aspirin with both anticoagulation and placebo, using a higher and potentially more effective aspirin dosage than AFASAK. In a manner reminiscent of SPAF-I, separate randomisation was performed for 669 anticoagulant eligible patients (mean age 71 years) randomised to anticoagulation, aspirin or placebo; and 338 anticoagulant ineligible patients (mean age 77 years), randomised to aspirin or placebo. Using a combined endpoint of ischaemic stroke and intracranial haemorrhage (Albers 1994), aspirin reduced events by 16% (p=NS) compared to placebo, while anticoagulation reduced events by 69% (p=0.04). The 16% reduction with aspirin was comparable to the finding of the AFASAK study in a similarly elderly population.

EAFT also confirmed the high rate of repeat thromboembolism in patients with AF, with a stroke risk of 12% in the placebo group. The study was also notable for the complete absence if intracranial haemorrhage in the anticoagulated group, confirming the safety of this treatment commenced in the weeks to months after the initial event.

Efficacy of aspirin

Three trials, AFASAK, SPAF-I and EAFT, have compared aspirin and placebo. In AFASAK, aspirin at 75 mg/day resulted in a non-significant 18% reduction in stroke (95%CI -60% to 58%, p=0.57) compared to placebo. In SPAF-I, using 325 mg/day aspirin , a significant 44% decrease in stroke was observed (95% CI 7%-66%, p=0.02) compared to placebo. When these two studies are combined (Albers 1994), a significant 36% decrease (95% CI 4% to 57%, p=0.03) was reported (Atrial Fibrillation Investigators 1994). This positive outcome largely reflects the size of SPAF-I, which accounts for two-thirds of patients and events in the combined analysis. Nevertheless, in combined analysis aspirin did not statistically significantly reduce either the endpoints of stroke with persistent deficit or death, although trends were observed in both instances. Subgroup analyses (Atrial Fibrillation Investigators 1994) showed that the benefits of aspirin were confined to patients with a history of hypertension (stroke reduction 59%, 95% CI 28-77%, p=0.002), while there was a non-significant increase in stroke on aspirin in patients without hypertension (10%, 95% CI 40-100%, p=0.76). In the EAFT study, discussed previously, 300 mg aspirin compared to placebo resulted in a non-significant 17% reduction in stroke (95% CI -9%-37%). When these three studies are combined, a risk reduction with aspirin of 21% (95% CI 1-37%, p=0.04) was observed (Albers 1994), with no clear relationship between dose and efficacy.

It is interesting to compare these results with the report of the Antiplatelet Trialists' Collaboration (1994). This overview reported a risk reduction of 20% (95% CI 10-30%) with antiplatelet therapy in the eight trials in patients with previous stroke or transient ischaemic attack, and a reduction also of 20% (95% CI 12-27%) in all 144 trials reviewed.

Three trials, AFASAK, SPAF-II and EAFT, have compared aspirin and warfarin in the prevention of ischaemic stroke. AFASAK reported a non-significant 51% risk reduction for warfarin compared to aspirin 75 mg/day (95% CI -16-80%), and SPAF-II reported a non-significant 32% reduction for warfarin (95% CI -13-59%).

EAFT, a secondary prevention study, showed a significant reduction for warfarin of 62% (95% CI 36-77%, p<0.001). The total risk reduction for all studies for warfarin compared to aspirin (Albers 1994) was 49% (95% CI 30-63%, p<0.001).

These findings led to speculation (eg Hart and Halperin 1994) that the effects of aspirin and warfarin on stroke prevention are not only quantitatively but also qualitatively different, in that different stroke mechanisms may be targeted by aspirin and warfarin. A report from the SPAF group (Miller et al 1993) found that aspirin reduced significantly more strokes categorised as non-cardioembolic than cardioembolic. Most AF-related stroke, particularly in the older, sicker patients such as the AFASAK cohort, is attributed to cardiogenic embolism with stasis leading to fibrin-rich red thrombi in the LA and particularly appendage, likely to be affected by warfarin but not aspirin. The Antiplatelet Trialists' Collaboration (1994) found a small benefit for aspirin in the prevention of deep venous thrombosis, with a pathogenesis probably similar to atrial thrombus.

Implications of the Randomised Trials

The following conclusions can be drawn from the randomised trials, relevant to clinical practice and to the considerations of this thesis.

1. The high rate of embolism in control groups confirms the risk of nonvalvular AF.

2. The risk is markedly reduced by antithrombotic therapy, consistent with a thrombotic aetiology for the events. Intention to treat analysis may underestimate the biological effect of warfarin.

3. Warfarin is more effective than aspirin, suggesting intracardiac stasis and subsequent thrombosis as the major mechanism of embolism.

4. Additional mechanisms of embolism such as platelet aggregation may explain

the partial efficacy of aspirin.

5. There is no clear relation between INR and efficacy, suggesting the efficacy of lower INR target ranges, with a minimum of 2.0. The efficacy of INR 1.5-2.0 has not been tested.

6. The bleeding risks are also significant, even in highly selected patients. In particular, warfarin may produce unacceptable rates of cerebral haemorrhage in the very elderly, particular at a high target INR. Conversely, some patient groups, including those with "lone" AF, have an embolic risk less than the bleeding risks of warfarin.

7. Risk stratification is important, and can be accomplished in part by clinical and TTE predictors.

8. Additional risk stratification, such as that potentially provided by TEE, should be investigated.

Cardioversion and Thromboembolism

Background

Clinical management of AF involves consideration of at least 3 components: restoration of sinus rhythm, ventricular rate control and antithrombotic therapy. Given the documented morbidity and mortality of chronic AF, attempts to achieve and maintain sinus rhythm, ie cardioversion by either pharmacologic or electrical means, is usually the primary management decision. Potential advantages include relief of symptoms, improved cardiac function, reduced potential for subsequent thromboembolism and hence reduced requirement for anticoagulation. Several studies have demonstrated the benefits of successful cardioversion, including improved LV function, cardiac output, functional capacity, exercise time and anaerobic threshold, decreased atrial size, and avoidance of adverse changes to atrial electrophysiology (Hansen et al 1952, Lipkin et al 1988, Atwood et al 1989, Alam and Thorstrand 1992, Karnegis et al 1989, Grogan et al 1992, Peters et al 1988, Van Gelder et al 1991, Gosselink et al 1993, Gosselink et al 1994, Gosselink et al 1994, Wijffels et al 1995).

History

"Embolism occurs in approximately 30 per cent of patients with chronic atrial fibrillation. It is therefore logical to conclude that this incidence will be greatly reduced by successful conversion to and maintenance of sinus rhythm. Although is the firm belief of many investigators in this field (including the author) that this is true, there are no extensive long term statistics available to prove the point at this time"

(Goldman 1960)

Reports of the use of quinidine compounds to treat "rebellious palpitations" date from De Senac in 1749 (quoted in Goldman 1960). In the modern era, with the

advent of electrocardiographic diagnosis of AF (Einthoven 1906, quoted in Flegel 1995), Frey in 1918 reported the success of quinidine in 21 of 50 patients with AF, and recognised its potential toxicity (Frey 1918, quoted in Goldman 1960). By 1960, Goldman was able to publish a comprehensive and still highly instructive review of the benefits and risks of quinidine cardioversion, and also described its use to prevent recurrences. The technique of quinidine cardioversion is still in occasional use today, and forms the historical basis of antiarrhythmic medication to prevent recurrences of AF.

The field was revolutionised by the introduction by Lown of electrical cardioversion in the early 1960's. Lown's first paper (Lown et al 1962) described the use of synchronised direct current discharges to the heart for the treatment of 9 episodes of ventricular tachycardia in 5 patients, and 13 episodes of AF in 12 patients. Cardioversion was successful in 11 of the 13 episodes of AF, and complications were limited to transient arrhythmias. Ten of the patients were treated immediately following surgical open mitral commisurotomy, if the LA was free of thrombus. Both patients with failed reversion were in the surgical group and had AF duration >5 months. One patient with atrial flutter and one with a supraventricular tachycardia were also treated.

The following year Lown et al (1963) reported "cardioversion", their preferred term, in 65 episodes of AF in 50 patients. Almost all patients had rheumatic disease. Reversion was achieved in 89% of the episodes, a marked increase from the 20-55% success rate expected from quinidine. Transient arrhythmias were again frequent, perhaps due in part to concomitant therapy with digoxin or quinidine. The single major complication was splenic embolism 2 days after successful reversion in a patient with mitral stenosis and AF of 4 weeks duration, who was not receiving anticoagulants.

The high initial success rates of electrical cardioversion rapidly led to its acceptance in clinical practice, and it remains the definitive form of cardioversion.

Numerous reports during the 1960's, listed subsequently, described the clinical role of the procedure. Like any new technique, initial highly favourable reports were followed by concerns regarding the procedure. Despite the high likelihood of initial reversion to sinus rhythm, subsequent return to AF was common. In the meta-analysis of Coplen et al (1990), only 25% of patients remained in sinus rhythm one year after initially successful cardioversion. Quinidine therapy doubled the proportion of patients remaining in sinus rhythm at the expense of a statistically significant increase in mortality (2.9% vs 0.9%). Although highly controversial at the time of publication, and calling into question the rationale for cardioversion, these findings were supported by Flaker et al (1992). This retrospective analysis from the SPAF-1 trial demonstrated increased mortality in patients with AF receiving antiarrhythmic therapy, specifically in the presence of congestive heart failure. The CAST study (The Cardiac Arrhythmia Suppression Trial Investigators 1989) confirmed the toxicity of class I antiarrhythmic therapy, until recently the mainstay of antiarrhythmic medication for AF. In summary, sinus rhythm is frequently not maintained without medication which itself is harmful. Further, the recent antithrombotic trials have demonstrated that the embolic risks can be reduced although not abolished by warfarin, despite continued AF. The two strategies, maintenance of sinus rhythm versus heart rate control alone, will be compared in the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) randomised trial, to be conducted by the NHLBI. At present, it has not been established that cardioversion reduces the long-term risk of embolism.

These considerations represent part of a series of advances relating to AF, which are outside the scope of this thesis but summarised here. These advances include the search for predictors of successful sinus rhythm, more effective drugs such as amiodarone, identification of a genetic locus for familial AF, and novel non-pharmacologic approaches including surgical approaches (the Maze operation), a non-surgical Maze procedure using radiofrequency energy, internal defibrillation, the implantable atrial defibrillator, various pacing techniques, and radiofrequency ablation or modification of the AV node (Disch et al 1994,

61

Williamson et al 1994, Nattel 1995, Levy et al 1992, Cox et al 1991, Brugada et al 1997, Brignole et al 1998). Predictors of recurrent AF include longer duration of AF, larger LA size, older age, multiple previous episodes of arrhythmia, AF rather than flutter, poor functional class, and presence of mitral valve disease (Crijns et al 1991, Van Gelder 1991, Dittrich et al 1989).

Embolism after cardioversion

In addition to the toxic effects of the drug itself, which have been discussed above, there remains one hazard which is probably the major fear in the use of quinidine in conversion of chronic atrial fibrillation. This is the possibility of embolism occurring at the time of or within 48 hours after conversion. It is postulated that loosely adherent atrial thrombi are broken loose from the atrial endocardium by the return of vigorous atrial contractions.

(Goldman 1960)

Embolism has been and remains the major complication of both pharmacologic and electrical cardioversion. Goldman (1960) reported embolism in 6 of 400 (1.5%) quinidine conversions. As noted, Lown (1963) et al also reported embolism in 1 of 65 (1.5%) electrical cardioversions. The incidence of embolism in various reported series is shown in Table 7. Only selected, larger series involving quinidine cardioversion are shown, while Table 7 includes all known series of electrical cardioversion, prior to the advent of TEE. The inclusion criteria for embolism, information on anticoagulant usage, and success rate of cardioversion all vary widely in these studies. It is remarkable that clinical decisions for have relied on studies of such relative age, with numerous methodological uncertainties. Table 7 indicates no major difference in embolic rate between pharmacologic and electrical conversion. Most embolic events occur not at the time of cardioversion but hours to days later, with almost all events occurring within the first week after cardioversion.

Table 7. Incidence of Embolism After Chemical Or Electrical Cardioversion of AF. Page 1 of 3.

Study	Year	n Pts	n CV	Method	AC Rx	Success %	Embolism n	%CV	%Conv	%Pt
Viko	1923	75	75	Quin	No	68	1	1.3	2.0	1.3
Fahr	1938	500	500	Quin	No	65	ND	ND	ND	some
Thomson	1956	485	485	Quin	Some	ND	11	2.3	ND	2.3
Sokolow	1956	177	214	Quin	Some	71	2	0.9	1.3	1.1
Goldman	1960	≈500	≈500	Quin	No	≈82	6	≈1.2	1.5	1.2
Freeman	1963	100	100	Quin	All	57	0	0	0	0
Rokseth	1963	274	274	Quin	All	47	2	0.7	1.6	0.7
Lown	1963	50	65	DCC	Some	89	1	1.5	1.7	2
Killip	1963	46	59	DCC	45%	90	0	0	0	0
Morris	1964	70	94	DCC	6%	70	3	3.2	4.5	4.2
Oram	1964	100	129	DCC	Some	84	2	1.6	1.9	2
Hurst	1964	121	158	DCC	No	96	2	1.3	1.3	1.6
Turner	1965	40	40	DCC	Some	90	3	7.5	8.3	7.5
Rabbino	1965	65	65	DCC	Some	91	2	3.1	3.4	3.1
Partridge	1965	83	83	DCC	None	78	0	0	0	0

Study	Year	n Pts	n CV	Method	AC Rx	Success %	Embolism n	%CV	%Conv	%Pt
Meltzer	1965	50	50	DCC	None	80	1	2	2.5	2
Reinikainen	1965	63	63	DCC	Some	79	2	3.2	4	3.2
Korsgren	1965	138	138	DCC	All	78	0	0	0	0
Morris	1966	108	167	DCC	Some	60	4	2.4	4	3.7
Halmos	1966	175	175	DCC	No	78	1	0.6	0.7	0.6
Selzer	1966	189	238	DCC	No	79	4	1.7	2.1	2.1
Lown	1967	350	456	DCC	29%	94	5	1.1	1.2	1.4
Resnekov	1967	204	204	DCC	Some	95	3	1.5	1.6	1.5
Wikland	1967	74	110	DCC	72%	81	1	0.9	1.1	1.3
Coelho	1967	250	250	DCC	Some	88	4	1.6	1.8	1.6
Hall	1968	149	149	DCC	39%	72	1	0.7	0.9	0.7
Radford	1968	156	156	DCC	17%	77	0	0	0	0
Aberg	1968	207	323	DCC	Most	87	2	0.6	0.7	0.9
McCarthy	1969	149	149	DCC	Some	83	2	1.3	1.6	1.3
Bjerkelund	1969	437	572	DCC	52%	79	13	2.3	2.9	3.0
					Yes(n=297)	79	2	0.7	0.8	0.8
					No(n=275)	79	11	4.0	5.0	5.3

Study	Year	n Pts	n CV	Method	AC Rx	Success %	Embolism n	%CV	%Conv	%Pt
Byrne-Quinn	1970	92	100	DCC	Some	90	1	1.0	1.2	1.1
Henry	1976	37	54	DCC	Some	ND	3	5.6	ND	8.1
Roy	1986	152	152	DCC	72%	ND	2	1.3	ND	1.3
Dittrich	1989	85	85	DCC	All	76	1	1.2	1.5	1.2
Weinberg	1989	79	79	DCC	Yes(n=51)≈84		0	0	0	0
					No(n=28) ≈84		2	7	≈8.5	7
Lesser	1990	69	69	DCC	All	93	1	1.5	1.6	1.5
O'Neil	1990	14	14	DCC	71%	100	1	7	7	7
Arnold	1992	ND	332	DCC	41%	100	6	1.8	1.8	ND
					Yes(n=153) 100		0	0	0	ND
					No (n=179) 100		6	3.3	3.3	ND

Abbreviations: AC = anticoagulation, CV = cardioversion, DCC = direct current cardioversion, quin = quinidine cardioversion, ND= missing data, pt = patient.

Notes: The incidence of embolism is provided as a % of the number of cardioversions (CV), the number of cardioversions with successful conversion to sinus rhythm (Conv), and the number of patients (Pt). Patients with rhythms other than AF have been excluded where possible. Almost all embolic events listed are systemic rather than pulmonary. Exceptions include one pulmonary embolism each in the series of Oram 1964, Rabbino 1965 and Reinikainen 1965, and two in Thomson 1956. Morris, Partridge/Halmos and Lown have the same patients in several publications. The Arnold study reported 454 successful cardioversion attempts in 428 patients with AF or flutter, including 332 successful cardioversions for AF. The total number of patients (including unsuccessful cardioversions) and cardioversion success rate are unknown. 93% of Weinberg's patients were electrically cardioverted, 7% pharmacologically. "Success" general refers to immediate success, ie return to sinus rhythm.

Mechanism of embolism after cardioversion

Anticoagulant therapy prior to quinidine administration is of theoretical consideration. It is believed that recently formed atrial thrombi are likely to be dislodged at the time of conversion. Pathological studies indicate that within 14 days there is sufficient fibroblastic infiltration to cause firm adherence of the thrombus to the atrial endocardium, thus reducing the likelihood of dislodgement. Hence if one can prevent formation of atrial thrombi by anticoagulant therapy for 14 days before beginning quinidine and continue this up to the time of conversion, the small incidence of embolism at the time of conversion may be reduced even further.

However, no adequate statistics are available as yet to prove this point.
(Goldman 1960)

The presence of thrombus in the LA cavity and its appendage in patients with AF or rheumatic heart disease has long been known from surgical (Wallach et al 1953) and autopsy (Aberg 1969, Hinton et al 1977) series. As stated by Goldman, it has long been assumed that cardioversion following embolism resulted from the dislodgement of *pre-existing* atrial thrombus.

A striking feature of cardioversion-related embolism is the typical delay between cardioversion and embolism, with a median delay of 2 to 3 days, and up to 1 week. This was attributed to observations that atrial mechanical function did not return to normal immediately after cardioversion. These observations were initially based on invasive haemodynamic studies (Ikram et al 1968, Thompson et al 1972), then on two-dimensional echocardiographic observations (DeMaria et al 1975), and subsequently on the simple and repeatable noninvasive method of pulsed Doppler of mitral inflow A wave, the P wave equivalent (Manning et al 1989, Shapiro et al 1988, O'Neil et al 1990). These studies have shown that atrial mechanical function does not return to normal until up to 4 weeks after cardioversion. Manning et al (1994) reported a positive correlation between the delay in return of atrial function

and the duration of preceding AF (Manning et al 1994). These observations suffered from the fact that the methods assessed only LA cavity function, not the appendage where most thrombi occur in patients with nonvalvular AF (Black et al 1991a). Furthermore, it should be noted that in distinction to the LA appendage "stunning" discussed subsequently, which involves an acute reduction in LA function after cardioversion, the traditional concept was that LA cavity mechanical function was essentially absent during AF, and gradually improved towards normal after cardioversion after some delay.

In summary, embolism following cardioversion was assumed to result from dislodgment of pre-existing atrial thrombi following the delayed return of atrial mechanical activity.

Anticoagulation for prevention of embolism - conventional therapy and rationale

Concern regarding the embolic risks of cardioversion led to recommendations for antithrombotic therapy with warfarin for a period before, during and after cardioversion. Although several formulations of this standard therapy have been promulgated, the current recommendations are those from the Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy (Laupacis et al 1995). These recommendations are as follows:

"It is strongly recommended that oral anticoagulants (INR of 2.0 - 3.0) be given for 3 weeks before elective cardioversion of patients who have been in AF for more than 2 days and be continued until normal sinus rhythm has been maintained for 4 weeks. Antithrombotic therapy is not recommended for cardioversion of supraventricular tachycardia or AF of less than 2 days' duration. Consideration should be given to managing atrial flutter similarly to atrial fibrillation"

The rationale for the 3 weeks of anticoagulation prior to electrical cardioversion was as described in Goldman's 1960 hypothesis that at least 14 days were

needed for fibroblastic infiltration and stabilisation of a thrombus in the LA. The rationale for 4 weeks of anticoagulation in the post cardioversion period was based on the delayed return of atrial mechanical function after cardioversion. In addition, the frequent recurrence of AF early after successful cardioversion also justified continued anticoagulation until sinus rhythm was well established.

Anticoagulation for prevention of embolism- the evidence

In addition to these theoretical considerations, the conventional anticoagulation approach has been based on several studies suggesting the efficacy of empiric anticoagulation in patients undergoing cardioversion. It is remarkable that the most quoted study is almost 30 years old, and reflects the major differences in clinical practice and methodology of that period. It is also remarkable that conventional therapy was not formally tested in a clinical trial until a study in this thesis (Chapter 13).

In 1969, Bjerkelund and Orning reported an observational study in 437 patients undergoing 572 attempts at electrical cardioversion for a variety of atrial arrhythmias. The study was not randomised, the number of patients with supraventricular tachycardia or atrial flutter is unknown, the duration, intensity and monitoring of anticoagulation is not clearly specified, and although the study is often described as prospective, the method and period of clinical follow-up was not specified. Patients (n=228) who were already on chronic anticoagulant therapy prior to the index admission were continued on such therapy, while anticoagulant therapy was not started on the remaining 209 patients. Cardioversion was successful in 454 attempts in 348 patients. Patients receiving anticoagulants included more women and were younger (mean 50 vs 53 years), but had more cardiomegaly, longer duration of arrhythmia, more previous embolism, poorer functional class and a higher prevalence of rheumatic mitral valve disease, principally mitral stenosis.

Embolic events occurred in 13 (3%) of the 437 patients; 2 (0.8%) of the 229 patients receiving anticoagulants and 11 (5.3%) of the 209 remaining patients (p=0.016). All embolic events occurred in the 454 successful cardioversion attempts, which included 236/297 attempts in patients on anticoagulants and 218/275 other patients (79% in both groups). Calculated in relation to successful cardioversion, embolism occurred in 2/186 (0.8%) patients on anticoagulants and 11/162 (6.8%) other patients (p=0.012). Anticoagulants were associated with a reduced rate of embolism both in patients with or without rheumatic valvular disease. Of the 13 patients with embolism, 7 had non-rheumatic AF and 2 had lone AF. There was no apparent difference in the incidence of embolism in non-anticoagulated patients between rheumatic heart disease (5.7% of successful cardioversion) and non-rheumatic disease (7.8%). The intensity of anticoagulation was therapeutic in the 2 patients with embolism who were receiving long-term anticoagulant therapy. The embolic events (5 cerebral and 8 peripheral) occurred 6 hours to 6 days after cardioversion. The rhythm at the time of embolism was sinus in 10 and AF in 3 patients. The efficacy of anticoagulation was particularly evident in patients with previous embolism, with new events occurring in 0/55 successful cardioversions in treated patients and 3/11 untreated patients.

It is worth quoting from the discussion:

Our results lead to the conclusion that prophylactic anticoagulant therapy is clearly indicated before and after attempts to convert atrial fibrillation in patients with a history of embolic episodes. In our opinion such prophylaxis should preferably be given in connection with attempts at cardioversion in all cases.

The question arises whether anticoagulant treatment started a week or two before electrical conversion would have the same prophylactic effect. This question can not be answered on the basis of the present study. There is some evidence, however, to support the opinion that the same effect may be obtained by short-term treatment: It has been shown that only freshly formed thrombi break off into the bloodstream and constitute emboli. If new.. thrombosis can be prevented, pre-

existing thrombi will soon become adherent to the wall; this step will be immediately followed by marginal organization which eliminates the risk of embolism. Therefore... it is almost certain that a thrombus that is more than 3 days old will not become detached, and a thrombus that is more than a few hours old will rarely become detached. The validity of this statement may be doubted, however, as basic knowledge is probably not good enough in this field.

(Bjerkelund 1969).

A more recent but also retrospective study of 454 successful electrical cardioversions of AF and flutter by Arnold et al (1992) at the Cleveland Clinic confirmed the utility of anticoagulation in preventing embolic stroke in patients undergoing cardioversion. The overall embolic stroke rate was 1.3%, with all the events occurring in patients not therapeutically anticoagulated at the cardioversion, and all occurring within the first week after cardioversion. The study included 454 pts, amongst whom 185 were therapeutically anticoagulated in a non-randomised fashion and 122 had atrial flutter. Only 19% of the cardioversion were performed in patients with anticoagulant therapy for > 2 weeks before cardioversion. All 6 embolic events occurred in patients with AF who were not anticoagulated. Five of the 6 patients had AF less than 7 days duration, including 2 patients with postoperative embolism. The incidence of embolism in patients with AF was 0/153 (0%) non-anticoagulated patients and 6/179 (3.3%) anticoagulated patients. The incidence of embolism in non-anticoagulated patients was 2/115 (1.7%) of post-operative AF and 4/64 (6.2%) of patients with "natural" AF. Drawbacks of this study were its non-randomised and retrospective nature, and incomplete description of differences between the two groups and duration of anticoagulation.

In another retrospective study of 79 patients, Weinberg et al (1989), reported that embolism occurred in 2/28 (7%) non-anticoagulated patients and in none of the 51 anticoagulated patients.

Problems with Conventional Therapy

Despite the suggestion of benefit from anticoagulation in these studies, conventional anticoagulant therapy as described by Laupacis et al (1995) suffers from several drawbacks.

1) The approach had not been tested in any trial, and in particular in no randomised trial.

2) The approach does not stratify anticoagulation therapy according to risk. Pre-cardioversion anticoagulation is given unnecessarily for the approximately 90% of patients with AF who do not have thrombus (Black et al 1991a). Conversely, patients with thrombi despite pre-cardioversion anticoagulation are not identified. Post-cardioversion anticoagulant therapy is given even for patients with rapid return of atrial mechanical function and no recurrent AF.

3) Pre-cardioversion anticoagulation extends the total duration of anticoagulation, therefore potentially increases the risk of bleeding and increasing cost.

4) Increased duration of AF is a risk factor for unsuccessful maintenance of sinus rhythm after cardioversion. Pre-cardioversion anticoagulation delays cardioversion and may prejudice the success of eventual cardioversion.

5) Atrial size and dysfunction progressively increase as AF persists. Pre-cardioversion anticoagulation prolongs the duration of AF, and may theoretically prolong the recovery of atrial function after cardioversion and perhaps increase the risk of subsequent thromboembolism.

6) Patients requiring early cardioversion due to haemodynamic instability are exposed to a risk of embolism.

7) Prophylactic anticoagulation does not eliminate the risk of embolism.

(Bjerkelund et al 1969, Resnekov et al 1967, Aberg and Cullhed 1968, Henry et al 1976, Dittrich et al 1989, Lesser 1990)

8) Delayed cardioversion is inconvenient for both patient and physician.

Above all, reflecting these concerns, conventional therapy is not routinely followed in contemporary clinical practice, with less than 19% of patients in Arnold's large series (1992) receiving conventional therapy.

Thus, the stage was set for the use of TEE in facilitating safer and easier cardioversion, with this author reporting the first such use in the literature (Black et al 1991b, Black et al 1991c).

PART 2

Left Atrial Spontaneous Echo Contrast

CHAPTER 2

Left Atrial Spontaneous Echo Contrast: A Clinical and Echocardiographic Analysis

ABSTRACT

Objectives and Methods. The clinical and echocardiographic variables related to LA SEC were prospectively evaluated in a consecutive series of 400 patients undergoing TEE with a 5 MHz single plane transducer.

Results. LA SEC was found in 75 patients (19%). The presence of SEC was significantly associated with AF, mitral stenosis, the absence of mitral regurgitation, increased LA dimension and a history of suspected embolism. Seventy-one (95%) of the patients with SEC were in AF or had mitral stenosis. Anticoagulant therapy had no significant association with SEC. Multivariate analysis in 89 patients with mitral stenosis or mitral valve replacement showed that SEC was the only independent predictor (p=0.03) of LA thrombus and/or a history of suspected embolism. In 60 patients with nonvalvular AF, SEC (p=0.01) and age (p=0.03) were the only independent predictors of LA thrombus and/or a history of suspected embolism.

Conclusions. LA SEC is 1) A common finding in patients undergoing TEE, 2) Associated with conditions favouring stasis of LA blood, and 3) A marker of previous thromboembolism in patients with nonvalvular AF and in patients with mitral stenosis or mitral valve replacement.

INTRODUCTION

Dynamic smoke-like echoes in the LA cavity, known as SEC, are an occasional finding with TTE (Iliceto et al 1985, Chia et al 1989, Beppu et al 1985). TEE provides superior imaging of the LA (Aschenberg et al 1986, Obeid et al 1989), and LA SEC has been detected more frequently by this technique (Erbel et al 1986, Daniel et al 1988, Castello et al 1990, Chen et al 1990). LA SEC has been noted in conditions favouring stasis of LA blood, particularly mitral stenosis, and has been reported to be an independent predictor of thromboembolic risk in patients with mitral stenosis or mitral valve replacement (Daniel et al 1988) . However, the significance of LA SEC in patients without mitral stenosis is not well understood. To determine the prevalence and clinical significance of LA SEC in patients referred for TEE, the clinical and echocardiographic relationships of LA SEC were prospectively studied in a large series of patients undergoing TEE.

METHODS

Study patients
The study population comprised 400 consecutive patients undergoing TEE. Eighteen patients (5%) were ventilated patients in intensive care units. There were no intraoperative studies. All clinical and echocardiographic data were collected prospectively, and only the initial study was included in patients also undergoing follow up studies. The indication for study, patient age, cardiac rhythm at the time of study, history of previous mitral valve replacement and details of anticoagulant therapy were specifically recorded. There were 202 men and 198 women, age 59 ± 16 years, range 18-90 years. All patients were studied for strictly clinical indications, comprising source of embolism (30%), mitral valve disease (21%), suspected endocarditis (13%), suspected aortic dissection or other aortic disease (11%), cardiac masses (7%), aortic valve disease (6%), congenital heart disease (3%) and miscellaneous (9%).

One hundred nineteen patients (30%) were referred to detect potential sources of clinically suspected cardiogenic embolism following cerebral or systemic arterial ischaemic events. The suspected embolic event had occurred within 1 month of study in 108 (91%) of the 119 patients. Ninety-seven (82%) of the 119 patients were referred following cerebral ischaemic events. Cerebral computed tomography or magnetic resonance imaging was performed in 73 patients and demonstrated cerebral infarction in 55 (75%) of the patients. No patient had cerebral haemorrhage. Twenty of the 119 patients were referred following acute peripheral arterial occlusion. Thromboembolism was confirmed at surgery in 15 of these 20 patients (75%). One patient had a coronary embolism and one patient had a mesenteric embolism.

Echocardiography

Patients underwent two-dimensional and Doppler (including colour flow mapping) TTE immediately prior to TEE, using 2.5 MHz transducers (HP77020 AC). LA dimension was determined by standard M-mode criteria (Sahn et al 1978). Overall LV systolic function was graded as normal or mild, moderate or severe impairment. Significant LV dysfunction was defined as moderate or severe overall LV systolic impairment. The mean mitral diastolic gradient was determined by continuous wave Doppler and mitral valve area was determined by the Doppler half-time method (Hatle et al 1979). Significant mitral stenosis was defined as a mitral valve area ≤ 2 cm^2.

TEE was performed with a 5 MHz single plane phased array transducer (HP21236A). Written informed consent was obtained, and patients were examined in the fasting state unless urgent study was required in acute aortic dissection. Intravenous sedation was given in 289 patients (72%) using midazolam mean dose 1.8 ± 1.0 mg with fentanyl mean dose 70 ± 23 μg. Sixty patients (15%) received antibiotic prophylaxis. The hypopharynx was sprayed with 10% topical lignocaine and the probe introduced using standard techniques (Seward et al 1988) The study duration was usually 10-20 minutes and technically adequate

images were obtained in all studies. Three patients had transient hypoventilation following sedation. Esophageal intubation was unsuccessful in an additional 5 patients who were excluded from analysis. There were no other complications.

The presence of SEC and of thrombi in the LA, including the LA appendage, were specifically examined. LA SEC was diagnosed by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artefact (Beppu et al 1985). Gain settings were adjusted as required to distinguish LA SEC from echoes due to excessive gain. The presence or absence of LA SEC was determined independently by two observers without regard to the clinical data, and any discrepancy resolved by consensus. LA thrombus was diagnosed by the presence of a clearly defined echodense intracavitary mass, acoustically distinct from underlying endocardium and not due to the pectinate muscles of the LA appendage (Beppu et al 1984). Mitral regurgitation was assessed using all echocardiographic data including colour flow mapping, graded qualitatively as absent or mild, moderate or severe, and defined as significant if moderate or severe.

Statistical analysis
Unpaired Student's t tests were used for continuous variables and the chi-square test or Fisher's exact test were used for categorical variables. Multiple logistic regression analysis was used to determine independent predictors of SEC and of LA thrombi and/or embolism. Odds ratios are shown with 95% confidence limits. Statistical significance was defined as two-tailed $p<0.05$.

RESULTS

Prevalence and associated factors
LA SEC was detected by TEE in 75 patients (19%). No patient had SEC detected by TTE ($p<0.001$). Three patients with severe LV dysfunction had LV SEC. Eight patients had right atrial SEC, including 6 with AF, 1 with severe LV dysfunction and

1 with constrictive pericarditis.

The clinical and echocardiographic features of patients with and without LA SEC are shown in Table 1. The prevalence of LA SEC was significantly greater in patients with AF, mitral stenosis, anticoagulant therapy, LA thrombus and a history of embolism. Patients with LA SEC were also significantly older (mean 65 vs 58 years) and had a greater LA dimension (mean 56 vs 43 mm). LA SEC was significantly less frequent in patients with significant mitral regurgitation. LA SEC was more frequent in patients with a mitral valve prosthesis, without reaching statistical significance. Gender and LV dysfunction were not significantly related to SEC.

Multiple logistic regression analysis was performed to determine independent predictors of LA SEC found at TEE, using the clinical and TTE variables significantly related to LA SEC by univariate analysis (Table 2). AF, mitral stenosis, history of embolism and LA enlargement were independent predictors of the presence of LA SEC, whilst mitral regurgitation independently predicted the absence of LA SEC. Age and anticoagulant therapy were not significantly related to LA SEC by multivariate analysis.

Cardiac rhythm

AF was the most powerful single predictor of LA SEC. Only 10 (13%) of the 75 patients with LA SEC were in sinus rhythm. Six of these 10 patients had mitral stenosis, with a mitral valve area of 0.9 ± 0.3 cm^2, range 0.5-1.3 cm^2. Patients with mitral stenosis in sinus rhythm without LA SEC (n=15) had a mean mitral valve area 1.3 ± 0.3 cm^2, range 1.0-1.8 cm^2 (p<0.02). Two of the 10 patients had severe LV dysfunction, and 1 patient was studied several hours after spontaneous conversion from AF to sinus rhythm, with a small A wave on the mitral inflow Doppler signal. Only 1 patient with LA SEC had no evidence of mitral valve disease, AF or LV dysfunction. This patient, referred for the assessment of suspected endocarditis, had myxoedema with marked sinus bradycardia (heart

rate 38/min) at the time of study.

Mitral valve disease

Mitral stenosis was independently associated with the presence of LA SEC. The severity of mitral stenosis in patients with and without LA SEC was compared. Mitral valve area in patients with mitral stenosis and LA SEC (n=27) was 1.1 ± 0.3 cm^2 compared to 1.4 ± 0.3 cm^2 in patients (n=22) without LA SEC (p<0.02). The mitral diastolic gradient was 8.7 ± 4.7 mmHg and 8.9 ± 4.7 mmHg respectively (p=NS). Forty patients had a mitral valve prosthesis, including 35 patients with mechanical prostheses and 5 with porcine bioprostheses. LA SEC was found in 12 (30%) of the 40 patients, all with AF.

Mitral regurgitation was independently associated with the absence of LA SEC. Moderate or severe mitral regurgitation was present in 44 patients (22%) including 7 patients with a mitral prosthesis. Only 3 of the 44 patients (7%) had LA SEC. All 3 patients had mitral valve prostheses, AF and LA enlargement (mean dimension 70 mm).

LA thrombus and embolism

LA thrombi were detected by TEE in 21 patients (5%), all except 2 in the LA appendage (Figure 1). One of the LA appendage thrombi and one of the LA cavity thrombi were detected by TTE. LA thrombi were accompanied by LA SEC in 17 (80%) of the 21 patients. Conversely, LA thrombi were found in 17 (23%) of the 75 patients with LA SEC but in only 4 (1%) of the 325 patients without SEC (p<0.001).

Mitral valve disease and thromboembolism

LA SEC has been previously reported to be an independent predictor of thromboembolic risk in patients with mitral valve disease (Daniel et al 1988). We analysed predictors of the previously reported (Daniel et al 1988) combined endpoint of LA thrombus and/or history of suspected cardiogenic embolism, which

provides information about both previous and potential future thromboembolic risk. The 89 patients with mitral stenosis (n=49) or a mitral valve prosthesis (n=40) were analysed. LA SEC was found in 39 (44%) of the 89 patients, including 33 (63%) of the 52 patients with AF and 6 (16%) of the 37 patients in sinus rhythm (p<0.001). LA thrombus was found in 13 patients (15%) and 16 patients (18%) were referred with suspected embolism. Seventeen of the 39 patients with LA SEC had LA thrombus and/or suspected embolism (44%) compared to 9 of the 50 patients (18%) without LA SEC (p=0.008). The positive predictive value of LA SEC for LA thrombus and/or suspected embolism was 43.6% and the negative predictive value was 82.0%. Multiple logistic regression analysis for the prediction of LA thrombus and/or embolism (n=26) was performed, using LA SEC, age, LA dimension, anticoagulation, AF and LV dysfunction as independent variables. LA SEC (p=0.03) was the only independent predictor of LA thrombus and/or embolism (Table 3).

Nonvalvular atrial fibrillation and thromboembolism

We also analysed the association between LA SEC and thromboembolism in the 60 patients with nonvalvular AF, comprising 47% of the 129 patients with AF. Nonvalvular AF was defined as chronic AF in the absence of a mitral valve prosthesis, any degree of mitral stenosis, or moderate or severe mitral regurgitation. In addition, no patient in this group had AF due to aortic valve disease. LA SEC was found in 28 patients (47%) in this group. Thirty-three patients (55%) were referred following suspected cardiogenic embolism, and 7 patients (12%) were found to have LA thrombus. Twenty-one of the 28 patients with LA SEC had LA thrombus and/or embolism (75%) compared to 12 of the 32 patients (38%) without LA SEC (p=0.004) (Figure 2). The positive predictive value of LA SEC for LA thrombus and/or suspected embolism was 75% and the negative predictive value was 62.5%. Multiple logistic regression analysis for the prediction of LA thrombus and/or embolism (n=33) was performed, using LA SEC, age, anticoagulation, LV dysfunction and LA dimension as independent variables. LA SEC (p=0.01) and age (p=0.03) were the only independent predictors of LA

thrombus and/or embolism (Table 4). Anticoagulation was not statistically significant, possible reflecting beta-error due to sample size.

Table 1. Univariate Analysis of Clinical and Echocardiographic Factors Related to LA SEC.

	SEC present (n=75)	SEC absent (n=325)	p
AF	65 (87%)	64 (20%)	<0.001
Mitral stenosis	27 (36%)	22 (7%)	<0.001
LA dimension (mm)	56	43	<0.001
LA thrombus	17 (23%)	4 (1%)	<0.001
Anticoagulation	37 (49%)	73 (22%)	<0.001
Age (years)	65	58	0.001
Embolism	33 (44%)	86 (26%)	0.003
Mitral regurgitation	3 (4%)	41 (13%)	0.032
Mitral prosthesis	12 (16%)	28 (9%)	0.055
Male/Female	33/42	169/156	NS
LV dysfunction	8 (11%)	21 (6%)	NS

Table 2. Multivariate Analysis of Clinical and Echocardiographic Factors Related to LA SEC.

Variable	p	Odds ratio	95% CI
AF	<0.001	17.40	7.32-41.4
Mitral stenosis	<0.001	7.23	2.87-18.2
LA dimension	0.002	1.08	1.03-1.13
Embolism	0.004	3.23	1.46-7.14
Mitral regurgitation	0.013	0.13	0.03-0.65
Anticoagulation	NS	1.23	0.60-2.54
Age	NS	1.01	0.98-1.04

Table 3. Multivariate Analysis of Factors Related to LA Thrombus And/or Embolism in Patients with Mitral Valve Disease.

Variable	p	Odds ratio	95% CI
LA SEC	0.03	3.60	1.11-11.6
Age	0.09	1.04	0.99-1.08
LA dimension	NS	0.99	0.94-1.04
Anticoagulation	NS	1.21	0.40-3.64
AF	NS	0.84	0.24-2.90
LV dysfunction	NS	0.85	0.07-10.8

Table 4. Multivariate Analysis of Factors Related to LA Thrombus And/or Embolism in Patients with Nonvalvular AF.

Variable	p	Odds ratio	95% CI
LA SEC	0.01	5.19	1.42-19.0
Age	0.03	1.11	1.01-1.21
Anticoagulation	NS	3.64	0.78-17.1
LV dysfunction	NS	0.52	0.08-3.25
LA dimension	NS	0.99	0.90-1.09
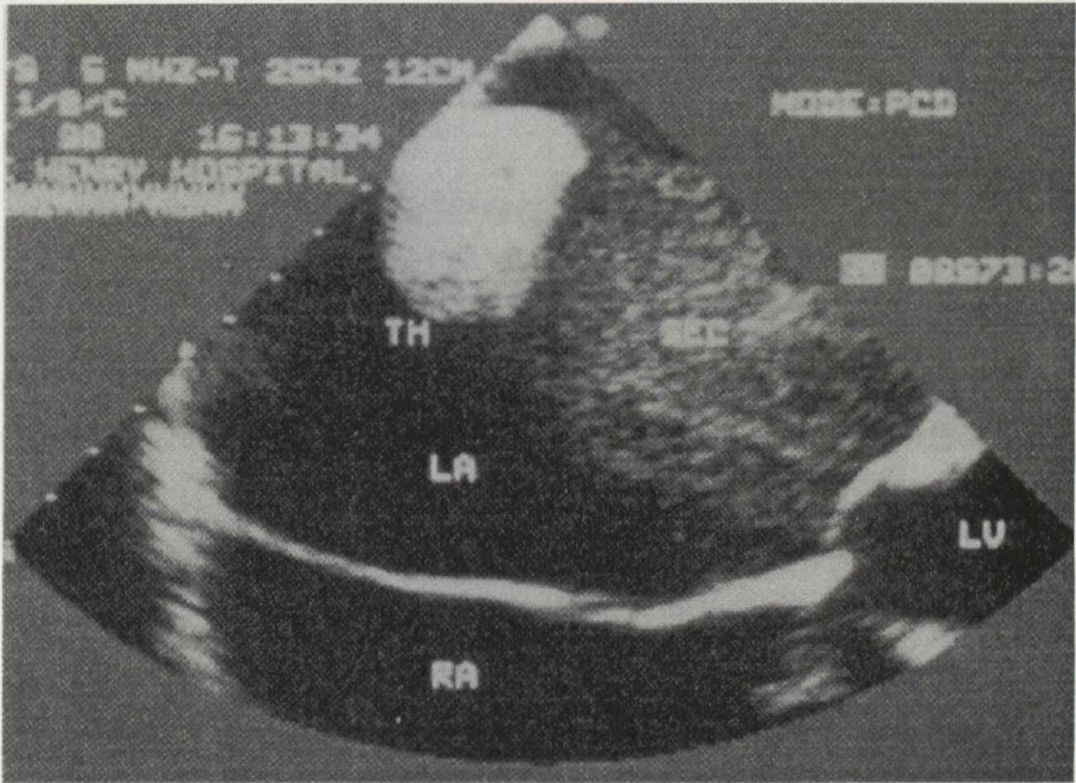
Figure 1. Left Atrial (LA) Spontaneous Echo Contrast (SEC) Associated With a Left Atrial Thrombus (TH). LV=left ventricle, RA=right atrium.
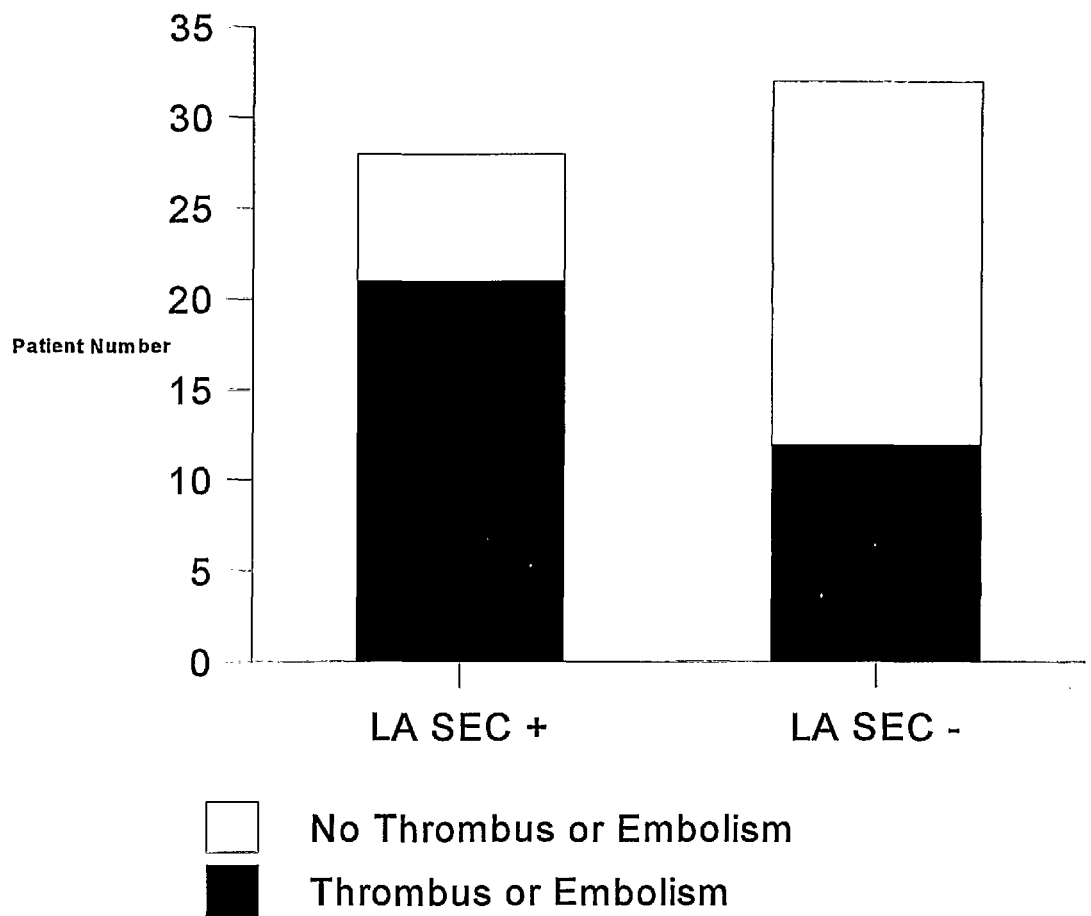
Figure 2. Association Between Presence (+) or Absence (-) of LA SEC and LA Thrombus and/or Embolism in 60 patients with Nonvalvular AF (p=0.004).

DISCUSSION

Prevalence

This report describes the largest series of patients specifically assessed for LA SEC detected by TEE. LA SEC was found in 75 (19%) of 400 consecutive patients referred for TEE for a broad range of clinical indications. No patient had SEC detected by TTE, and no patient with a normal heart had SEC. This prevalence is identical to that reported by Castello et al (Castello et al 1990) in patients with a similar range of cardiac abnormalities. Most previous reports concerning LA SEC have only studied patients with mitral valve disease (Beppu et al 1985, Daniel et al 1988, Chen et al 1990). Patients with mitral stenosis were noted in previous studies to have an prevalence in the range 25-67% whilst patients with mitral valve prostheses were noted to have an prevalence in the range 37-74%. In this study 27 (55%) of the 49 patients with mitral stenosis and 12 (30%) of the 40 patients with mitral valve prostheses had LA SEC. In addition we examined 60 patients with nonvalvular AF, including 33 patients (55%) referred following suspected embolic events. LA SEC was also frequent in this group, being found in 28 (47%) of the patients.

Associated factors

We found AF, mitral stenosis, LA enlargement and a history of suspected embolism to be independent predictors of LA SEC, while mitral regurgitation predicted the absence of LA SEC. No independent effect of anticoagulant therapy on LA SEC was demonstrated. Increasing severity of mitral stenosis, although not the mitral diastolic gradient, was associated with an increased prevalence of LA SEC. Patients with AF at the time of study and/or mitral stenosis accounted for 71 (95%) of the 75 cases of LA SEC. These factors are associated with low blood flow velocity in the LA and strongly support the hypothesis that LA SEC is a result of blood stasis in the LA. It was of interest that the only occurrence of LA SEC without AF, mitral stenosis or severe LV dysfunction occurred in a patient with marked sinus bradycardia. The possible association between bradycardia and LA

SEC may relate to a decrease in LA shear rate. Conversely, transient SEC has also been reported with rapid ventricular tachycardia (Daniel et al 1988).

Previous reports have shown associations between AF (Beppu et al 1985, Daniel et al 1988, Castello et al, 1990 Chen et al 1990), severe mitral stenosis (Beppu et al 1985, Chen et al 1990), LA size (Beppu et al 1985, Daniel et al 1988, Castello et al 1990, Chen et al 1990) and LA SEC. This is the first study to demonstrate that mitral regurgitation is an independent predictor of the absence of LA SEC. Only 3 (7%) of 43 patients with moderate or severe mitral regurgitation were found to have LA SEC. All 3 patients also had AF, mitral valve prostheses and LA enlargement. These findings differ from those of Castello et al (1990), who found a positive association between LA SEC with mitral regurgitation by univariate analysis. This may reflect differences in patient population such as the higher proportion of prosthetic mitral valves associated with mitral regurgitation in their series. We would concur with Beppu et al (1985) that mitral regurgitation tends to preclude the development of LA SEC, perhaps by a stirring effect on LA blood. It is of interest that Maze et al (1989) found that mitral regurgitation appeared to protect against LV thrombus in patients with dilated cardiomyopathy. Subsequent to the publication of the present study, other investigators (Karatasakis et al 1995) have confirmed that mitral regurgitation is associated with a lower prevalence of LA SEC.

Anticoagulant therapy is effective in the primary prevention of the thromboembolic complications of AF (Petersen et al 1989, Preliminary report of the Stroke Prevention in Atrial Fibrillation Study 1990). It is therefore of considerable interest to determine whether LA SEC is affected by anticoagulation. Although anticoagulant therapy was more frequent in patients with LA SEC, reflecting associated factors such as mitral valve prosthesis, AF and embolism, these data show for the first time that anticoagulation has no statistical relationship with LA SEC. Although we did not perform follow up studies in patients with LA SEC following anticoagulant therapy, these data are consistent with work by Sigel et al

(1981) which showed no change in the echogenicity of whole blood following heparin. Apart from a single case report regarding trifluoperazine (Mahony et al 1989), later refuted (Hoffman et al 1990) no agent has been shown to influence the appearance of LA SEC.

Spontaneous echo contrast and thromboembolism

Much of the clinical interest in LA SEC arises from a possible relationship with LA thromboembolism. Risk factors for LA SEC are similar to those for LA thromboembolism. Previous work shows that most (Beppu et al 1985, Castello et al 1990) or all (Daniel et al 1988, Chen et al 1990) LA thrombi demonstrated by TEE are accompanied by LA SEC. In the present study 17 (81%) of 21 LA thrombi were associated with LA SEC. Daniel et al (Daniel et al 1988) reported that in patients with mitral valve disease, LA SEC was an independent predictor of the combined endpoint of LA thrombus and/or suspected cardiogenic embolism. We have confirmed this finding, with comparable positive and negative predictive values (43.6% and 82%) to those reported by Daniel et al (47.5% and 93.4%). AF did not independently predict thromboembolism in either study. This may reflect the frequent association between AF and LA SEC, and the effect on LA SEC of additional factors such as the severity of mitral valve disease. We have also shown in this study population that LA SEC is an independent predictor of thromboembolic risk in patients with nonvalvular AF. However in neither subgroup could LA SEC be used to identify all patients with or without thromboembolism. The prognostic importance of LA SEC in patients with nonvalvular AF requires further study in large prospective trials.

Mechanism of spontaneous echo contrast

Our data show an association between LA SEC and conditions favouring stasis of blood in the LA. The study was not designed to directly determine the pathogenesis of SEC. Sigel et al (1981) showed that increased echogenicity of blood occurred with erythrocytes in plasma but not in serum or saline, and Mikell et al (1982) showed no increased echogenicity with platelet aggregates. However

91

Erbel et al (1986) found evidence of increased platelet aggregation in a series of 9 patients with LA SEC, and resolution of SEC with platelet disaggregatory therapy has been reported in a single patient (Mahony et al 1989), subsequently refuted (Hoffman et al 1990). Beppu et al (1985) showed that the indirectly measured shear rate of blood in the LA cavity was reduced in patients with LA SEC. Entry of blood into the LV cavity, which usually results in the immediate disappearance of LA SEC, is associated with a sudden increase in the shear rate. Ultrasonic backscatter from blood is greater at lower shear rates, (Yuan and Shung 1988a) and is also dependent on fibrinogen concentration and haematocrit (Yuan and Shung 1988b). These three factors are also major determinants of erythrocyte aggregation (Lowe 1987).

These data are consistent with the hypothesis that LA SEC is due to erythrocyte aggregation in low shear rate conditions, with a possible interaction with platelets. Further, they suggest why LA SEC appears to be a marker or precursor of thrombus formation. Virchow stated that thrombus resulted from the triad of stasis of blood flow, altered characteristics of the blood and vessel wall injury. LA SEC may reflect not only local stasis of blood flow but also altered blood characteristics. The association between LA SEC and conditions favouring stasis of blood in the LA is demonstrated in this study. Further work examining haematological factors in patients with LA SEC is required.

Technical factors

Sigel et al (1981) found that the echogenicity of static blood was seen with 7.5 MHz but not 3.5 MHz transducers. Other in vitro work (Yuan, Shung 1988b) has shown that ultrasonic backscatter from whole blood is proportional to transducer frequency. Thus the use of higher frequency transducers, together with lack of acoustic interference from the chest wall and lungs and proximity to the LA may explain the greatly increased yield for LA SEC by TEE compared to TTE.

Limitations

The diagnosis of suspected embolic events in this study was based on the assessment of recent arterial ischaemic events by the referring physician. However criteria for the diagnosis of cardiogenic embolism may be unreliable (Humphrey and Harrison 1985, Ramirez-Lassepas et al 1987). In addition, the study population represented a selected patient sample with a high probability of abnormal findings. Since patients with either suspected cardiogenic embolism or mitral valve disease comprised 52% of the study group, the prevalence of LA thrombus and LA SEC was relatively high. These data cannot be extrapolated to an unselected patient population in whom the prevalence of thromboembolism and LA SEC may be lower. Data on the extent of agreement between observers prior to consensus assessment of LA SEC is not available in the present study. However, other studies (Daniel et al 1988, Kronik et al 1995) have shown low interobserver variability. LA appendage flow velocities were not measured.

CONCLUSIONS

LA SEC was a frequent finding in patients with cardiac disease referred for TEE. LA SEC was associated with conditions favouring stasis of LA blood, including AF, mitral stenosis, the absence of significant mitral regurgitation and LA enlargement. Anticoagulant therapy had no association with LA SEC. LA SEC was an independent predictor of previous thromboembolism in patients with mitral stenosis or mitral valve prosthesis, and also in a selected group of patients with nonvalvular AF. Prospective studies, particularly in patients with nonvalvular AF, are required to determine the prognostic significance of LA SEC.

CHAPTER 3

Haematologic Correlates of Left Atrial Spontaneous Echo Contrast and Thromboembolism in Nonvalvular Atrial Fibrillation

ABSTRACT

Background and Objectives. LA SEC is associated with LA stasis and with thromboembolism in patients with nonvalvular AF. However, the haematological determinants of LA SEC in patients with nonvalvular AF are unknown. This study examined the relationship between haematological variables, LA SEC, and thromboembolism in patients with nonvalvular AF.

Methods. Clinical, haematological and echocardiographic variables were prospectively measured in 135 consecutive patients with nonvalvular AF undergoing TEE.

Results. Patients with LA SEC (n=74, 55%) had increased fibrinogen concentration (p=0.029), platelet count (p=0.045), haematocrit (p=NS), and LA dimension (p=0.005). Multivariate analysis showed that LA SEC was independently related to haematocrit (odds ratio = 2.24, p=0.002), fibrinogen concentration (odds ratio = 2.08, p=0.008), and LA dimension (odds ratio = 1.90, p=0.004), but not platelet count. LA SEC was also associated with LA thrombus (n=15, p=0.001) and with recent embolism (n=40, p<0.001). In 40 clinically stable outpatients without previous embolism, LA SEC was significantly related to haematocrit (p=0.005), fibrinogen concentration (p=0.035) and LA dimension (p=0.029), but not to coagulation factor VII, D-Dimer, erythrocyte sedimentation rate, platelet count, plasma beta-thromboglobulin, plasma glycocalicin or glycocalicin index.

Conclusions. LA SEC in patients with nonvalvular AF is independently related to haematocrit, fibrinogen concentration and LA dimension, indicating a relatively hypercoagulable state in addition to stasis. These findings support the hypothesis that LA SEC is due to erythrocyte aggregation. Haematological factors may contribute to the association between LA SEC and thromboembolism.

INTRODUCTION

Recent clinical trials have highlighted the risk of thromboembolism associated with nonvalvular AF (Cairns and Connolly 1991). LA SEC, detected by TEE, has been identified as a marker of LA thrombus and embolism in this patient group (Black et al 1991a). LA SEC refers to smoke-like echoes with a characteristic swirling motion distinct from white noise artefact. Previous studies have demonstrated an association between LA SEC and conditions favouring stasis of LA blood (Black et al 1991a, Beppu et al 1985). However, the haematological determinants of LA SEC in patients with nonvalvular AF are unknown. We prospectively examined the relationship between haematological parameters, LA SEC and thromboembolism in a large consecutive series of patients with nonvalvular AF undergoing TEE.

METHODS

Patients

The study population comprised 135 consecutive patients with nonvalvular AF undergoing TEE. Nonvalvular AF was defined as AF at the time of TEE, in the absence of mitral stenosis, moderate or severe mitral regurgitation, or a mitral valve prosthesis. Only the initial study was included in patients also undergoing follow up studies. This was an entirely separate cohort of patients to those described in Chapter 2.

There were 93 men and 42 women, age 66 ± 11 years, range 24-86 years. Of the 135 patients, 95 patients underwent TEE for clinical indications, comprising source of embolism (n=40), electrical cardioversion (n=38), endocarditis (n=6), and miscellaneous (n=11). There were no intraoperative studies. The 40 patients referred to detect sources of suspected cardiogenic embolism comprised patients with recent (< 1 month) cerebral (n=30), peripheral (n=8) or mesenteric (n=2) embolic events. The aetiology of AF in these 95 patients included hypertension

(n=30), coronary artery disease (n=13), postoperative (n=9), dilated cardiomyopathy (n=9), intercurrent medical illness (n=5), ethanol abuse (n=4), and miscellaneous (n=9), and was unknown in 16 patients.

The remaining 40 patients were clinically stable outpatients without previous embolism, all receiving 150 mg aspirin per day, who underwent TEE as part of a research protocol approved by the Research Ethics Committee of the Eastern Sydney Area Health Service. These 40 outpatients comprised 25 men and 15 women, age 65 ± 10 years, range 35-80 years. The aetiology of AF included hypertension (n=9), coronary artery disease (n=6), dilated cardiomyopathy (n=4), ethanol abuse (n=3) and miscellaneous (n=4), and was unknown in 14 patients.

Echocardiography

Two-dimensional and Doppler (including colour flow mapping) TTE was performed immediately prior to TEE, using 2.5 MHz or 3.5 MHz imaging transducers (HP77020 AC). LA dimension was determined by standard M-mode criteria (Sahn et al 1978).

TEE was performed with a 5 MHz single plane (n=46) or biplane (n=89) transducer (HP 21362A and HP 21363A). Patients were examined in the fasting state after intravenous sedation with midazolam (1.7 ± 1.1 mg) together with fentanyl (78 ± 21 μg), and pharyngeal anaesthesia with topical lignocaine. The presence of LA thrombus and SEC were specifically assessed. LA thrombus was diagnosed by the presence of a clearly defined intracavitary mass, acoustically distinct from underlying endocardium and not due to the pectinate ridges of the atrial appendage (Beppu et al 1984). LA SEC was diagnosed by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artefact (Black et al 1991a). Echocardiographic findings were recorded entirely independently prior to the availability of haematological results.

Haematology

Venous blood was drawn without stasis immediately prior to echocardiography. Haematocrit, fibrinogen concentration, platelet count and white blood cell count were measured in all 135 patients. Haematocrit, platelet count and white blood cell count were measured in a commercial analyser (Sysmex NE cell counter, TOA Electronics). Fibrinogen concentration was measured with an automated functional assay (Rossi et al 1988).

The 40 clinically stable outpatients underwent additional haematological investigations including erythrocyte sedimentation rate (ESR), plasma beta-thromboglobulin, plasma glycocalicin, coagulation factor VII and D-Dimer. ESR was determined with the Westergren method. Plasma beta-thromboglobulin, a protein secreted from platelet alpha granules during platelet activation, was measured by radioimmunoassay (Gavaghan et al 1990). Plasma glycocalicin, a fragment of platelet glycoprotein Ib, was measured by an ELISA method (Bessos and Murphy 1990). The glycocalicin index, a dimensionless number calculated as the ratio of the plasma glycocalicin concentration (ng/ml) to the platelet count (10^9/l) multiplied by 100, is an index of platelet turnover (Steinberg et al 1987). Coagulation factor VII was measured with an automated analyser (Chantarangkul et al 1987). The plasma level of D-Dimer, the principal degradation product of cross-linked fibrin, was measured with the Dimertest EIA (AGEN, Brisbane) (Whitaker et al 1984).

Statistical analysis

All data were collected prospectively. The chi-square test or Fisher's exact test were used to compare categorical variables. Student's t test was used to compare continuous variables, with the exception of ESR which was not normally distributed and was compared with the Mann-Whitney U test. Pearson's correlation coefficient was used to evaluate the correlation between continuous variables. Multivariate logistic regression analysis was used to assess the independent relationship of variables with LA SEC, embolism and LA thrombus. The odds ratios refer to the

effect of the presence or absence of categorical variables and to the effect of 1 SD increment in continuous variables, and are shown with 95% confidence intervals. Statistical significance was defined as two-tailed p<0.05, and values are reported as mean ± 1 SD.

RESULTS

Haematological factors and LA SEC

LA SEC was detected in 74 (55%) of the 135 patients. The characteristics of patients with and without LA SEC are shown in Table 1. Significant increases in patients with LA SEC were found for fibrinogen concentration, platelet count, embolism, LA thrombus, LA dimension and age. There was a significant negative correlation between haematocrit and fibrinogen concentration (r=-0.45, p<0.001). LA dimension did not correlate with either haematocrit (r=0.12, p=NS) or fibrinogen concentration (r=-0.06, p=NS).

Multivariate logistic regression analysis was performed with age, anticoagulation, LA dimension, and all haematological parameters as independent variables (Table 2). Haematocrit, fibrinogen concentration, LA dimension and age were independently related to LA SEC. The odds ratios in Table 2 indicate that a 1 SD increase in haematocrit (1 SD = 5.90%) was associated with a two-fold increase (odds ratio = 2.24) in the probability of LA SEC. A 1 SD increase in fibrinogen concentration (1 SD = 1.68 g/l) was also associated with a two-fold increase (odds ratio = 2.08) in the probability of LA SEC. Anticoagulation, platelet count and white cell count were not significantly related to LA SEC in multivariate analysis.

Embolism and LA thrombus

The characteristics of patients with and without recent embolism are shown in Table 3. Patients with recent embolism (n=40) had a significantly increased prevalence of LA SEC, LA thrombus and anticoagulation, increased fibrinogen concentration, and increased platelet and white cell count. Multivariate analysis

99

was performed with age, LA dimension, all haematological parameters and LA SEC as independent variables. Only LA SEC (p<0.001, odds ratio=9.60 (95% CI 2.84-32.38)) and fibrinogen concentration (p=0.002, odds ratio=2.60 (1.42-4.77)) were independently related to recent embolism.

LA thrombi were detected in 15 (11%) of the 135 patients. All thrombi were located in the LA appendage, with an extension onto the lateral LA wall in 1 patient. The diameter of the thrombi ranged from 0.7 cm to 2.6 cm, mean 1.3 cm. Three patients had mobile thrombi, all associated with recent embolism and with LA SEC. Patients with LA thrombus (n=15) had significantly increased prevalence of LA SEC (14/15 patients (93%) vs 60/120 patients (50%), p=0.001), increased LA dimension (50.8 ± 4.7 mm vs 46.9 ± 7.4 mm, p=0.047), with a trend to increased fibrinogen concentration (5.43 ± 1.50 g/l vs 4.93 ± 1.70 g/l, p=NS) compared to the remaining patients. The same factors associated with embolism by univariate and multivariate analyses were also significantly related to the combined endpoint of embolism and/or LA thrombus (n=46).

Stable outpatients without previous embolism

Table 4 shows the characteristics of the 40 clinically stable outpatients without previous embolism in whom additional haematological studies were performed, related to LA SEC. Haematocrit, fibrinogen concentration and LA dimension were significantly increased in patients with LA SEC. There was no correlation between haematocrit and fibrinogen concentration in these patients (r=0.11, p=0.52). In multivariate analysis, LA dimension (p=0.03, odds ratio=3.59 (95% confidence interval 1.12-11.50)), haematocrit (p=0.02, odds ratio=3.51 (1.19-10.30)) and fibrinogen concentration (p=0.03, odds ratio=2.70 (1.08-6.73)) were independently related to LA SEC. Other variables, including platelet count and indices of platelet activation and turnover, were not significantly related to LA SEC. D-Dimer levels remained similar in both groups when the 3 patients with thrombus (mean D-Dimer 106 ng/ml) were excluded.

Table 1. Characteristics of 135 Patients with Nonvalvular AF Related to LA SEC.

Variable	LA SEC absent (n=64)	LA SEC present (n=75)	p
Embolism	5 (8%)	35 (47%)	<0.001
LA thrombus	1 (2%)	14 (19%)	0.001
LA dimension (mm)	45.4 ± 7.0	48.9 ± 7.1	0.005
Age (yr)	63.8 ± 11.3	68.0 ± 10.5	0.027
Fibrinogen (g/l)	4.64 ± 1.73	5.27 ± 1.59	0.029
Platelet count (10^9/l)	230 ± 80	262 ± 98	0.045
Haematocrit (%)	41.3 ± 6.7	42.8 ± 5.1	NS
White cell count (10^9/l)	6.98 ± 3.01	7.97 ± 2.96	NS
Anticoagulation	21 (34%)	26 (35%)	NS

Table 2. Multivariate Analysis of Factors Related to LA SEC.

Variable	p	Odds ratio	(95% CI)
Haematocrit	0.002	2.24	(1.33 - 3.78)
Fibrinogen	0.008	2.08	(1.21 - 3.55)
LA dimension	0.004	1.90	(1.23 - 2.95)
Age	0.03	1.64	(1.05 - 2.59)
Platelet count	NS	1.44	(0.84 - 2.46)
White cell count	NS	1.06	(0.62 - 1.79)
Anticoagulation	NS	0.64	(0.27 - 1.51)

Table 3. Patient Characteristics Related to Recent Embolism.

Variable	No embolism (n=95)	Embolism (n=40)	p
LA SEC	39 (41%)	35 (87%)	<0.001
Fibrinogen (g/l)	4.56 ± 1.64	6.00 ± 1.32	<0.001
White cell count (10^9/l)	7.03 ± 2.59	8.69 ± 3.61	0.003
LA thrombus	6 (6%)	9 (23%)	0.006
Age (yr)	64.5 ± 11.3	69.7 ± 9.7	0.01
Anticoagulation	27 (28%)	20 (50%)	0.02
Platelet count (10^9/l)	237 ± 81	273 ± 109	0.04
LA dimension (mm)	47.0 ± 7.5	47.9 ± 6.6	NS
Haematocrit (%)	42.5 ± 6.0	41.4 ± 5.8	NS

Table 4. Characteristics of 40 Clinically Stable Outpatients Without Previous Embolism Related to LA SEC.

Variable	LA SEC absent (n=19)	LA SEC present (n=21)	p
Haematocrit (%)	42.2 ± 3.7	45.7 ± 3.6	0.005
LA dimension (mm)	46.0 ± 5.6	50.8 ± 7.5	0.029
Fibrinogen (g/l)	3.28 ± 0.84	3.93 ± 1.00	0.035
LA thrombus	0 (0%)	3 (14%)	NS
Age (yr)	62.0 ± 11.8	68.0 ± 8.3	NS
Platelet count (10^9/l)	221 ± 44	228 ± 66	NS
White cell count (10^9/l)	6.08 ± 2.03	7.03 ± 1.85	NS
ESR (mm/hr)	4.8 ± 4.1	7.8 ± 8.8	NS
Factor VII (%)	97.6 ± 19.4	101.2 ± 19.0	NS
Glycocalicin (ng/ml)	1.92 ± 0.33	1.82 ± 0.53	NS
Glyocalicin index	0.97 ± 0.32	0.83 ± 0.31	NS
Beta-thromboglobulin (ng/ml)	21.4 ± 7.5	21.6 ± 5.6	NS
D-Dimer (ng/ml)	101 ± 32	111 ± 54	NS

ESR=erythrocyte sedimentation rate.

DISCUSSION

This is the first study to examine the relationship between systemic haematological variables and LA SEC in patients with nonvalvular AF. Haematocrit and fibrinogen, but not platelet indices, were independently related to LA SEC. These findings are consistent with a role for erythrocytes and fibrinogen in the pathogenesis of LA SEC. The study also confirmed the association between LA SEC and thromboembolism in patients with nonvalvular AF, which may be mediated in part by haematological factors.

Mechanism of spontaneous echo contrast

Sigel et al reported that SEC in vitro required erythrocytes and fibrinogen (Sigel et al 1981, Sigel et al 1982, Sigel et al 1983), and that the intensity of SEC correlated with haematocrit and fibrinogen concentration. Erbel et al (1986) reported fibrinogen levels in 9 patients with LA SEC associated with mitral valve disease which were similar to the present study (mean 5.2 g/l). However, haematological parameters were not examined in patients without SEC (Erbel et al 1986). The present study shows that haematocrit and fibrinogen concentration are important determinants of LA SEC in patients with nonvalvular AF. Haematocrit was significantly related to LA SEC in unselected patients only by multivariate analysis, which may reflect the negative correlation between haematocrit and fibrinogen concentration in this population. However, haematocrit was significantly related to LA SEC by both univariate and multivariate analysis in clinically stable outpatients.

Sigel also showed (Sigel et al 1983) that the intensity of SEC in vitro was inversely related to the blood shear rate, which is the velocity gradient between adjacent fluid layers. Beppu et al reported that the shear rate of blood in the LA cavity was reduced in patients with LA SEC (Beppu et al 1985). LA shear rate is proportional to mean LA blood velocity divided by LA dimension (Beppu et al 1985). Recent studies (Pozzoli et al 1991) have shown that LA SEC is associated with decreased LA appendage flow velocities. The relationship between LA dimension and SEC

in the present study is consistent with an inverse relationship between LA SEC and LA shear rate.

Haematocrit, fibrinogen concentration, and shear rate are also the major determinants of erythrocyte aggregation (Chien et al 1966, Goldsmith and Turitto 1986). Erythrocyte aggregation reflects a balance between fibrinogen bridging between erythrocytes and electrostatic repulsion by sialic acid residues on the erythrocyte membrane (Fabry 1987, Izumida et al 1991). The length of the fibrinogen molecule appears to be a key property in its ability to link erythrocytes, by keeping adjacent erythrocytes at "arm's length", thereby diminishing the effect of repulsive forces (Izumida et al 1991). Increasing shear rate results in progressive disruption of existing aggregates (Goldsmith and Turitto 1986).

Sigel et al (1983) concluded that erythrocyte aggregation was the predominant cause of increased echogenicity at low shear rates, with the increased size of erythrocyte aggregates compared to single cells increasing the amplitude of backscattered ultrasonic signals. The relationship between haematocrit, fibrinogen concentration, LA dimension and LA SEC demonstrated in the current study support the hypothesis of Sigel et al (1983) and suggests that LA SEC is a manifestation of erythrocyte aggregation.

Some investigators have proposed a role for platelet aggregation in the formation of SEC. Erbel et al (1986) found evidence of increased platelet aggregation in 9 patients with LA SEC, and resolution of SEC with platelet disaggregatory therapy was reported in a single patient (Mahony et al 1989), later refuted (Hoffman et al 1990). However, other studies (Mikell et al 1982, Sigel et al 1984) have shown no echogenicity with platelet aggregates. Infused platelets may produce large, discrete echoes (Monsuez et al 1990) distinct from the smoke-like echoes of SEC. Platelet aggregates do not share the association with stasis which characterises LA SEC (Black et al 1991a, Beppu et al 1985). In contrast, platelet aggregation is favoured by high shear rate conditions (Badimon et al 1992). Although platelet

count was increased in unselected patients with LA SEC in the present study, this relationship was not significant when adjusted for other variables. There was no relationship between SEC and platelet count or indices of platelet activity in stable outpatients, who were receiving aspirin. Nevertheless, the elevated fibrinogen levels associated with LA SEC may also favour platelet aggregation due to interplatelet fibrinogen bridging (Harker and Mann 1992), and it is possible that intermittent platelet aggregation may accompany erythrocyte aggregation and contribute to the association between LA SEC and thromboembolism.

Spontaneous echo contrast and thromboembolism

Daniel et al (1988) reported that LA SEC was an independent marker of LA thrombus, previous embolism or both in patients with mitral stenosis or a mitral valve prosthesis. We extended this association to patients with nonvalvular AF (Black et al 1991a), confirmed in a separate patient cohort in the present study. Virchow stated that thrombosis resulted from the triad of blood stasis, altered blood characteristics and vessel wall injury. Previous studies (Black et al 1991a, Beppu et al 1985) have shown an association between LA SEC and conditions favouring LA stasis, such as nonvalvular AF and mitral stenosis. These conditions are also associated with thromboembolism. We have now shown that LA SEC also reflects altered blood characteristics, therefore indicating a relatively hypercoagulable state in addition to stasis.

Although Sigel et al (1984) found that SEC preceded thrombosis at low shear rates in vitro, the relationship between SEC and in vivo thrombosis is uncertain. Nevertheless, there are several potential mechanisms by which SEC may represent a pre-thrombotic state. The findings of the present study support erythrocyte aggregation as the mechanism of SEC. Erythrocyte aggregation increases blood viscosity at low shear rates (Chien et al 1966), thereby reducing blood flow and increasing the propensity to thrombosis. Intracardiac thrombosis occurs when activation of coagulation factors in low shear rate conditions, rather than activation of platelets, leads to fibrin formation (Halperin and Petersen 1992).

In vitro (Mikell et al 1982) and in vivo (Beppu et al 1985) studies suggest that dense SEC may represent a transition stage in the development of a fibrin-rich red thrombus, with the network of erythrocytes and fibrinogen forming a framework for subsequent thrombus formation. Clinical studies (Tanahashi et al 1989, Fisher and Meiselman 1991) have shown increased erythrocyte aggregation in patients with stroke, including cardiogenic stroke, compared to controls.

Elevated haematocrit and fibrinogen levels associated with LA SEC may favour thrombosis by mechanisms other than erythrocyte aggregation. Both LA SEC and fibrinogen were independently associated with thromboembolism in the present study. This may reflect an independent effect of fibrinogen on the likelihood of thrombosis, or could result from acute elevation of fibrinogen concentration following embolic events. Several studies have shown that fibrinogen concentration is an independent predictor of cardiovascular disease, including stroke (Wilhelmsen et al 1984, Kannel et al 1987). Fulton and Duckett (1976) found a close relation between elevated fibrinogen levels and thromboembolism after myocardial infarction, and suggested that fibrinogen may have contributed to the thrombogenic state. Fibrinogen is intimately involved in thrombogenesis (DiMinno et al 1990), with effects on platelet aggregation, as a major determinant of blood viscosity, and by effects on atherogenesis. A report from the Framingham study (Kannel et al 1972) also showed that patients with elevated haematocrit had an increased risk of subsequent stroke.

Previous studies have reported elevated D-Dimer, a marker of intravascular coagulation, in patients with nonvalvular AF compared to healthy controls (Kumagai et al 1990). Yasaka et al (1991) reported marked elevation of D-Dimer in patients with mobile intracardiac thrombi, with no significant difference between patients with non-mobile thrombi and those without thrombi. In the present study, D-Dimer levels were not related to the presence of SEC. LA SEC in the absence of formed, mobile thrombus does not appear to be associated with sufficient solid phase fibrin formation to result in elevated D-Dimer.

It is an interesting paradox that SEC and erythrocyte aggregation are not influenced by anticoagulant therapy (Sigel et al 1981, Schmid-Schonbein et al 1968), although anticoagulant therapy reduces the incidence of thromboembolism in patients with AF (Cairns and Connolly 1991). The clotting factors affected by anticoagulant therapy are therefore unlikely to be required for the formation of SEC. Factor VII levels in the present study were similar in patients with and without LA SEC.

Prognostic value of spontaneous echo contrast

A major potential clinical role of LA SEC is as a predictor of subsequent thromboembolic events, thereby identifying patients likely to benefit most from anticoagulant therapy. The present study indicates that LA SEC reflects haematological as well as haemodynamic variables. Fibrinogen is an acute phase protein and rises in response to a number of stimuli. Several studies have shown acute activation of the coagulation system, including elevated fibrinogen, after stroke (Fisher and Meiselman 1991, Takano et al 1991). Yasaka et al (1990) reported acute increases in haematocrit at the time of appearance or enlargement of intracardiac thrombus in patients with cardioembolic stroke. Fisher and Meiselman (1991) found increased erythrocyte aggregation in patients early after cardiogenic stroke compared with the same patients 2 months later. Hospital inpatients without recent embolism also had significant increases in fibrinogen concentration and a slight increase in red cell aggregation compared to healthy controls (Fisher and Meiselman 1991). Tanahashi et al (1989) also demonstrated increased erythrocyte aggregation in patients with acute compared to chronic stroke. It should be noted that the independent relationship between haematocrit, fibrinogen and LA SEC in the present study was present in the 40 stable outpatients without previous embolism as well as in the whole study population.

The results of the present study have diverging implications for the prognostic value of LA SEC. The association between haematological factors and LA SEC

suggests additional mechanisms for the association between LA SEC and thrombotic events. However, it is likely that LA SEC will be acutely increased following embolic events, and may not reflect the baseline state. Long term follow-up studies of patients with LA SEC will need to consider the clinical status of the patient at the time of initial study, specifically a history of recent embolism, which may influence the haematological determinants of SEC.

Limitations

Erythrocyte and platelet aggregation in the LA itself were not directly measured in the present study. However, measurement of the systemic determinants of erythrocyte aggregation and of platelet indices were consistent with erythrocyte aggregation as the mechanism of LA SEC. The present study comprised patients with nonvalvular AF only. Haemodynamic factors may be more important in the formation of LA SEC in other patients, such as those with mitral valve disease.

CONCLUSIONS

This study has shown that haematocrit, fibrinogen concentration, and LA dimension are determinants of LA SEC in patients with nonvalvular AF. LA SEC therefore reflects a systemic hypercoagulable state in addition to local LA stasis. The study also confirmed the association between LA SEC and thromboembolism. These findings support the hypothesis that LA SEC is due to erythrocyte aggregation in low shear rate conditions, and suggest that haematological factors may contribute to the association between LA SEC and thromboembolism. Acute variations in haematological parameters, particularly fibrinogen, may affect the presence and intensity of SEC.

CHAPTER 4

Prognostic Implications of Left Atrial Spontaneous Echo Contrast in Nonvalvular Atrial Fibrillation

ABSTRACT

Background and Objectives. LA SEC is associated with AF and a history of previous stroke or other embolic events. However, the prognostic implications of LA SEC are unknown. The aim of the study examined the influence of LA SEC on the subsequent stroke or embolic event rate and on survival in patients with nonvalvular AF.

Methods. The study group comprised 272 consecutive patients with nonvalvular AF referred for TEE. Clinical and echocardiographic data were collected at baseline and patients were prospectively followed up with all strokes, other embolic events and deaths documented.

Results. LA SEC was detected at baseline in 161 patients (59%). The mean follow up was 17.5 months. The stroke or other embolic event rate was 12%/year in patients with baseline LA SEC and 3%/year in patients without LA SEC ($p=0.002$). In patients without a history of thromboembolic events (n=149), the event rate was 9.5%/year in patients with baseline LA SEC and 2.2%/year in patients without ($p=0.003$). Patients with LA SEC had a significantly reduced survival ($p=0.025$). On multivariate analysis, LA SEC was the only positive predictor (odds ratio 3.5, $p=0.03$) and warfarin therapy on follow up the only negative predictor (odds ratio 0.23, $p=0.02$) of subsequent stroke or other embolic events.

Conclusions. TEE can be used to risk stratify patients with nonvalvular AF by identifying LA SEC. Patients with LA SEC have both a significantly higher risk of developing stroke or other embolic events and reduced survival. These patients may represent a subgroup in whom the risk/benefit ratio of long term anticoagulation therapy with warfarin may be most favourable.

INTRODUCTION

LA SEC refers to swirling smoke like echoes in the LA which are detected by TEE in conditions favouring stasis of blood in the LA. LA SEC is significantly associated with the presence of AF, mitral stenosis, LA enlargement and LA thrombus (Black et al 1991a). LA SEC is also associated with a history of thromboembolism, both in patients with mitral stenosis or prosthetic mitral valves (Black et al 1991a, Daniel et al 1988) and in patients with nonvalvular AF (Black et al 1991a). However, the prognostic implications of LA SEC in patients with nonvalvular AF are unknown. The aim of the present study was to prospectively determine the influence of LA SEC on both the subsequent development of stroke or other embolic events and on survival in a large series of patients with nonvalvular AF.

METHODS

Study patients

The study patients comprised 272 consecutive patients with nonvalvular AF undergoing TEE. Criteria for inclusion were AF with a duration longer than 7 days with no evidence of mitral stenosis, moderate or severe mitral regurgitation and no history of mitral valve surgery. Clinical characteristics including patient gender and age, details of previous stroke or embolic events and study indication were recorded at baseline. There were 185 males and 87 females with a mean age of 68 ± 11 years (range 24-87). The indications for TEE studies were to assess LA thrombus in patients without previous thromboembolism (n=129, 47%), suspected cardiac source of embolism (n=106, 39%), suspected infective endocarditis (n=11, 4%), assessment of mitral regurgitation (n=5, 2%), aortic valve disease (n=6, 2%) and miscellaneous (n=15, 6%).

Echocardiography

All patients underwent both TTE and TEE studies with all echocardiographic data recorded prospectively at baseline. TTE studies were performed using a 2.5 MHz

and 3.5 MHz phased array transducers using all standard echocardiographic windows. Global LV systolic function was assessed semiquantitatively from the parasternal and apical views and graded as normal or mild, moderate or severe impairment. LA dimension and LV wall thickness were measured according to standard M-mode criteria (Sahn et al 1978). Significant LV hypertrophy was defined as wall thickness ≥ 13 mm. Mitral annular calcification was diagnosed on M-mode and two dimensional echocardiography by the presence of an echodense band posterior to the posterior mitral leaflet at the atrioventricular junction with motion parallel to that of the free LV wall (Hirschfeld and Emilson 1975). Mitral regurgitation was assessed semiquantitatively by colour and continuous wave Doppler and was graded as trivial or mild, moderate or severe (Helmcke et al 1987).

TEE was performed using a 5 MHz phased array transducer according to standard protocols (Seward et al 1988, 1990 and 1993). Written informed consent was obtained in all patients. Biplane examination was performed in 145 patients, monoplane in 115 and multiplane in 12 patients. No complications were recorded. Only the first study was analysed if patients had subsequent studies.

The presence of LA SEC and LA thrombus were specifically examined. LA SEC was diagnosed by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artefact (Black et al 1991a). The presence or absence of LA SEC was determined by two independent experienced observers and any discrepancy resolved by consensus. LA thrombus was diagnosed by the presence of an echodense mass in the LA or the LA appendage distinct from the endocardium and the pectinate muscles of the LA appendage (Beppu et al 1984). The presence of atheroma in the thoracic aorta was examined and classified into simple or complex (Karalis et al 1991).

Follow up

Patients were prospectively followed up to determine the incidence of subsequent

114

stroke or other embolic events. Follow up information was obtained by telephone interviews, careful review of hospital records and direct contact with the patients' primary physicians. Patients' medication history, including warfarin and aspirin therapy at the time of follow up, was recorded. The primary end point was stroke or other embolic events. Stroke was defined as a definite focal neurological deficit of acute onset consistent with a vascular event lasting for > 24 hours. A transient ischaemic attack was defined as focal neurological deficit of sudden onset which resolved completely in < 24 hours. Transient ischaemic attack was considered an embolic event. The criteria for embolism to a viscera or an extremity were pain and other symptoms and signs consistent with acute vascular occlusion. The results of investigations performed after the suspected thromboembolic event were also recorded. The secondary endpoint was all cause mortality. Sudden death was not considered an embolic event. All endpoint events were assessed blinded to the results of the echocardiographic studies.

Statistical analysis

Values were reported as mean ± 1 SD unless otherwise stated. Unpaired Student's t test was used to compare continuous variables and Chi Square test to compare categorical variables. Multivariate logistic regression analysis was used to identify independent predictors of subsequent thromboembolic events. Actuarial survival and freedom from stroke or other embolic events were plotted by Kaplan-Meier method and subgroups were compared by the log rank test. Odds ratios were shown with 95% confidence intervals and statistical significance was defined as a two tailed $p < 0.05$.

RESULTS

Baseline clinical and echocardiographic findings

LA SEC was detected by TEE in 161 of the 272 patients (59%). Forty two patients (15%) had moderate or severe LV systolic dysfunction and 29 patients (11%) had significant LV hypertrophy. Mitral annular calcification was detected in 84 patients

115

(31%). Ninety six patients (35%) had simple thoracic aortic atheroma and 28 patients (10%) had complex atheroma. Eighty eight patients (32%) had history of stroke or transient ischaemic attack and 24 patients (9%) had history of an embolic event affecting either an extremity or a visceral organ.

The clinical and echocardiographic findings of patients with and without baseline LA SEC are compared with univariate analysis in Table 1. Patients with LA SEC were significantly older (p<0.001) and had a higher incidence of previous thromboembolic events (p<0.001). They also had a larger LA dimension (p<0.001) and higher prevalence of complex thoracic aortic atheroma (p=0.009). The prevalence of mitral annular calcification, moderate or severe LV systolic dysfunction or significant LV hypertrophy were not different between the two groups.

Nineteen patients (7%) were found to have a LA thrombus and 3 patients had LV apical thrombus. The LA thrombus was situated in the atrial appendage in 16 patients and at the orifice of the appendage in 3. All 19 patients with LA thrombus had LA SEC. These patients were excluded from all subsequent analysis.

Follow up

Follow up was complete in 233 patients with a mean duration of follow up of 17.5 ± 10 months (maximum 47 months). Seventeen patients (6%) were lost to follow up. Forty five patients (34%) with LA SEC and 11 patients (11%) without LA SEC were receiving anticoagulation therapy with warfarin on follow up (p<0.001) whereas 42 patients (32%) with LA SEC and 47 patients (47%) without LA SEC were on aspirin therapy (p=0.02).

Twenty five patients suffered a stroke or other embolic event on follow up (overall event rate 7% per year). The total event rate was 12% per year in patients with LA SEC and 3% per year in patients without LA SEC, and the event rate for stroke or transient ischaemic attack only was 10.5% per year with LA SEC and 3% per year

116

without LA SEC. Patients with LA SEC had a significantly decreased freedom from stroke or other embolic event (p=0.002, Figure 1).

In patients with LA SEC, 15 patients suffered a stroke of which 2 were fatal. Fourteen patients had cerebral CT scan performed after the event which showed non haemorrhagic cerebral infarction in 13 and no significant abnormality in the other. The 1 patient who did not have CT scan died within 24 hours of the onset of neurological deficit and autopsy was not performed. Three patients had a transient ischaemic attack. A CT scan was performed in 1 of these 3 patients and showed no significant abnormalities. One patient had an acute embolism to the right brachial artery and another patient had an acute embolism to the left femoral artery. These 2 patients underwent surgical embolectomy which confirmed the diagnosis. In the 45 patients with LA SEC receiving warfarin therapy, the incidence of stroke or other embolic events was 7% per year which compared to 14.5% per year in the 88 patients not receiving warfarin therapy (p = 0.15). Thirty of these 45 patients (67%) receiving warfarin therapy had previous embolism whereas only 34 patients (39%) of the 88 patients not receiving warfarin had such history (p=0.002).

In patients without LA SEC, 5 patients suffered a stroke on follow up of which 2 were fatal. Three patients had CT scan performed which showed non haemorrhagic cerebral infarction in 1 and no significant abnormalities in two. One of the latter 2 patients had a brain stem event which was confirmed by magnetic resonance imaging. The 2 patients who died did not have CT scan performed. No patient without LA SEC had peripheral embolism or transient ischaemic attack on follow up.

There were a total of 36 deaths on follow up (overall all cause mortality 10.5% per year). According to life table analysis, patients with LA SEC had a significantly reduced survival (p=0.025, Figure 2). In patients with LA SEC, there were 25 deaths. Nine patients died of cardiovascular causes, 2 died of fatal stroke, 6 died of complications secondary to a stroke or peripheral embolism, 4 died of cancer

117

and 4 of other non cardiovascular causes. In patients without LA SEC, there were 11 deaths. Four patients died of cardiovascular causes, 2 died of fatal stroke, 3 died of cancer and 2 of other causes.

Patients without a history of stroke or embolic events

One hundred and forty nine patients did not have a history of previous stroke or other embolic events. LA SEC was detected in 69 of these patients (46%). In these 149 patients, the event rate for stroke or other embolic events was 9.5% per year in patients with baseline LA SEC and 2.2% per year in patients without. In the patients with SEC, 7 patients suffered a stroke and 1 patient had an acute embolism to the left femoral artery. In the patients without SEC, 3 patients suffered a stroke. In these patients with no history of previous thromboembolism, patients with LA SEC had a significantly decreased freedom from stroke or other embolic events (p=0.003, Figure 3). There were 18 deaths on follow up, 12 in the group with LA SEC and 6 in the group without. On life table analysis, patients with LA SEC had a significantly reduced survival (p=0.02, Figure 4).

Predictors of subsequent stroke or other embolic events

Table 2 shows the results of multivariate logistic regression analysis performed to identify independent predictors of subsequent stroke or other embolic events in this cohort of 233 patients based on clinical characteristics, baseline echocardiographic parameters and warfarin or aspirin therapy on follow up. The presence of LA SEC at baseline was the only independent positive predictor and anticoagulation therapy with warfarin on follow up the only independent negative predictor of subsequent stroke or other embolic events. Gender, age, previous thromboembolism, moderate or severe LV systolic dysfunction, significant LV hypertrophy, LA dimension, LA SEC, mitral annular calcification, complex thoracic aortic atheroma, warfarin or aspirin therapy on follow up were used as covariates.

Complex thoracic aortic atheroma was not a significant predictor on either univariate (p = 0.5) or multivariate analysis. The results of the multivariate analysis

118

were not altered after patients with complex atheroma were excluded from the analysis with LA SEC being an independent positive predictor (p value 0.04, odds ratio 3.3, 95% CI 1.1 - 10.2) and warfarin therapy on follow up a negative predictor (p = 0.02, odds ratio 0.2, 95% CI 0.05 - 0.75).

Table 1. Baseline Clinical and Echocardiographic Findings Related to Presence (+) or Absence (-) of LA SEC (Univariate Analysis).

	LA SEC+ (n=161)	LA SEC- (n=111)	p
Previous thromboembolism	86 (53%)	26(23%)	<0.001
LA thrombus	19(12%)	0	<0.001
Age (yrs)	70 ± 9	65 ± 12	<0.001
LA dimension (mm)	50 ± 7	45 ± 7	<0.001
Complex aortic atheroma	23 (14%)	5 (4.5%)	0.009
Mitral annular calcification	57 (35%)	27(24%)	0.06
Male gender	103 (64%)	58 (52%)	NS
>Moderate LV dysfunction	28 (17%)	14 (13%)	NS
LV hypertrophy	18 (11%)	11 (10%)	NS

Table 2. Multivariate Analysis of Clinical and Echocardiographic Factors Related to Subsequent Thromboembolism in 233 Patients with Nonvalvular AF.

	p value	Odds ratio	95% CI
LA SEC	0.03	3.5	1.1-10.5
Warfarin therapy on followup	0.02	0.23	0.07 - 0.8
Previous thromboembolism	0.11	2	0.8 - 5.6
> Moderate LV dysfunction	0.17	2.3	0.7 - 7.3
Aspirin therapy	0.19	0.5	0.2-1.4
Significant LV hypertrophy	NS	0.4	0.05 - 3.1
Female gender	NS	1.6	0.6-4.2
Mitral annular calcification	NS	1.3	0.5-3.4
LA dimension	NS	1	0.9 - 1
Age	NS	1	0.9 - 1
Complex aortic atheroma	NS	1	0.2-4.3

121
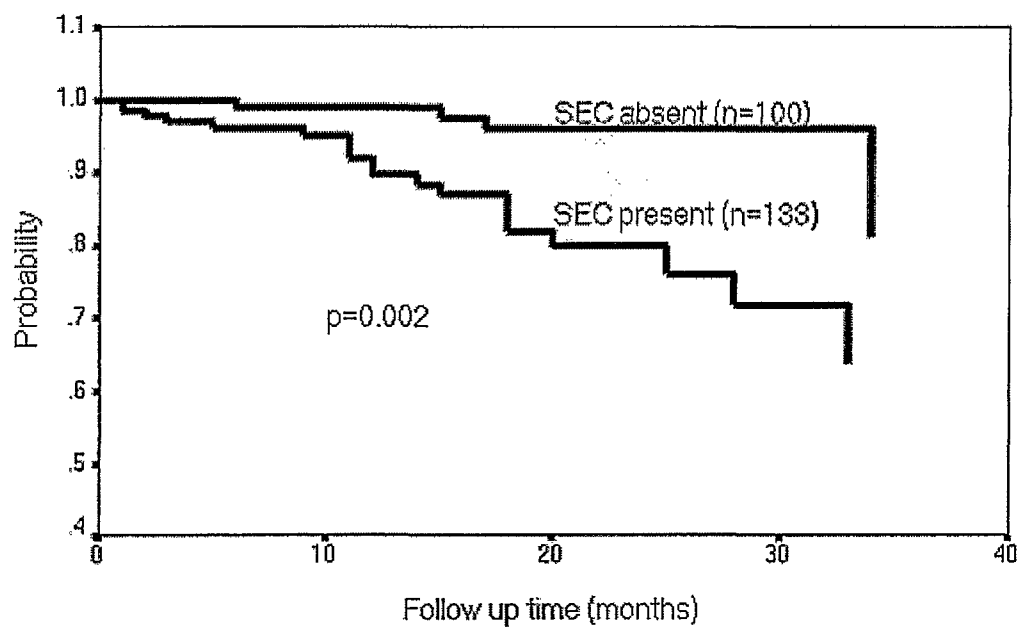
Figure 1. Cumulative Freedom From Stroke or Other Embolic Events in Patients With and Without Baseline Left Atrial Spontaneous Echo Contrast (SEC).
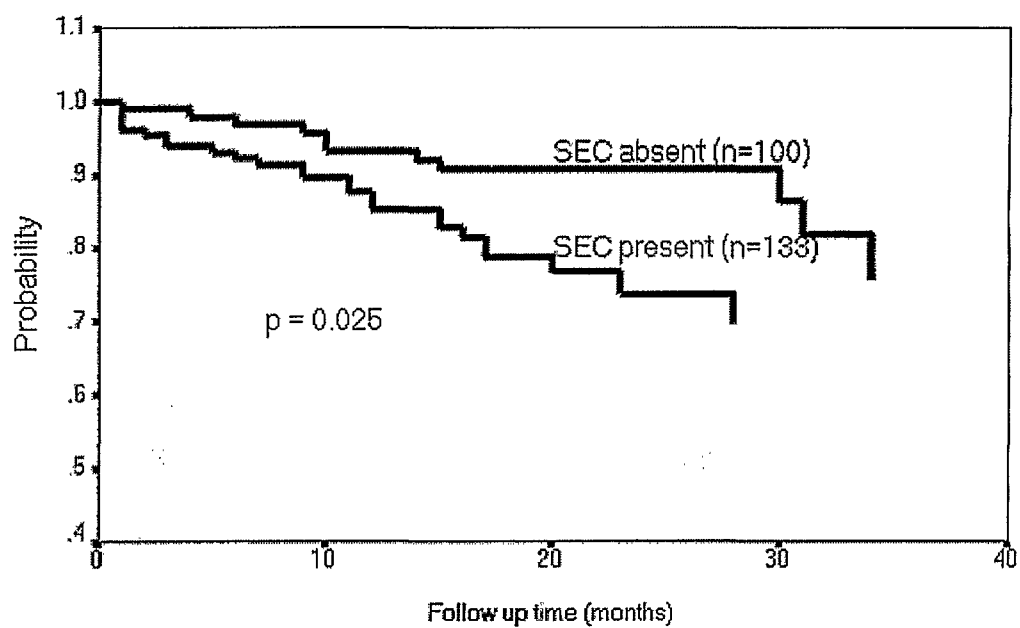
Figure 2. Survival Curves of Patients With and Without Baseline Left Atrial Spontaneous Echo Contrast (SEC).
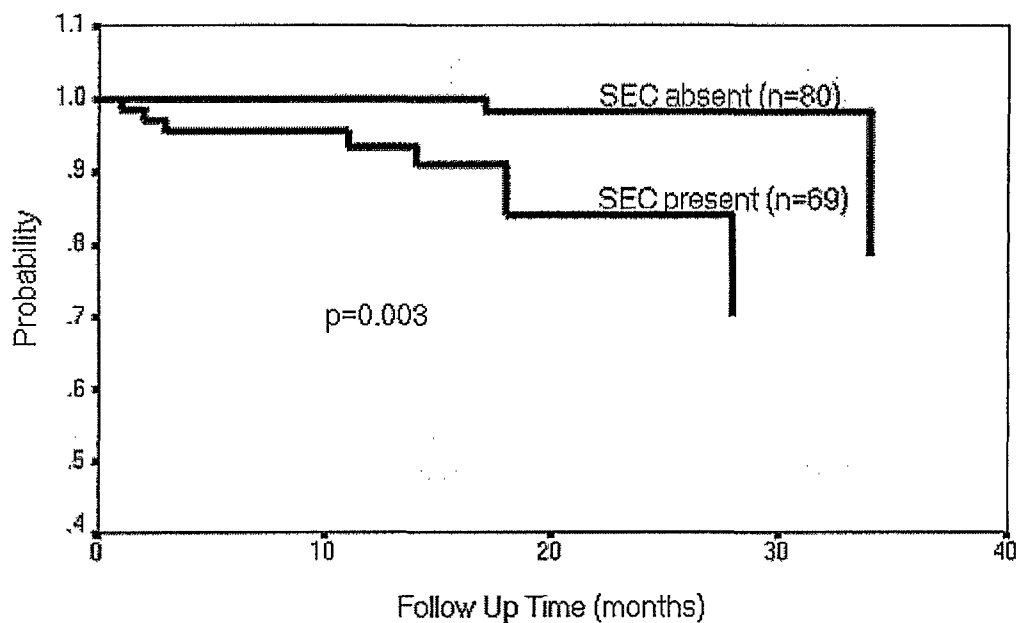
Figure 3. Cumulative Freedom From Stroke or Other Embolic Events in the 149 Patients Without a History of Thromboembolism. SEC = Left atrial spontaneous echo contrast.
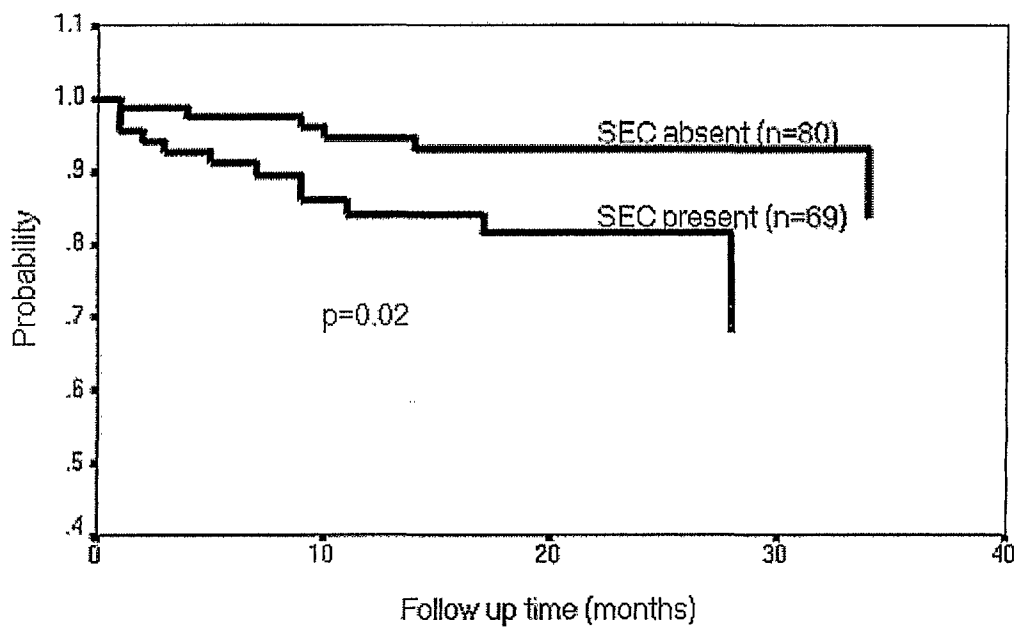
Figure 4. Survival Curves in the 149 Patients Without a History of Thromboembolism. SEC = Left atrial spontaneous echo contrast.

DISCUSSION

This large prospective study is the first to examine the prognostic implications of LA SEC in patients with nonvalvular AF. Patients with LA SEC have on follow up both a higher risk of developing stroke or other embolic events and a reduced actuarial survival. Moreover, the presence of LA SEC and the absence of warfarin therapy were the only significant independent predictors of subsequent thromboembolic events including stroke, transient ischaemic attack and peripheral embolism.

Prevalence of LA SEC

LA SEC was detected in 59% of the patients. The reported prevalence of LA SEC ranges from 16% to 19% (Black et al 1991a, Castello et al 1990) in all patients undergoing TEE and is higher in patients with mitral stenosis or a mitral prosthesis (25%-74%) (Black et al 1991a, Daniel et al 1988, Castello et al 1990). LA SEC has been shown to be strongly associated with the presence of AF (Black et al 1991a) but previous reports of its prevalence in nonvalvular AF are sparse. Black et al 1991a reported a prevalence of 47% in a smaller series of patients and Tsai et al (Tsai et al 1992) reported a prevalence of 24% in a series of 103 patients.

Thromboembolic risk in nonvalvular AF

There is a definite increase in the risk of stroke or other embolic events in patients with nonvalvular AF (Wolf et al 1991, Cairns and Connolly 1991). The reported incidence of stroke or other embolic events in these patients ranges from 3% per year to 7.4% per year (Petersen et al 1989, Stroke Prevention in Atrial Fibrillation Investigators 1991, Connolly et al 1991, Ezekowitz et al 1992, The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990). In the placebo arm of the Stroke Prevention in Atrial Fibrillation study, the event rate for stroke, transient ischaemic attack or systemic embolism was 9% per year (Stroke Prevention in Atrial Fibrillation Investigators 1991). The present study confirmed the significantly increased risk of thromboembolism in these patients with an event

rate for stroke of 5.8% per year, for stroke or transient ischaemic attack of 6.7% per year and for all thromboembolic events of 7% per year.

The risk of subsequent stroke and other embolic events is clearly not uniform among patients with nonvalvular AF (Cairns and Connolly 1991). There has been considerable interest in identifying clinical risk factors for thromboembolism in these patients. Female gender (Cabin et al 1990), older age group (Flegel and Hanley 1989), hypertension (Stroke Prevention in Atrial Fibrillation Investigators 1991, Flegel and Hanley 1989, Corbalan et al 1992), previous myocardial infarction (Petersen et al 1990), recent congestive heart failure (Stroke Prevention in Atrial Fibrillation Investigators 1992a) and a history of thromboembolism (Flegel and Hanley 1989, Stroke Prevention in Atrial Fibrillation Investigators 1992a) have been reported to be useful clinical predictors in some studies. Analysis of the result of the Copenhagen AFASAK Study for risk factors found that only a history of myocardial infarction predicted thromboembolism. Beta error due to small sample size may account in part for the variability in predictors of thromboembolism.

The search for echocardiographic predictors of thromboembolism has also yielded varying results, in part reflecting beta error with small sample size. While LA enlargement is the most frequently reported predictor (Cabin et al 1990, Corbalan et al 1992, Stroke Prevention in Atrial Fibrillation Investigators 1992b, Aronow et al 1989, Caplan et al 1986), LV dysfunction (The Stroke Prevention in Atrial Fibrillation Investigators 1992b), LV hypertrophy (Aronow et al 1989) and mitral annular calcification (Stroke Prevention in Atrial Fibrillation Investigators 1991, The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990) have been shown to be significant in some studies. However, these echocardiographic parameters have not been predictive in other series (Petersen et al 1990, Wiener 1987). Many of these studies were limited by being retrospective in design (Tsai et al 1992, Flegel and Hanley 1989, Corbalan et al 1992, Caplan et al 1986, Wiener 1987) and factors associated with a history of thromboembolism may not necessarily be risk factors for subsequent events.

127

Presence of LA thrombus, now reliably detectable by TEE (Aschenberg et al 1986, Bleifeld et al 1986, Matsumura et al 1989, Acar et al 1991, Hwang et al 1992, Lin et al 1992, Olson et al 1992, Manning et al 1995, Fatkin et al 1996) may define a subgroup of patients at higher risk of thromboembolic events who require anticoagulation. However, LA thrombus was detected in only 19 of the 272 patients (7%) in the present study and 9 of the 150 patients (6%) of Castello et al (1990) and therefore may have limited clinical applicability.

Black et al (1991) have previously shown that LA SEC and LA thrombus are strongly linked and are associated with previous thromboembolic events (Black et al 1991a). Therefore, we postulated that LA SEC may also be predictive of subsequent thromboembolic events. The present study has shown that LA SEC is the only significant independent predictor of the increased risk of subsequent stroke or other embolic events. Since the total patient group included a number of patients with a history of previous thromboembolism with a higher prevalence of LA SEC who might be expected to have a higher risk of recurrent stroke or other embolic events, the patient subgroup who did not have a history of previous thromboembolism was also analysed. Life table analysis demonstrated that these latter patients with LA SEC also have both a significantly decreased freedom from stroke or other embolic events and reduced survival compared to those without LA SEC.

LA enlargement and older age group, although more prevalent in patients with LA SEC, were not significant predictors in the present study. Complex thoracic aortic atheroma has been suggested as a useful predictor of embolic events in retrospective studies (Karalis et al 1991, Tunick et al 1991). Complex aortic atheroma was not predictive of embolism in the present study even on univariate analysis. However, the number of patients with this abnormality was small in this series.

LA SEC and thromboembolism

128

The strong predictive value of LA SEC raises the question as to the possible mechanism linking LA SEC with thromboembolism. Black et al (1993) showed that LA SEC was independently related to haematocrit and fibrinogen concentration and may represent a hypercoagulable state resulting from the interaction between haematological factors favouring erythrocyte aggregation and haemodynamic factors favouring stasis. It is therefore postulated that LA SEC may be a precursor of thrombus formation, especially in foci of low blood flow such as the LA appendage. These thrombi may then subsequently embolise to major organs.

The present study has also shown that LA SEC is associated with more advanced atherosclerotic disease in the thoracic aorta which suggest that these patients may also have more extensive atherosclerotic disease elsewhere in the aorta and in the cerebral vessels. Systemic embolisation, such as those responsible for stroke in these patients with AF, may arise from abnormal segments in these vessels and not necessarily from the heart.

LA SEC and mortality

The all cause mortality rate of patients in AF is about twice that of patients in sinus rhythm (Cairns and Connolly 1991, Kannel et al 1982, Cameron et al 1988). This study is the first to show that the mortality risk of patients with nonvalvular AF can be further stratified according to the presence or absence of LA SEC. The reduced survival of patients with LA SEC is most probably related to the excess thromboembolic risk and associated vascular disease. Patients with LA SEC were older, had a higher prevalence of complex aortic atheroma and a more frequent history of previous thromboembolism consistent with more extensive atherosclerotic vascular disease.

Role of anticoagulant therapy

Recent placebo controlled studies have shown that anticoagulation with warfarin decreases the thromboembolic risk in patients with nonvalvular AF (Petersen et al 1989, Stroke Prevention in Atrial Fibrillation Investigators 1991, Connolly et al

129

1991, Ezekowitz et al 1992, The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990). In the present study, warfarin therapy was a significant negative predictor of subsequent stroke or other embolic events on multivariate analysis. In patients with baseline LA SEC, the incidence of stroke or other embolic events in those on warfarin therapy was 7% per year in contrast to 14.5% per year in those not on warfarin therapy. Although it did not reach statistical significance on univariate analysis, this trend towards risk reduction with warfarin therapy occurred despite a higher incidence of previous embolism in the former group of patients. Patients receiving warfarin therapy were a highly selected subgroup in whom the risk of developing an event was considered high. However, these findings must be interpreted with caution as the study was only observational and not controlled for anticoagulation therapy. Nevertheless, these results are consistent with the findings of the randomised multicenter trials (Petersen et al 1989, Stroke Prevention in Atrial Fibrillation Investigators 1991, Connolly et al 1991, Ezekowitz et al 1992, The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990).

Limitations

This was an observational study on a cohort of patients where the presence or absence of LA SEC and anticoagulation therapy were not controlled and there were differences in the baseline characteristics of the two patient subgroups. Nevertheless, LA SEC was present in about half of the patients at the baseline study and multivariate analysis was used to allow for these differences in the clinical characteristics of the two patient subgroups. The adverse prognostic implications of the presence of LA SEC was highly significant and was independent of history of previous thromboembolism.

No information was available about the natural history of LA SEC as TEE was not routinely performed on follow up or at the time of a thromboembolic event. More information is required to more precisely characterise any changes in LA SEC with time or with subsequent thromboembolic events.

CONCLUSIONS

Patients with nonvalvular AF have about a five-fold increase in stroke rate compared to patients in sinus rhythm (Cairns and Connolly 1991). Anticoagulation therapy with warfarin in patients with nonvalvular AF has been shown to reduce this thromboembolic event rate (Petersen et al 1989, Stroke Prevention in Atrial Fibrillation Investigators 1991, Connolly et al 1991, Ezekowitz et al 1992, The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990). However, warfarin therapy for patients with nonvalvular AF is not uniformly prescribed because of concern about bleeding risk in this predominantly elderly patient population (Stroke Prevention in Atrial Fibrillation Investigators 1996). This is illustrated by the fact that only 24% of patients in the present study were receiving warfarin therapy on follow up. In the Stroke Prevention in Atrial Fibrillation Study (Stroke Prevention in Atrial Fibrillation Investigators 1991), 53% of the study patients were considered ineligible for anticoagulation. In the Stroke Prevention in Non-rheumatic Atrial Fibrillation trial (Ezekowitz et al 1992), 40% of the patients screened were considered to have contraindications to anticoagulation. Despite careful screening, warfarin therapy is associated with a significant increase in the risk of bleeding (Petersen et al 1989, Stroke Prevention in Atrial Fibrillation Investigators 1991, Connolly et al 1991, Ezekowitz et al 1992, The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990, Stroke Prevention in Atrial Fibrillation Investigators 1996) in patients with nonvalvular AF. In large carefully controlled randomised trials, the reported incidence of major bleeding on warfarin therapy ranged between 0.4% and 3.5% per year (Table 4, Chapter 1). The risk/benefit ratio of systemic anticoagulation can be optimised by treating patients at higher risk of developing subsequent thromboembolism. This study has shown that TEE can be used to risk stratify patients with nonvalvular AF by identifying patients with LA SEC who have both a significantly higher risk of developing stroke, transient ischaemic attack or other embolic events and a reduced survival. These patients may represent a group of patients in whom the risk/benefit ratio of long term anticoagulation with warfarin

therapy appears most favourable. The results of this study were supported by the subsequent publication of the SPAF III TEE Study (Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography 1998), in which LA SEC was a predictor of subsequent stroke, with the risk reduced in patients randomised to adjusted dose warfarin.

CHAPTER 5

Integrated Backscatter for Quantification of Left Atrial Spontaneous Echo Contrast

ABSTRACT

Background and Objectives. LA SEC has previously only been graded qualitatively as mild or severe. This study was designed to develop a quantitative method of LA SEC assessment using integrated backscatter and to compare integrated backscatter LA SEC measurement with independent qualitative grades of LA SEC and clinical and echocardiographic predictors of thromboembolism.

Methods. We performed TEE in 43 patients and acquired digital integrated backscatter image sequences of the interatrial septum to internally calibrate the LV cavity and LA cavity under different gain settings. Patients were independently assessed as having no, mild or severe LA SEC. We compared intensity of integrated backscatter in the LA cavity relative to that in the LV as well as to the independently assessed qualitative grades of LA SEC. The integrated backscatter was compared with clinical and echocardiographic predictors of thromboembolism. Fourier analysis characterised the temporal variability of LA SEC.

Results. The LA cavity integrated backscatter intensity of the mild LA SEC subgroup was 4.7 dB higher than that from the LV cavity, and the LA intensity of the severe LA SEC subgroup was 12.5 dB higher than that from the LV cavity. The LA cavity integrated backscatter intensity correlated well with the qualitative grade ($r=0.89$, $p<0.001$). Fourier transforms of LA SEC integrated backscatter sequences revealed a characteristic dominant low frequency/high amplitude spectrum, distinctive from no LA SEC. There was a close relationship between integrated backscatter values and AF, LA size, LA appendage flow velocities and thrombus.

Conclusions. Integrated backscatter provides an objective quantitative measure of LA SEC that correlates well with qualitative grade and is closely associated with clinical and echocardiographic predictors of thromboembolism.

134

INTRODUCTION

LA SEC refers to dynamic smoke-like echoes detected by TEE that are associated with thrombus formation and an increased risk of thromboembolism (Black et al 1991a, Leung et al 1994). These smoke-like echoes are characterised by increased intensity and a distinctive "swirling pattern", which are though to result from aggregates of red blood cells in the presence of low shear rates (Black et al 1993, Fatkin et al 1994). LA SEC is a frequent finding in patients with mitral stenosis, AF, LA enlargement and previous embolisation (Black et al 1991a, Daniel et al 1988).

To date, the degree of LA SEC has been graded qualitatively as mild or severe based on the detection of dynamic intracavity echoes at high or low gains, respectively (Daniel et al 1988, Beppu et al 1985). Severe LA SEC has been more strongly associated with LA thrombus and thromboembolism (Daniel et al 1988). However, a major limitation of SEC assessment has been the lack of objective or quantitative measures of either intensity or temporal variability.

In the last 15 years, ultrasonic tissue characterisation has been used to determine the composition of cardiac tissue by comparing the reflectance of echoes emanating from tissue to infer information about structure and function (Skorton et al 1991, Perez et al 1994). Integrated backscatter, a measure of the total backscattered energy from a specific volume of interrogated tissue, has been used to characterise abnormalities in various diseases (Barzilai et al 1990, Vered et al 1989, Glueck et al 1985, Barzilai et al 1988, Vered et al 1987, Chandrasekaran et al 1989, Masuyama et al 1990). Ultrasonic integrated backscatter has also been used to describe the echogenic properties of thrombus formation in clotted blood (Shung et al 1986, McPherson et al 1988), the different morphologic components of thrombi (Sigel et al 1990), and red blood cell aggregation in vitro (Yuan et al 1993, Yuan et al 1988). We hypothesise that integrated backscatter may be used to characterise the acoustic properties of LA SEC, which may represent a

transition stage to thrombus formation (Daniel et al 1988, Black et al 1993, Fatkin et al 1994).

The objectives of this study were 1) to develop a quantitative, numerical approach to SEC using integrated backscatter in characterising the increased intensity and temporal variability of LA SEC, 2) to determine the extent to which quantitative measures of LA SEC using integrated backscatter can differentiate independently assessed qualitative grades to LA SEC, and 3) to compare this quantitative approach to clinical and echocardiographic predictors of thromboembolism.

METHODS

Patients

We studied a convenience sample of 43 patients (23 men and 20 women; mean age 65 ± 11 years, range 36 to 87) undergoing TEE for clinical indications. Associated cardiac diseases included 11 patients with prosthetic valves, 8 with mitral regurgitation/stenosis, 5 with aortic regurgitation/stenosis, 4 with LV hypertrophy, 3 with LV dysfunction and 2 with other diseases. Of the 43 study patients, 18 patients were in AF, 16 were in normal sinus rhythm, 5 in atrial flutter and 4 in junctional rhythm at the time of the study.

TTE examination

A complete TTE study was performed in all patients using a 2.5-MHz transducer. Two-dimensional directed M-mode echocardiography was used to derive the LV end-diastolic and end-systolic dimensions and LA dimension. LV ejection fraction was calculated using the method of Quinones et al (1981).

TEE examination

A complete TEE examination was performed according to previous methods (Seward et al 1990 and 1993) using a 5-MHz biplane or multiplane transducer attached to a commercially available echo machine (Hewlett-Packard Sonos 1500)

equipped with an acoustic densitometry software system for the analysis of integrated backscatter. Special attention was given to imaging the LA and LA appendage to assess for the presence of SEC or thrombus. Pulsed Doppler recordings of the LA appendage were made by placing the sample volume 1 to 2 cm into the mouth of the LA appendage.

Study subgroups by qualitative assessment

LA SEC was qualitatively assessed during TEE by two experienced independent observers by consensus into no, mild or severe SEC subgroups. These qualitative groups were defined only after careful observation of the LA for SEC, after transient manipulation of the transmit power at high or low settings and then returning the gain settings to the optimal settings. Mild LA SEC was defined as dynamic intracavitary echoes observed at high gain and in only some parts of the LA, whereas severe LA SEC was observed at low gain (Daniel et al 1988, Beppu et al 1985).

Echocardiographic measurements

LA appendage peak emptying, late diastolic Doppler flow velocities were digitised using a computer tablet (Dextra Inc.). Peak velocities were averaged over 6 cardiac cycles for AF and 3 cardiac cycles for normal sinus rhythm. Mitral regurgitation was assessed qualitatively using Doppler colour flow mapping (mild = 1+; moderate = 2+; moderately severe = 3; severe = 4+) (Yoshida et al 1990).

Integrated backscatter system presets and data acquisition

Integrated backscatter is a relative measure of the total ultrasonic energy backscattered by a small volume of the interrogated tissue (Skorton et al 1991). In the backscatter mode of operation, the beam-formed signal at the ultrasonic receiver is not rectified, enveloped-detected and log-compressed as in conventional ultrasonography. The integrated backscatter image data are independent of the nonlinear compression control and video postprocessing

functions and have a useful dynamic range of about 44 dB (Douglas et al 1994, HP Acoustic Densitometry 1994)

To ensure in-vivo standardisation of the integrated backscatter acquisition, the TEE imaging was performed in a four-chamber view, typically at a depth of 10 or 12 cm, with the initial instrument gain settings of transmit power and receiver time-gain-compensation profiles adjusted to achieve uniform and optimal visualisation of the two-dimensional image. The overall gain was then adjusted such that the integrated backscatter intensity within the proximal (closest to valves) interatrial septum (IAS) (the brightest area) was about 40 dB. This calibration establishes the IAS, which is the brightest target in the image, as the internal intensity reference and guarantees that all subsequent intensity measurements will be made in the linear dynamic range of the integrated backscatter signal, well below the full-scale or saturation level of 44 dB of the integrated backscatter signal range.

Other important control setting of the imaging chain such as preprocessing, focus position, persistence, compression, frame rate and postprocessing were maintained constant throughout the study. The integration time of the filer used to estimate the power of the backscatter signal was maintained at a constant value of $3.2\mu s$ (Vered et al 1987) for the entire study. In the HP 1500, the positions of all the imaging controls (potentiometers) are digitised and are stored along with the acquired cineloop images on to an optical disk in a digital format. Furthermore, the acoustic densitometry system allows the operator to display the state of the system control settings in a pull-down menu format so that the reproducibility of studies can be effectively controlled and established.

For quantitative measurements of integrated backscatter intensity, the analysis system was configured (preset) to analyse 60 frames of integrated backscatter image data from cineloop memory. The region of interest was circular figure with a diameter of 21 pixels. The display graph was preset to span the integrated backscatter intensity values in the range from 0 to 64 dB. The smoothing filter for

138

reducing noise in the time-intensity samples was present to "off", and the curve-fitting option was present to "no curve fit." The measures obtained were the peak intensity and peak-to-peak variability of the integrated backscatter signal in each of the regions of interest.

Study protocol and data analysis

Figure 1 outlines the details of the study protocol. With the interatrial septum as the internal reference, the study protocol included placing a 21-pixel diameter region of interest in stable position in the interatrial septum, LV and LA for digitally acquired images in order to determine the peak intensity of the integrated backscatter signal. These integrated backscatter values were obtained by a completely independent observer. The region of interest was placed in a stable position in the LA cavity in the visually assessed region of the most intense SEC, usually near the medial or lateral aspects of the LA cavity at a similar level to the calibration of the interatrial septum. We consistently used a circular region of interest measuring 21 pixels in diameter to acquire the mean integrated backscatter in the interatrial septum, the LV cavity, and the LA cavity. The 21-pixel diameter region of interest provided the best match for sampling the interatrial septum, and meticulous care was taken to position the region of interest within the interatrial septum and exclude specular reflections at the endocardial boundaries. None of the patients had lipomatous hypertrophy of the interatrial septum or an interatrial septal aneurysm.

Differences between the LA cavity SEC values and the LV cavity values in decibels were converted to a LA/LV power ratio (Appendix 1).

Technical variables

To address the influence of gain settings (transmit power and time-gain-compensation) on the quantification of LA SEC, we made each technical adjustment in an independent and systematic fashion. After each adjustment was made, care was taken to standardise the system with the interatrial septum

139

intensity maintained at 40 dB (<44 dB) and thus within the linear dynamic range of the system. To determine the effect of varying transmit power settings, we increased the transmit power by 3 dB for each patient and acquired an additional integrated backscatter sequence on line. In order to determine the effect of time-gain-compensation on the quantitative measures, we additionally acquired an integrated backscatter sequence on each patient with the time-gain-compensation settings in an "unadjusted" or uniform (vertical) position.

Intraobserver and interobserver variability

Tests of intraobserver and interobserver reliability of integrated backscatter analysis were obtained in 5 randomly selected patients. Comparing these repeated measurements on the same acquisition, the root mean square differences of the integrated backscatter peak intensities for intraobserver were 0.5, 1.0 and 0.5 dB for the LA cavity, LV cavity and interatrial septum, respectively. This difference amounted to a 4% variability in the quantitative measurements. For interobserver variability the root mean square differences were 0.9, 1.3 and 0.9 dB for the LA cavity, LV cavity and interatrial septum, respectively.

In addition, we compared two separate acquisitions of SEC obtained 4 min apart in another random sample of 5 patients in order to determine the minute-by-minute variability in the integrated backscatter intensities. Comparison of these repeated acquisitions analysed by the same observer found the root mean square differences of the integrated backscatter peak intensities to be 1.0 dB, 0.6 dB for the LA cavity, LV cavity and interatrial septum, respectively.

Fourier analysis

To assess the temporal variability of the swirling pattern of LA SEC, we performed frequency analysis of the 60 consecutive integrated backscatter LA values derived from the intensity analysis (Figure 2). Fourier frequency-domain transformation was computed using LabView VI (National Instruments Corporation) (Appendix 2). Fourier frequency-domain transformation of the intensity sequence provides a

gain-independent method of characterising the temporal variability of LA SEC, because this analysis focuses on the frequency pattern rather than the absolute amplitude of the signal (Bracewell 1978). The Fourier analysis was used to determine the frequency of the LA SEC swirling pattern as it enters and exits the stable region of interest within the atrium, and the 21-pixel diameter region of interest was selected to capture the representative swirling "waves" of LA SEC.

Statistical analysis

Comparisons between LA cavity measurements and reference measurements on the interatrial septum or in the LV cavity were made by paired t tests. Analysis of variance and t tests were used to compare values for the mean peak intensity for the three qualitative grades and to compare the mean centroid frequency. The Spearman rank-order correlation coefficient was used to assess the association between the qualitative grade of LA SEC and quantitative measure of LA SEC intensity. A linear regression model was used to correlate the quantitative measure of LA SEC intensity with echocardiographic measures. Clinical and echocardiographic discrete variables were compared to the peak integrated backscatter values using Fisher's exact test. A proportional odds model (McCullaugh 1980) was used to assess the predictive value of the quantitative measures of LA SEC relative to qualitative grades (no SEC, mild SEC and severe SEC). Data are presented as mean ± SD. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Clinical and echocardiographic variables and qualitative grade of SEC
The clinical and echocardiographic findings of the patients characterised by qualitative grade of SEC are shown in Table 1. There were 10 patients with no SEC, 15 with mild SEC and 18 with severe SEC. Patients in the no SEC subgroup tended to be younger than those patients in the other subgroups. Patients with

mild and severe SEC were more likely to be in AF at the time of the TEE, taking warfarin and to have a mitral valve prosthesis or mitral stenosis compared to the no SEC group. There was no difference in previous thromboembolic events in the different subgroups. The severe SEC subgroup tended to have a larger LA dimension than the other subgroups. LA appendage or cavity thrombus was detected exclusively in the severe SEC subgroup, and this subgroup was associated with lower LA appendage emptying flow velocities and correspondingly higher integrated backscatter intensities.

Integrated backscatter intensity and qualitative grade of SEC

The integrated backscatter values obtained from the interatrial septum, LV cavity and LA cavity for the three qualitative grade of LA SEC are shown in Figure 3 and Table 2. The mean quantitative measures of LA SEC correlated well with the independently assessed qualitative grade of LA SEC (r = 0.89, p <0.001). The mean integrated backscatter LA peak intensities differed among the three qualitative subgroups of LA SEC (P = 0.001), whereas there was no significant difference among these intensities from the LV cavity. With the protocol used for standardising the system, the mean LA peak intensity or amplitude was 12.1 dB greater than the mean LV cavity intensity for the severe SEC subgroup. Similarly, the mean LA peak intensity was 4.6 dB greater than the mean LV cavity intensity for the mild SEC subgroup. The power ratios of these differences between the LV cavity and the SEC in the LA was a factor of 15.8 for the severe SEC subgroup and a factor of 2.9 for the mild SEC subgroup. In contrast, there was no significant difference (0.5 dB) in intensity for the mean LA peak intensity in the no SEC subgroup compared to the mean LV cavity intensity (1.1 power ratio) (Figure 3). A scattergram showing the LA peak integrated backscatter for all 43 patients is shown in Figure 4.

A proportional odds model was used to assess the predictive value of the quantitative measures of LA SEC intensity relative to qualitative subgroup (no SEC, mild SEC and severe SEC) (Figure 4). The proportional odds model

142

assumes that for each unit increase in the quantitative measure of peak intensity (decibels), the odds of being in a relatively higher SEC subgroup (severe versus mild/normal or severe/mild versus normal) increase by a constant amount (McCullaugh 1980). This is the analog to logistic regression for an ordinal outcome with more than two subgroups. With this model, it was found that the LA quantitative SEC measurement, using integrated backscatter, is very sensitive relative to SEC qualitative assessment. The odds of being in the next higher SEC subgroup increase by a factor of 2.6 (85% CI 1.5 to 4.7, p = 0.001) for every 1 dB increase in integrated backscatter peak intensity (Figure 4).

Fourier frequency spectra

The mean Fourier spectra of integrated backscatter intensity sequences in the LA cavity of the mild and severe SEC patients were characterised by a low dominant frequency with high amplitude, whereas the corresponding Fourier spectrum in the no-SEC patients was of a more uniform and random nature (Figure 5). This characteristic low-frequency spectrum in patients with SEC corresponds well with the observed swirling motion of SEC. The mean Fourier (centroid) frequency was significantly lower in those patients with LA SEC compared to no SEC (P = <0.001), and there was no difference in the mean Fourier frequency between the LA cavity in the no SEC patients and either interatrial septum or LV cavity. Similarly, we found no difference in the mean Fourier frequency for the LA cavity between the severe and mild SEC subgroups.

Integrated backscatter intensity and clinical/echocardiographic variables

Patients with LA or LA appendage thrombus showed a higher peak integrated backscatter intensity than patients without thrombi (22.2 ± 1.2 dB vs. 14.9 ± 5.7 dB, p = 0.015). Patients with AF had a higher integrated backscatter intensity compared to patients in normal sinus rhythm (18.6 ± 4.7 dB vs. 10.4 ± 3.2 dB, p=0.001). There was a significant relationship between the peak integrated backscatter values and increasing LA size (r = 0.45, p = 0.01, SEE 4.37) and a significant inverse relationship between the peak integrated backscatter values

143

and peak LA appendage emptying velocities (r = -0.69, p = 0.001, SEE 4.05).

Integrated backscatter technical variables

In a separate acquisition, increasing the transmit power by 3 dB tended to increase the intensity measurements for the interatrial septum, LV cavity or LA cavity (Table 2). For the no SEC subgroup, the LA cavity measurements significantly increased (P = 0.03) under higher transmit power compared to normal transmit power (Table 1). Although increasing transmit power from normal to higher transmit raised the quantitative measures and power ratios proportionately for all sub-groups, the ability of the quantitative measures of integrated backscatter to discriminate among the qualitative grades of LA SEC remained excellent, and thus the results are relatively gain independent. Under the high transmit power, the mean quantitative measures of LA SEC obtained correlated strongly with the three independently assessed qualitative grades of LA SEC (r = 0.77, p <0.001).

In a separate acquisition, altering the time-gain-compensation also influenced the quantitative measures of integrated backscatter (Table 2). Despite altering the time-gain-compensation setting to a uniform setting, the ability of the quantitative measures of integrated backscatter to discriminate among the qualitative grades of LA SEC still remained, again suggesting the relative gain independence of the model.

Table 1. Characteristics of Study Patients Categorised by the Qualitative Grade of LA SEC.

	No SEC (n = 10)	Mild SEC (n = 15)	Severe SEC (n = 18)
Clinical data			
Age (yr)	53.8 ± 12.1*	69.9 ± 10.1	65.6 ± 8.4
Male gender	5 (50%)	13 (86%)	10 (56%)
AF	0 (0%)*†	7 (46%)	14 (78%)
Warfarin	1 (10%)*	7 (46%)	17(94%) ‡
Mitral stenosis	1 (10%)*	2 (13%)	9 (50%) ‡
CHF NYHA class III-IV	2 (20%)	3 (20%)	2 (12%)
Prior thromboembolism	2 (20%)	3 (20%)	4 (22%)
TTE			
LVED dimension (mm)	47.3 ± 9.0	46.7 ± 8.2	50.4 ± 8.3
LVES dimension (mm)	28.2 ± 6.2	29.3 ± 8.6	33.0 ± 7.3
LV EF (%)	69 ± 11	65 ± 32	55 ± 19
LA dimension (mm)	43 ± 7*	47 ± 8	53±8‡
TEE			
Peak LA integrated backscatter			
(dB)	8.7± 1.8*	13.5 ± 2.2	21.1 ± 3.6
LA or LAA thrombus	0 (0%)	0 (0%)	4(22%)
LAA flow velocity (cm/s)	48.4 ± 22.0*†	26.2 ± 10.2	14.2 ± 8.6
Complex aortic atheroma	1 (10%)	6 (40%)	5 (27%)
MR≥moderate	1 (10%)	2 (13%)	1 (6%)

* p < 0.01 among groups. †p<0.01, No SEC versus other subgroups. ‡p <0.01, severe SEC versus other subgroups. CHF = congestive heart failure, EF = ejection fraction, LVED = LV end-diastolic, LVES = LV end-systolic, MR = mitral regurgitation.

Table 2. Effect of Normal and High Transmit Power Settings and Optimal Versus Uniform Time-gain-compensation on Integrated Backscatter Peak Intensity for Three Qualitative Grades of LA SEC in 43 Patients.

	No SEC (n = 10)				Mild SEC (n = 15)				Severe SEC (n = 18)			
	IAS (dB)	LV (dB)	LA (dB)	LA/LV Power Ratio	IAS (dB)	LV (dB)	LA (dB)	LA/LV Power Ratio	IAS (dB)	LV (dB)	LA (dB)	LA/LV Power Ratio
Transmit power												
Normal	39.5±2.8	8.5±2.5	8.7±1.8	1.12	41.0±1.3	8.6±2.0	13.5±2.2	2.89	41.1±1.7	9.1±2.0	21.1±3.6	15.84
High	41.3±0.9	8.2±2.2	9.9±2.3†	1.56	41.9±0.6†	10.0±1.7*	17.0±2.9*	4.67	41.9±1.1	9.6±3.0	23.3±5.0	23.43
TGC setting												
Optimal	39.5±2.8	8.5±2.5	8.7±1.8	1.12	41.0±1.3	8.6±2.0	13.5±2.2	2.89	41.1±1.7	9.1±2.0	21.1±3.6	15.84
Uniform	38.9±0.6	5.9±0.6	7.2±1	1.7	39.2±2.1†	6.8±0.5*	10.9±1.9*	2.50	40.2±1.5	6.9±1.0*	14.9±3.3*	6.30

*$p<0.001$ for differences versus values obtained from normal transmit power at optimal time-gain-compensation (TGC) setting. †$P <0.05$ for differences versus values obtained from normal transmit power at optimal time-gain-compensation setting. IAS = interatrial septum.
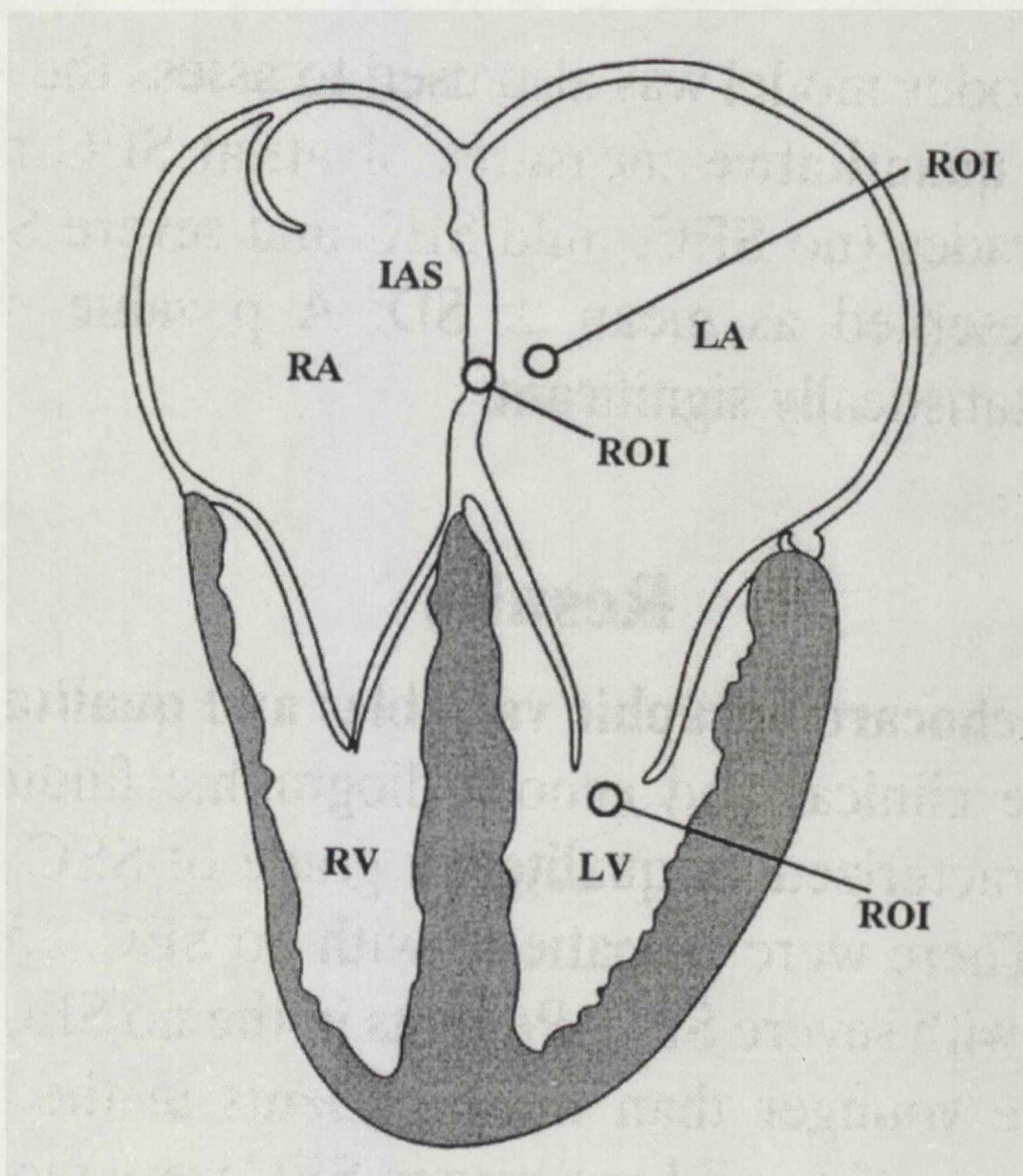
Figure 1. Diagram of the Study Protocol with a 21-Pixel Diameter Region of Interest Placed in the Interatrial Septum, Which Was Used as an Internal Standard, the Left Ventricular Cavity and the Left Atrium.

IAS= interatrial septum, LA=left atrium, LV=left ventricle, RA=right atrium, ROI=region of interest.
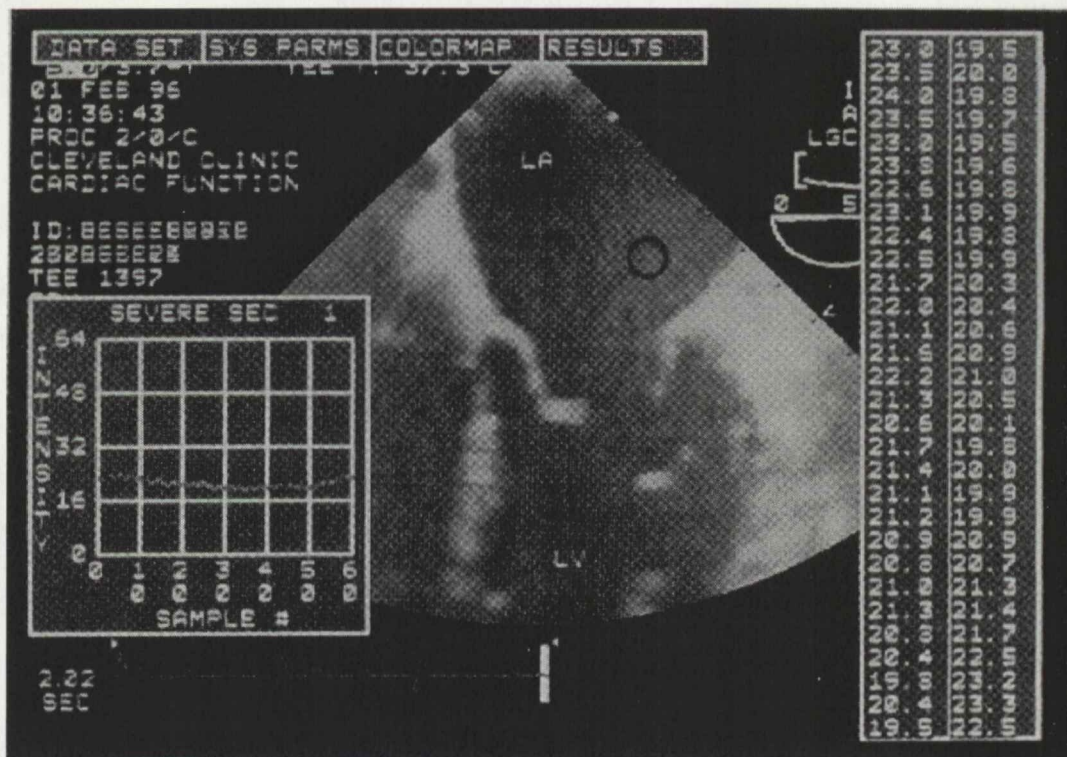
Figure 2. Integrated Backscatter Analysis of Spontaneous Echo Contrast (SEC) Interrogated From the Left Atrium of a Patient with Severe SEC.

Note the location of the region of interest (circle) in the area of the most intense SEC. Note the series of 60 integrated backscatter intensity values (dB) that are generated on the right side of the screen. LA=left atrium, LV=left ventricle.
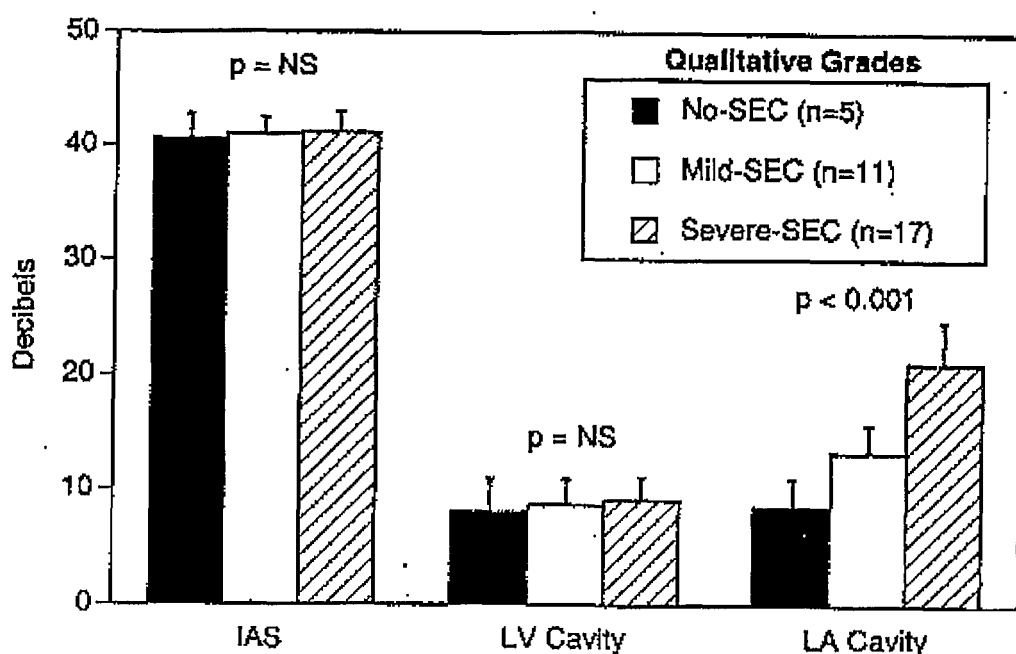
Figure 3. Bar Graph of Integrated Backscatter Mean Peak Intensities in Decibels (dB) from the Interatrial Septum, Left Ventricular Cavity and Left Atrial Cavity in the No SEC, Mild SEC and Severe SEC Subgroups.

Note the 21-dB and 13-dB mean intensity in the left atrial cavity of the severe SEC and mild SEC subgroups, respectively, compared with a constant 8-dB intensity of the left ventricular cavity. In contrast, in the no SEC subgroup, the intensity in the left atrial cavity is similar to the intensity of the left ventricular cavity. IAS=interatrial septum, LA=left atrium, LV=left ventricle, SEC =spontaneous echo contrast.

149
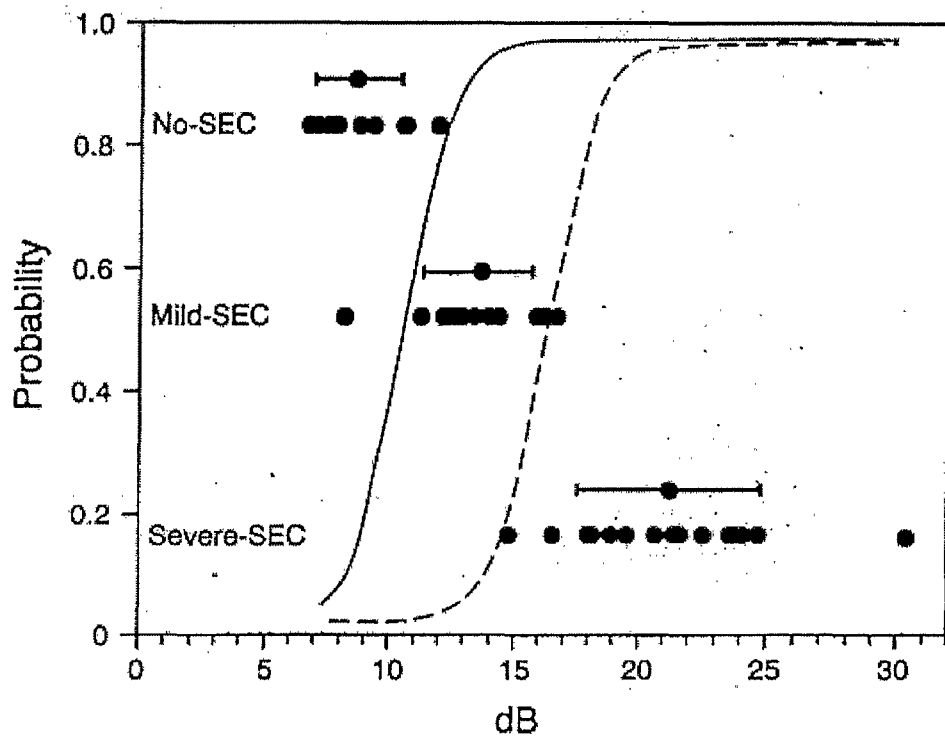
Figure 4. Proportional Odds Model Shown as a Scattergram of the Left Atrial Integrated Backscatter Peak Intensity in Decibels for 43 Patients.

The model is used to assess the predictive value of the quantitative integrated backscatter measures of atrial SEC relative to qualitative subgroups (no SEC, mild SEC and severe SEC). The *solid curve* shows the best fit separating the no SEC subgroup and the mild SEC/severe SEC subgroups. The *dashed curve* shows the best fit separating the no SEC/mild SEC subgroups from the severe SEC subgroup. *Error bars* represent the integrated backscatter means and standard deviations (dB) for patients independently assigned to each qualitative subgroup. SEC=spontaneous echo contrast.

150
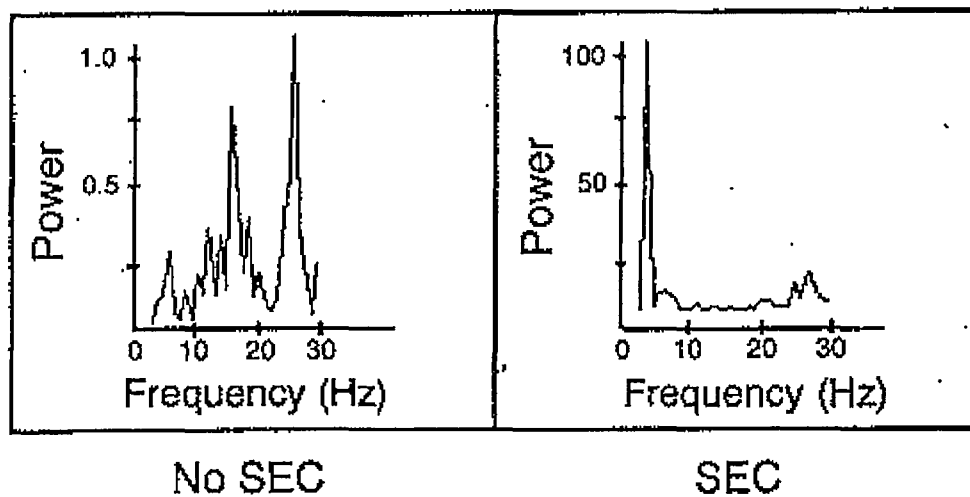
Figure 5. Diagram of Fourier Transformation From the Temporal Integrated Backscatter Sequences From the Left Atrium of a Patient with no SEC (Left) and a Patient with SEC (Right).

The characteristic low frequency spectrum in patients with SEC corresponds well with the visually observed swirling motion of SEC. The spectrum from the patient with no SEC is characterised by random high frequency frame-to-frame changes. SEC=spontaneous echo contrast.

151
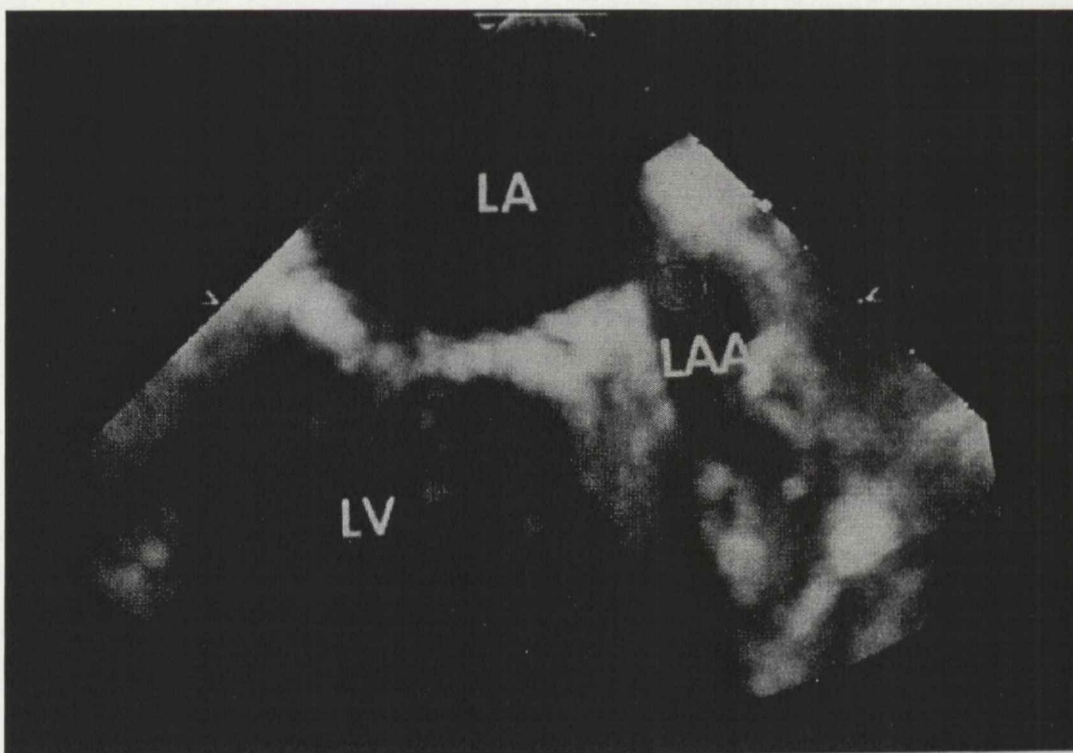
Figure 6. Integrated Backscatter Image of the Left Atrial Appendage Showing the Ability to Measure Increased Intensities in a Patient With Severe SEC.

Note the region of interest (circle) in the mouth of the left atrial appendage. LA=left atrium, LAA=left atrial appendage, LV=left ventricle.

DISCUSSION

LA SEC has received increasing attention as a marker of thromboembolic risk, particularly in patients with mitral valve disease and in patients with nonvalvular AF (Black et al 1991a, Fatkin et al 1994, Daniel et al 1988, Leung et al 1994). Recent studies (Stroke Prevention in Atrial Fibrillation Investigators 1994, Stroke Prevention in Atrial Fibrillation Investigators 1996) have shown that the benefits of warfarin in reducing ischaemic stroke in AF may be offset by unacceptable bleeding toxicity, particularly in elderly high risk patients. LA SEC may potentially be used to identify patients at higher risk, in whom warfarin may be of most benefit (Leung et al 1994). Patients with a higher grade of LA SEC may be at particular risk (Fatkin et al 1994, Beppu et al 1985) however, the apparently subjective nature of grading LA SEC and differentiation from artifact has hindered its clinical applicability in risk stratification.

This study shows for the first time that the intensity of LA SEC can be assessed quantitatively using integrated backscatter. The integrated backscatter intensity is successful in distinguishing among the qualitative grade of LA SEC and is associated with clinical and echocardiographic parameters of thromboembolism including LA size, left appendage flow velocities, AF and thrombi. The Fourier spectral frequency demonstrates that LA SEC is a unique echocardiographic phenomenon that is clearly distinguishable from either tissue or artifact.

Uses of integrated backscatter

Integrated backscatter has been previously used to characterise the physical properties of the myocardium, using the backscattered radiofrequency energy redirected from inhomogeneities in the tissue to the transducer (Skorton et al 1991). The mean amplitude and the cyclic variation of ultrasound backscatter from a region of interest in the myocardium has been used in vivo to assess the physical properties of the myocardium over the cardiac cycle (Barzilai et al 1990) including ischaemia or infarction (Sagar et al 1987). Other uses of ultrasonic

backscatter have been to characterise the echogenicity of intracardiac thrombus formation in blood, the morphology of blood clots and red blood cell aggregates in vitro (Shung et al 1986, McPherson et al 1988, Yuan et al 1988). De Kroon et al (1991) used off-line videodensitometry to show increased red blood cell echogenicity with decreasing flow rates and to assess the cyclic changes of SEC in the iliac artery. The present study is the first to quantify LA SEC intensity in vivo using integrated backscatter.

Intensity of SEC

We demonstrated that the integrated backscatter intensity of the LA cavity in the severe SEC subgroup was 12.0 dB higher or 15.4 times (power ratio; Appendix 1) greater than that in the LV cavity. whereas the integrated backscatter intensity of the LA cavity in the mild-SEC subgroup was 4.9 dB higher or 2.9 times (power ratio) greater than the intensity of the LV cavity. In contrast there was no appreciable difference between the intensity from the LA cavity and the intensity from the LV cavity in the no SEC subgroup. The relative intensity of the LA cavity compared to the LV cavity may be an indicator of the severity of LA SEC and may have important clinical applications.

Recognising the clinical utility of defining specific numerical cutoff points to discriminate between the SEC subgroups, we observed that an approximate cutoff of 14 dB could distinguish between severe SEC and no SEC, but there was significant overlap between no SEC and mild SEC and between mild and severe SEC subgroups in this limited study population. With a 19% prevalence of LA SEC during TEE for various clinical indications (Black et al 1991a) and a 95% confidence interval, a study of 350 patients would provide adequate power to provide definitive numeric cutoff points between the qualitative grades.

The LA SEC temporal pattern

To quantify the visually observed swirling pattern of LA SEC, we performed Fourier analysis of the temporal integrated backscatter sequences. Fourier transformation

of LA SEC intensity sequences showed a distinctive low frequency spectrum that differed from the random high frequency spectra produced by the sequences from the LA cavities from the patients of the no SEC subgroup. We consider these unique low-frequency spectral characteristics to represent the described temporal variability observed with swirling pattern of LA SEC as it enters and exits the sample region of interest.

Mechanism of increased backscatter of LA SEC

The increased backscattered energy emanating from the LA SEC results from the interaction of ultrasound with the principal determinants of LA SEC: red blood cell aggregates and the presence of macromolecules including fibrinogen. It has been shown in vivo and in vitro that the blood echogenicity depends on shear rates, with aggregation of red blood cells occurring at low shear rates (Yuan et al 1988, Sigel et al 1982). Fibrinogen facilitates the intercellular bridging of red blood cells by reducing the electrostatic repulsion of the sialic acid residues on the membrane of the red blood cell, thus acting as the "glue" keeping the red blood cells together (Black et al 1993). Thus, the increased amplitude of backscatter results from these large networks of red cell aggregates (red cell diameter 7 μm) in the presence of low shear rates and fibrinogen macromolecules (Black et al 1993, Fatkin et al 1994, Sigel et al 1983, Merino et al 1992, Goldman et al 1995).

Relationship between integrated backscatter intensity and clinical/ echocardiographic variables

We found higher LA cavity integrated backscatter intensities in patients with LA cavity or LA appendage thrombi as well as in patients with AF. Furthermore, these quantitative measures were significantly related to lower LA appendage peak velocities and increasing LA size. This suggests that integrated backscatter intensities may be a significant marker for thromboembolism. A larger series with adequate study power would be required to address the relationship between integrated backscatter and subsequent embolic events and mortality.

155

Influence of technical variables

The ability of integrated backscatter intensity to discriminate among the three qualitative grades of LA SEC was retained despite minor effects by altering transmit power and time-gain-compensation setting. The technical variables had little effect on the discriminating result of this model because of the use of an internal reference standards (interatrial septum intensity at ~40 dB) within the linear dynamic range of the system (Douglas et al 1994).

Integrated backscatter compared with conventional videodensitometry and qualitative grade

Integrated backscatter has the advantage of being acquired in an on-line digital format before scan conversion and postprocessing, with a broad dynamic range displayed in decibels. In contrast, conventional videodensitometry is typically measured off line from a video image of poorer quality with a reduced dynamic range. Furthermore, videodensitometry is affected by nonlinear system transformations including the influence of log compression and postprocessing and thus would be affected by the different settings in commercially available echo machines (HP Acoustic Densitometry 1994, Wells 1977). On the other hand, integrated backscatter is now recently commercially available, and the monitor image is visually distinctive with a smoothed image with reduced speckle (Perez et al 1992). Integrated backscatter has the advantage over the "eyeball" qualitative grading of LA SEC because of significant interobserver variability of qualitative grading (kappa value = 0.65) (Kronik et al 1995). Excessive gain may artificially enhance white noise artifact, whereas low gain may decrease the likelihood of detecting LA SEC. In contrast, the interobserver variability in the quantitative assessment of LA SEC by experienced technicians is approximately 4%.

Integrated backscatter using the acoustic densitometry system is relatively simple to use with a total setup, calibration and acquisition time of less than 2 min. Furthermore, analysis can be conducted on line or digitally saved to an optical disk for later analysis. The ease of acquisition and analysis would make this system

156

and method feasible to use in clinical practice to quantify SEC and stratify risk.

Study limitations

There are several limitations to the study. This report represents only an initial investigation on quantitation of SEC, which has been graded qualitatively in the past. A comparison between integrated backscatter quantitative measures is limited because of the lack of an adequate gold standard to assess SEC severity. Interobserver variability of qualitative assessment was not performed in the present study.

Another possible limitation is that integrated backscatter measures of SEC may be affected by attenuation. However, because the region of interest was usually placed at the same depth as the interatrial septum (within 1 to 2 cm), the relative loss in integrated backscatter intensity resulting from attenuation was negligible. The TEE examination also avoids an attenuation problem because the sonification path is through blood rather than tissue. Blood attenuation is one order of magnitude less (1/10) than that of tissue (0.7 to 1.0 dB/MHz per cm), and we estimate that the 1-2 cm maximal difference (in depth) between the interatrial septal and LA measurements amounts to less than 0.5 dB attenuation. However, LA SEC itself may increase the attenuation of blood if LA SEC is severe. Yuan and Shung (1988) have shown a modest species-specific increase in attenuation when blood is under conditions that favour the aggregation of red blood cells such as low shear rates and high fibrinogen concentration or high haematocrit. If attenuation of blood increases with the severity of LA SEC, the LV/LA power ratio may be modestly exaggerated in the mild and severe LA SEC subgroups. Further studies are needed to determine the attenuation properties of human blood with LA SEC.

Calibration may be a limitation (Shiba et al 1991). We used the interatrial septum (the brightest region) for calibration, and this internal reference has never been used before. However, the interatrial septum is typically the most intense structure in the near field by TEE and is adjacent to the LA cavity and thus the best internal

157

reference. Studies are needed to ensure the uniformity of backscattering of the interatrial septum between patients and the uniformity of the backscatter signal at different locations in the same patient. Also, confounding diseases such as lipomatous hypertrophy or infiltrative disease may have an effect on the backscatter properties of the interatrial septum. In this study, none of the patients had lipomatous hypertrophy or interatrial septal aneurysms. We also meticulously ensured that the backscatter measurements were within the dynamic range of the measurement system (0 - 44 dB) by calibration before the digital acquisitions.

Finally, we obtained integrated backscatter of the LA cavity but not of the LA appendage. The LA appendage SEC may be more important for thrombi and embolic potential than the LA cavity, and LA appendage digital acquisitions that include the interatrial septum (internal standard) and LA appendage are indeed possible (Figure 6).

Clinical implications

The ability to quantify the degree of LA SEC has important clinical implications. Previous investigation has demonstrated the close association between the presence of LA SEC and LA thrombi and embolism, with patients with severe LA SEC showing a stronger association than those with mild LA SEC (Daniel et al 1988). Integrated backscatter quantitative indices of LA SEC may now potentially provide a better predictor of thromboembolic risk compared to simple qualitative measurements, which may be difficult to distinguish from artifact. A larger trial is needed to prospectively assess the utility of these measurements of LA SEC as predictors of subsequent events and to risk-stratify patients who should best be given anticoagulant drugs. The relative ease and rapid acquisition of digital data would make this an ideal objective method to quantify LA SEC in clinical trials and subsequent clinical practice. Recommendations for routine clinical use must however await future studies regarding the clinical relevance and cost effectiveness of objective measurement of LA SEC.

CONCLUSIONS

A quantitative measure of LA SEC using integrated backscatter can be acquired by TEE using the interatrial septum for calibration of the backscatter intensity. We have shown that the integrated backscatter quantitative measure of LA SEC correlates well with an independent qualitative assessment of LA SEC and with other clinical and echocardiographic indicators of thromboembolic risk. Fourier frequency analysis of LA SEC shows that the swirling pattern or temporal variability of SEC has a distinct frequency pattern, clearly distinguished from the random frequency spectrum of blood in the absence of SEC.

Appendix 1 - Integrated backscatter voltage and power ratios

Differences between the LA cavity SEC values and the LV cavity values in decibels were converted to a voltage ratio (equation 1). A LA/LV power ratio was derived by squaring the voltage ratio (equation 2). The LA/LV power ratios and V_{LA}/V_{LV} voltage ratios were computed as follows:

$$LA_{(dB)} - LV_{(dB)} = 20 \log(V_{LA}/V_{LV}) = 10 \log(V_{LA}/V_{LV})^2 \qquad [1]$$

$$LA/LV \text{ power ratio} = (V_{LA}/V_{LV})^2 \qquad [2]$$

Where $LA_{(dB)}$ = image intensity of LA in decibels, $LV_{(dB)}$ = image intensity of LV in decibels V_{LA} = LA voltage, and $V_{LV}=$ LV voltage.

Hence, the LA/LV power ratio evaluates the antilog of the difference between the measured decibel intensity between the LA and LV, divided by 10.

Appendix 2 - Fourier analysis

Fourier transformation of 60 intensity values at 30 Hz yielded a Nyquist limit of 15 Hz and the integrals from 0 and 15 Hz with a 0.5 Hz resolution. Suppressing the 0 Hz component (mean intensity) and squaring the Fourier amplitude components yielded the power spectrum $\rho(f)$ from which the mean or centroid frequency (f_c) was calculated as

$$f_c = \frac{\displaystyle\int_{0.5}^{15} f\, \rho(f)\, df}{\displaystyle\int_{0.5}^{15} \rho(f)\, df}$$

where f = frequency, $\rho(f)$ = power at frequency f, and df = difference between two discrete frequencies, 0.5 Hz.

CHAPTER 6

Resolution of Left Atrial Spontaneous Echo Contrast Following Percutaneous Mitral Valvuloplasty: Implications for Thromboembolic Risk

ABSTRACT

Background and Objectives. LA SEC is a marker of increased thromboembolic risk in patients with mitral stenosis. This prospective study evaluated the effect of percutaneous transeptal mitral valvuloplasty (PTMV) on LA SEC.

Methods. TEE was performed 1 day before and 3 months after PTMV on 88 patients with mitral stenosis.

Results. LA SEC was present in 65 patients (74%) before PTMV and was associated with absence of moderate or severe mitral regurgitation (p=0.01), smaller valve area (p=0.02), older age (p=0.04) and AF (p=0.05). PTMV resulted in a mean absolute and relative increase in valve area measured at 3 months of 0.54 ± 0.36 cm^2 and $53 \pm 43\%$ respectively. LA SEC resolved in 37 patients but persisted in 28 patients (32%) at the 3 month study. The absolute and relative increase of valve area and worsened mitral regurgitation after PTMV were predictors of resolution of LA SEC with the relative increase in valve area being the only significant predictor on multivariate analysis.

Conclusions. PTMV frequently results in resolution of LA SEC, which may have important implications in reducing the thromboembolic risk in these patients.

INTRODUCTION

LA SEC is frequently seen by TEE in mitral stenosis and other conditions favouring LA stasis (Black et al 1991a, Daniel et al 1988, Beppu et al 1985, Castello et al 1990), and is an independent predictor of increased thromboembolic risk in patients with mitral stenosis (Black et al 1991a, Daniel et al 1988).

Percutaneous transeptal mitral valvuloplasty (PTMV) is increasingly used as an alternative to surgery in the management of patients with symptomatic mitral stenosis with good short term and midterm outcome (Vahanian et al 1991). The effect of PTMV on LA SEC and hence the thromboembolic risk in patients with mitral stenosis is unclear. The aim of the present study was to prospectively examine the effect of PTMV on LA SEC and identify factors which determine the resolution of LA SEC with PTMV.

METHODS

Study patients

The study population comprised 88 consecutive patients with rheumatic mitral stenosis who underwent PTMV and had TEE before and after the procedure. Twenty-three patients were reported in part previously (Black et al 1991b).

Echocardiography

All patients underwent TTE and TEE 1 day before PTMV. Repeat TTE study was performed 24 to 48 hours after the procedure and follow up TTE and TEE studies were performed 3 months later. TTE studies were performed using a 2.5 MHz and a 3.5 MHz phased array transducers with a Hewlett Packard Sonos 1000 system (Hewlett Packard, Andover, Massachusetts) from all standard echocardiographic windows. LA dimension was determined by standard M mode criteria (Sahn et al 1978). The mean diastolic gradient across the mitral valve was measured by continuous wave Doppler (1.9 MHz transducer) and the mitral valve area was

determined using the Doppler pressure half-time method (Hatle et al 1979). The average of 3 heart beats and 5 heart beats were taken for patients in sinus rhythm and AF respectively. Mitral regurgitation was graded semiquantitatively by colour and continuous wave Doppler as trivial, mild, moderate or severe (Helmcke et al 1987). The morphology of the mitral valve leaflets and subvalvular apparatus were scored according to a previously described scoring system (Wilkins et al 1988). The results of PTMV was assessed echocardiographically by measuring the relative and absolute increase in the mitral valve area at 3 months. The relative increase in the mitral valve area was defined as ratio of the increase in mitral valve area following valvuloplasty to the initial valve area. The absolute increase was defined as the difference in mitral valve area before and after the procedure. PTMV was considered successful if it resulted in a relative increase in mitral valve area of $\geq$ 25% and a final mitral area of $\geq$ 1.5 cm^2 (Abascal et al 1990).

TEE was performed with 5 MHz transducer according to standard protocols (Seward et al 1988, 1990). All patients were examined in the fasting state after intravenous sedation with fentanyl and midazolam and topical anaesthesia with 10% xylocaine spray. Informed consent was obtained on all patients. There were no complications. The presence of LA SEC was specifically examined. LA SEC was diagnosed offline by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artefact (Black et al 1991a). LA SEC, if present, was graded as mild or severe (Beppu et al 1985). The presence and intensity of LA SEC was determined by two independent experienced observers. Any discrepancy was resolved by consensus. All echocardiographic studies were recorded on VHS videotapes and reviewed at random by 2 experienced echocardiographers who were blinded to the clinical history of the patients, the results of the PTMV and the order of the echocardiographic studies.

Percutaneous transeptal mitral valvuloplasty

Left and right heart catheterisation was performed via the right and left femoral

approach. Transeptal catheterisation was performed via the right femoral approach. Cardiac output was determined with the thermodilution method before transeptal puncture and after dilatation before removal of transeptal catheters. A double balloon technique (McCredie et al 1990) was utilised in the initial 7 patients and the single Inoue balloon method was used in the remaining 81 patients (Inoue et al 1984).

Statistical Analysis

All values were reported as mean ± 1 SD unless otherwise stated. The paired or unpaired Student's t test was used to compare continuous variables and Chi Square test to compare categorical variables. The Mann-Whitney test was used to compare ranked categories. Multivariate logistic regression analysis was used to identify independent predictors of the presence of LA SEC at baseline and of resolution of LA SEC with PTMV. Odds ratios are shown with 95% confidence intervals and statistical significance was defined as a two tailed p value of < 0.05.

RESULTS

Baseline clinical and echocardiographic findings

There were 77 females and 11 males with a mean age of 53 ± 13 years (range 22-78). All patients had symptomatic mitral stenosis without evidence of LA thrombus on TEE. Forty two patients (48%) were in stable sinus rhythm, 40 patients (45%) were in chronic AF and 6 patients (7%) had paroxysmal AF. Twelve patients (14%) had history of thromboembolism. This comprised 10 patients with cerebral embolism, 1 with femoral embolism and another with brachial embolism. Three patients were pregnant at the time of the PTMV. Eight patients had previously undergone surgical valvotomy including 1 patient who had 2 previous surgical valvotomies and 1 PTMV. Eight patients (9%) were in NYHA functional class II, 71 (81%) in functional class III and 9 (10%) in functional class IV.

LA SEC was present before PTMV in 65 patients (74%), mild in 44 patients and severe in 21 patients. Mitral regurgitation was mild in 31 patients (35%) and moderate in 4 (4.5%). Fifty three patients (60%) had trivial or no mitral regurgitation. The clinical, haemodynamic and echocardiographic variables of patients in relation to the presence or absence of LA SEC are listed in Table 1. The presence of LA SEC at baseline was associated with AF (p=0.05), an older patient age (p=0.04), a smaller mitral valve area (p=0.02) and absence of moderate or severe mitral regurgitation (p=0.01). Multivariate analysis showed that the absence of moderate or severe mitral regurgitation (p=0.006), a smaller mitral valve area (p=0.01) and an older age group (p=0.03) were significant independent predictors of the presence of LA SEC at baseline.

Mitral valvuloplasty

PTMV resulted in an increase in the echocardiographic mitral valve area from 1.2 $\pm$ 0.3 cm^2 to 1.7 $\pm$ 0.4 cm^2 (p<0.001) and a decrease in mean diastolic transmitral gradient from 9.5 $\pm$ 4 to 5.8 $\pm$ 2.6 mmHg (p<0.001) after the procedure. The results were maintained at 3 months with a mean mitral valve area of 1.7 $\pm$ 0.4 cm^2 and a mean gradient of 5.9 $\pm$ 2.7 mmHg. The mean absolute and relative increase in mitral valve area 3 months following valvuloplasty was 0.54 $\pm$ 0.36 cm^2 and 53 $\pm$ 43% respectively. The LA dimension decreased from a mean of 53 $\pm$ 7 mm before valvuloplasty to 52 $\pm$ 7 mm 3 months afterwards (p = 0.02). There were no significant differences in the mean mitral valve area, the mean gradient and the LA dimension between the two TTE studies performed after PTMV. There was a significant increase in cardiac index measured at cardiac catheterisation with PTMV from 2.3 $\pm$ 0.5 l/min/m^2 to 2.6 $\pm$ 0.7 l/min/m^2 (p<0.001). PTMV was considered successful in 51 patients (58%) according to the predefined echocardiographic criteria. Mitral regurgitation worsened by $\geq$ 1 grade in 37 patients (42%). After PTMV, 50 patients (57%) had mild and 13 (15%) had moderate mitral regurgitation. Two patients developed severe mitral regurgitation which required early mitral valve replacement. Follow up studies were complete at 3 months in the 86 medically treated patients. Sixty one patients (71%) were in

New York Heart Association functional class I, 19 (22%) in functional class II and 6 (7%) in functional class III (p<0.001).

Effects of mitral valvuloplasty on LA SEC

The effects of PTMV on LA SEC are shown in the Figure. LA SEC was present 3 months after PTMV in 28 patients (32%), mild in 23 patients and severe in 5 (p<0.001). LA SEC resolved after PTMV in 37 patients. Of the 28 patients with persistent LA SEC, the intensity decreased from severe to mild in 9 patients and remained unchanged in 19 patients. No patient had new or increased LA SEC following valvuloplasty.

The effect of PTMV on LA SEC in relation to the clinical, echocardiographic and haemodynamic variables of patients are shown in table 2. Patients whose LA SEC resolved had a significantly larger absolute and relative increase in mitral valve area (p=0.002) and a smaller postdilatation LA size(p=0.01) compared to patients with persistent LA SEC after valvuloplasty. In addition, the PTMV was considered successful in more of the patients whose LA SEC resolved (p=0.02) and the prevalence of moderate or severe mitral regurgitation following PTMV was also higher in these patients (p=0.04). There were no differences in the prevalence of AF, age, postdilatation mitral valve area, mean transmitral gradient, mitral valve score and cardiac index between the two groups of patients. Multivariate analysis showed that only the relative increase in mitral valve area with PTMV was predictive of resolution of LA SEC (p = 0.002, odds ratio 8.5, 95% CI 2.2 - 33.8).

When the combined end point of resolution or decrease in severity of LA SEC was analysed, the relative increase in mitral valve area (p = 0.01), the absolute increase in valve area (p = 0.015) and worsened mitral regurgitation (p = 0.04) following PTMV were significant predictors on univariate analysis. The relative increase in mitral valve area was the only significant predictor on multivariate analysis (p = 0.018, odds ratio 4.4, 95% CI 1.3 - 15).

168

Before PTMV **After PTMV**

Severe SEC   21 →5→ 5

                9
                7

Mild SEC   44 →14→ 23

                30

No SEC   23 →23→ 60
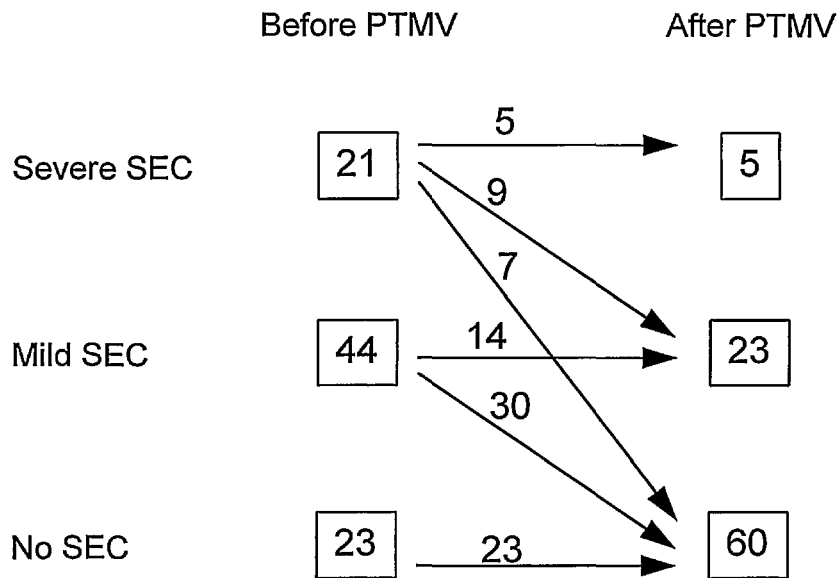
Figure. Effect of Percutaneous Transseptal Mitral Valvuloplasty (PTMV) on Left Atrial Spontaneous Echo Contrast (SEC).

Table 1. Characteristics Related to LA SEC Before PTMV.

	SEC + (n=65)	SEC - (n=23)	p
Moderate or severe MR	2 (1.5%)	2 (8.7%)	0.01
Mitral Valve Area (cm^2)	1.1 ± 0.3	1.3 ± 0.3	0.02
Age (years)	54 ± 12	48 ± 13	0.04
AF	38(58%)	8(35%)	0.05
Female Gender	56(86%)	21(91%)	NS
NYHA Functional Class	3 ± 0.4	2.9 ± 0.4	NS
LA Size (mm)	54 ± 7	51 ± 6	NS
Mean Echo Gradient (mmHg)	9.7 ± 4	8.9 ± 4	NS
Mitral valve score	8 ± 1.6	7.5 ± 1.4	NS
Cardiac index (l/min/m^2)	2.27 ± 0.5	2.42 ± 0.6	NS

MR = Mitral regurgitation, NYHA = New York Heart Association

Table 2. Clinical, Echocardiographic and Haemodynamic Variables in Relation to the Effect of PTMV on LA SEC.

	SEC Resolved (n=37)	SEC Persisted (n=28)	p
Relative increase in MVA	73 ± 50%	40 ± 30%	0.002
Absolute increase in MVA(cm^2)	0.7 ± 0.4	0.4 ± 0.3	0.002
Successful PTMV n(%)	28 (76%)	13 (46%)	0.02
Post-PTMV LA size (mm)	50 ± 7	54 ± 5	0.01
≥Moderate MR post-PTMV	8 (22%)	1 (4%)	0.04
AF	18 (49%)	20 (71%)	0.06
Age	52 ± 13	58 ± 10	NS
Post-PTMV MVA (cm^2)	1.7 ± 0.4	1.6 ± 0.3	NS
Post-PTMV transmitral gradient (mmHg)	5.5 ± 2.5	5.7 ± 2.3	NS
Mitral valve score	7.8 ± 1.5	8.3 ± 1.8	NS
Post-PTMV Cardiac index (l/min/m^2)	2.6 ± 0.7	2.6 ± 0.9	NS

MR = mitral regurgitation, MVA = Mitral valve area.

DISCUSSION

The present study prospectively examined the effect of percutaneous transeptal PTMV on LA SEC in a large series of patients. The prevalence of LA SEC decreased from 74% before valvuloplasty to 32% three months afterwards. This study showed that the absolute or relative increase in mitral valve area and a successful outcome defined previously (Abascal et al 1990) as measures of the effectiveness of valvuloplasty were predictors of the resolution of LA SEC.

LA SEC before and after mitral valvuloplasty

The presence of LA SEC in patients with mitral stenosis is associated with a more severe disease (Black et al 1991a, Daniel et al 1988, Beppu et al 1985, Cormier et al 1993). Using TTE, Beppu et al (1985) studied 116 patients with mitral stenosis of whom 99 (85%) were in AF. Thirty seven patients (32%) were found to have LA SEC. A lower cardiac output, larger LA size and smaller mitral valve area were associated with the presence of LA SEC. Daniel et al (1988) using TEE, reported a 67.3% prevalence of LA SEC in 52 patients with predominant mitral stenosis. Patients with LA SEC had significant larger LA size. However, haemodynamic data was available in only 21 of the 52 patients and there was no significant difference in cardiac index, mean diastolic transmitral gradient and angiographic mitral valve area between the two groups. In a more recent series of 82 patients by Cormier et al (1993) LA SEC was detected in 53 patients (65%) at baseline and was associated with AF, larger LA dimension, lower cardiac index, older patient age and smaller mitral valve area. The present study results are consistent with these data with smaller mitral valve area, older age group, absence of moderate or severe mitral regurgitation and AF being significantly associated with the presence of LA SEC before valvuloplasty. The findings of the present study are also consistent with the reduction in markers of coagulation activity reported after PTMV (Yamamoto et al 1997).

With the exceptions of mitral valve replacement (Beppu et al 1985, Voci et al 1991)

and cardioversion of atrial fibrillation (Grimm et al 1993), PTMV is the only intervention that has been shown to affect LA SEC. Only 28 of the 88 patients (32%) had LA SEC present 3 months after valvuloplasty. This compares with the series by Cormier et al (1993) in which the prevalence of LA SEC decreased from 65% to 50% immediately after PTMV and to 27% 6 months later. LA SEC is a stable phenomenon over time in patients with mitral stenosis (Peverill 1997), suggesting that day to day variability does not explain the results of the present study.

Determinants of resolution of LA SEC

One other large series has examined the incidence and determinants of resolution of LA SEC following PTMV. Cormier et al (1993) found that sinus rhythm was the only independent predictor of disappearance of LA SEC 6 months after PTMV in all patients. In patients with AF, the development of severe mitral regurgitation following valvuloplasty was associated with disappearance of LA SEC. In the present series, sinus rhythm was not a significant predictor on either univariate or multivariate analysis. This discrepancy may in part be explained by the higher proportion of Cormier's patients being in stable sinus rhythm (72% vs 47%). The present study also confirmed that moderate or severe mitral regurgitation after valvuloplasty was associated with resolution of LA SEC. Although the presence of LA SEC at baseline is associated with a smaller mitral valve area, the postdilatation mitral valve area at 3 months was not a predictor of resolution of LA SEC. In Cormier's series, the final mitral valve area postdilatation was also not a predictor of resolution of LA SEC. However, the absolute or relative increase in the mitral valve area were not examined as possible predictors.

The fact that the relative increase in mitral valve area was the only predictor on multivariate analysis is perhaps not surprising given the relationship between the mitral valve area and the transmitral gradient. According to the Gorlin equation, the mitral valve area at a given cardiac output is related to the pressure gradient in an inverse square manner. Thus the haemodynamic benefit of a given absolute

173

increase in the mitral valve area with valvuloplasty is much greater at a smaller initial valve area. This is reflected by a significantly higher likelihood of LA SEC resolving following PTMV with a higher relative increase in the mitral valve area.

Limitations

Assessment of LA SEC on TEE is qualitative and careful adjustment in gain settings is needed in differentiating mild LA SEC from background white noise. In the present study, instrument settings were carefully adjusted and individualised to optimise image quality and 2 experienced echocardiographers, through common consensus, decided on the presence and absence and the grading of LA SEC. Parameters of haemodynamic significance such as the shear rate in the LA and factors of haematological significance such as fibrinogen level and haematocrit were not measured in the study.

Clinical implications

Thromboembolism is an important cause of morbidity and mortality in patients with rheumatic mitral stenosis (Casella et al 1964, Neilson et al 1978, Easton et al 1980). Surgical valvotomy has been reported to decrease the incidence of systemic embolism in patients with mitral stenosis in some reports (Greenwood et al 1963) but not others (Deverall et al 1968, Coulshed et al 1970). However, little data is available regarding the effect of PTMV on the subsequent thromboembolic risk in these patients. LA SEC, with its strong association with LA thrombi or a history of arterial thromboembolism or both in patients with mitral valve disease, (Black et al 1991a, Daniel et al 1988, Hwang et al 1992) has been suggested as an indicator of increased thromboembolic risk in these patients (Black et al 1991a, Daniel et al 1988). The present study has shown that PTMV can have favourable effects on LA SEC which may have important implications in reducing the thromboembolic risk in these patients. This potential benefit of PTMV contrasts with the increased thromboembolic risk of prosthetic mitral valve replacement. This study is also the first to suggest that the degree of the relief of obstruction by PTMV is an important determinant of its favourable effects on LA SEC and hence

the thromboembolic risk in these patients.

Significant mitral regurgitation has been found to be protective against the formation of LA SEC (Black et al 1991a, Beppu et al 1985, Movsowitz et al 1993) and, in Cormier's series (1993), development of severe mitral regurgitation was predictive of resolution of LA SEC in patients with AF. Movsowitz et al (1993) reported a trend towards a lower prevalence of stroke or transient ischaemic attack in patients with significant mitral regurgitation. The present study has also shown that worsened mitral regurgitation following PTMV was associated with resolution of LA SEC. This finding may suggest that some degree of worsening of mitral regurgitation with PTMV, although potentially deleterious from a haemodynamic point of view, may actually be beneficial in terms of reducing the thromboembolic risk.

LA SEC persisted after PTMV in a significant proportion of the patients. Patients with indications for warfarin prior to PTMV may continue to require warfarin after the procedure, especially when the haemodynamic response to PTMV is suboptimal.

CONCLUSIONS

Although the haemodynamic benefits of PTMV are well established, the implications of the procedure for thromboembolic risk has remained unclear. This prospective study demonstrates that LA SEC, a principal determinant of thromboembolic risk in mitral stenosis, frequently resolves after successful valvuloplasty. These findings suggest that haemodynamic benefits of the procedure may be accompanied by a reduction in thromboembolic risk. In addition to symptomatic relief, reduction of thromboembolic risk in patients with mitral stenosis may be an additional indication for PTMV.

PART 3

Left Atrial Thrombus

CHAPTER 7

Determinants of Left Atrial Thrombus Location and Mobility

ABSTRACT

Background and Objectives. Although LA thrombi may occur in either the LA cavity or appendage, determinants of their location and mobility are not known. This study assessed the determinants of LA thrombus location and mobility in patients undergoing TEE.

Methods. 193 patients with thrombus in either the LA cavity or appendage were identified from a series of 10,767 TEE studies, with analysis of clinical and echocardiographic variables.

Results. Seventy-six percent of the thrombi were located in the appendage. Ninety-eight percent of patients had typical risk factors for thrombosis including AF (91%), mitral stenosis or prosthesis (56%), or LV systolic dysfunction (26%). By univariate analysis, LA cavity thrombus was associated with mitral stenosis or prosthesis (p=0.00004), greater LA dilatation (p=0.00003), and larger thrombus size (p=0.00001). LA appendage thrombus was associated with nonvalvular AF (p=0.0002), previous embolism (p=0.01) and LV dysfunction (p=0.048). By multivariate analysis, LA cavity thrombus was predicted by larger LA dimension (odds ratio = 1.75 for 1 cm increment, p=0.008) and LA appendage thrombus was predicted by a history of embolism (odds ratio = 2.3, p=0.03). Mobile LA thrombus, in 21% of patients, was associated by univariate analysis with previous embolism (p=0.02), location in the appendage (p=0.059), nonvalvular AF (p=0.005) and the absence of mitral valve disease.

Conclusions. LA thrombus location and mobility are dependent on the associated cardiac disease.

178

INTRODUCTION

LA thrombi are a major cause of stroke and systemic embolism, particularly in patients with AF (Cairns and Connolly 1991) or mitral stenosis (Daley et al 1951, Jordan et al 1951, Wallach et al 1953, Ellis and Harken 1961, Szekely 1964, Aberg 1969, Coulshed et al 1970, Hinton et al 1977, Wolf et al 1978, Davison and Greenland 1991). LA thrombi may occur in either the LA cavity or appendage, with potentially different pathophysiologic and clinical implications. It has long been known from surgical series (Wallach et al 1953, Nicols et al 1962) that LA thrombi in patients with mitral valve disease occur with similar frequency in the LA cavity and LA appendage. However, the factors determining thrombus location in mitral stenosis are not known. In addition, the distribution and determinants of LA thrombus location in other conditions, including nonvalvular AF, have not been defined. TEE enables accurate detection of LA cavity and appendage thrombus (Aschenberg et al 1986, Bleifeld et al 1986, Matsumura et al 1989, Acar et al 1991, Hwang et al 1992, Lin et al 1992, Olson et al 1992, Manning et al 1995, Fatkin et al 1996) in both surgical and non-surgical patients. TEE also enables in vivo assessment of the mobility of LA thrombus, a potential marker of increased embolic risk. The purpose of this study therefore was to examine clinical and echocardiographic determinants of LA thrombus location and mobility in a very large series of patients undergoing TEE.

METHODS

Patients

Patients were identified from a computer database in which all echocardiographic findings including LA thrombus were specifically coded. From 10,767 consecutive TEE studies in 8,675 patients, 193 patients (2.2%) with isolated LA cavity or appendage thrombus were identified. Patients with both cavity and appendage thrombi, or with thrombus attached to a mitral prosthesis, were excluded. The LA

cavity and appendage were routinely inspected for thrombus as part of the standard TEE examination (Seward et al 1988, Seward et al 1990, Seward et al 1993). TEE probes used were single plane in 75 pts (39%), biplane in 61 (32%), and multiplane in 57 (29%).

Clinical data were derived from the database and from chart review, and included demographic data, study indication, presence of chronic or paroxysmal AF, duration of AF, anticoagulant therapy, history of embolism, and surgical findings. Due to the difficulty in assessing mechanism of stroke (Humphrey and Harrison 1985, Ramirez-Lassepas et al 1987), embolism was broadly defined to include all ischaemic stroke, transient ischaemic attack or systemic embolism. The duration of AF could not be determined in 10 patients. Nonvalvular AF was defined as chronic or paroxysmal AF in the absence of mitral stenosis or a mitral valve prosthesis.

TTE and TEE data were determined from the computerised database. In addition, the presence, location, size and mobility of LA thrombus, and the presence of LA SEC, were determined by review of the original videotapes. LA thrombus was diagnosed by the presence of a clearly defined echodense intracavitary mass, acoustically distinct from underlying endocardium and not due to the pectinate muscles of the LA appendage (Beppu et al 1984). The junction of the LA cavity and appendage was defined as a line from the tip of the limbus separating the LA appendage and the left upper pulmonary vein to the opposing wall at the mouth of the appendage. Thrombus mobility was defined as motion independent of the underlying atrial wall. The size of the thrombus was assessed by freezing the videotape frame showing the largest thrombus size and calculating the maximal two-dimensional area of the thrombus using the internal echocardiographic system software. LA SEC was by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artefact (Black et al 1991a). TTE studies were performed within 1 month prior to TEE in 191 patients. LA dimension was determined from TTE (Sahn et al 1978) in 177

patients. Significant LV dysfunction was defined as moderate or severe overall systolic dysfunction assessed during TEE. Significant mitral regurgitation was defined as moderate or severe mitral regurgitation assessed by colour flow mapping (Helmcke et al 1987, Yoshida et al 1990, Castello et al 1992, Enriquez-Sarano et al 1993) during TEE. Mitral valve area was determined by the Doppler half-time method (Hatle et al 1979). The mean mitral gradient was determined by continuous wave Doppler. Mitral stenosis was defined by the presence of typical echocardiographic features (Vaziri et al 1994). All 74 patients with mitral stenosis had a mitral valve area ≤ 2.5 cm^2, and 71 of these 74 patients had a mitral valve area ≤ 2.0 cm^2.

Data Analysis

The chi-square test or Fisher's exact test were used to compare categorical variables. Student's t test was used to compare continuous variables. Multivariate logistic regression analysis was used to assess the independent predictors of LA thrombus location. Statistical significance was defined as two-tailed $p < 0.05$, and values are reported as mean $\pm$ SD.

RESULTS

General

One hundred ninety three patients with thrombus in the LA cavity (n=46, 24%) or LA appendage (n=147, 76%) were identified by TEE. These included 1 patient with a ball thrombus in the LA cavity, reported in detail in Chapter 8. The 193 patients comprised 102 women and 91 men, aged 64.4 $\pm$ 12.0 years, range 29-87 years. TTE in 176 patients had detected 17/40 (42%) of the LA cavity thrombi compared to only 3/136 (2%) of the LA appendage thrombi (p<0.0001). Previous embolism had occurred in 90 (47%) of the patients, including events within 1 month prior to TEE in 62 (32%) of the patients. Forty-six patients (26%) underwent cardiac surgery following TEE with inspection of the LA. The presence of LA thrombus was

confirmed in all 21 patients with cavity thrombus, and 21 of 25 patients with appendage thrombus. The overall positive predictive value of TEE for LA thrombus compared to surgical findings was therefore 91%.

Risk factors for thrombus

Of the 193 patients, 189 (98%) patients had typical risk factors for thrombosis including AF (n=176, 91%), native mitral stenosis (n=74, 38%), a mitral prosthesis (n=35, 18%), or LV systolic dysfunction (n=51, 26%). The duration of AF was 3 days-32 years. Only 6 patients had LV systolic dysfunction as the only risk factor. The 4 patients without these risk factors comprised 3 patients with diastolic dysfunction due to constrictive pericarditis or restrictive cardiomyopathy and 1 patient with an apparently normal heart.

The LA appendage was the predominant site of thrombus in patients with each of the major risk factors. In the 74 patients with nonvalvular AF, 67 (91%) had LA appendage thrombus. In 109 patients with mitral stenosis or prosthesis, the predominance of appendage thrombus was less marked, occurring in 71 (65%) of the patients (p=0.00009 compared to nonvalvular AF). Conversely, 38 (83%) of the 46 LA cavity thrombi were associated with mitral stenosis or prosthesis. Thrombus was located in the appendage in 44 (86%) of the 51 patients with LV systolic dysfunction (p=NS compared to nonvalvular AF).

Predictors of thrombus location

Table 1 summarises clinical and echocardiographic variables related to the location of LA thrombus. Compared to patients with LA cavity thrombus, patients with LA appendage thrombus had significantly *increased* prevalence of nonvalvular AF (p=0.0002), previous embolism (p=0.01), recent embolism (p=0.005), male gender (p=0.003), and LV dysfunction (p=0.048); and significantly *smaller* LA dimension (p=0.00003), smaller thrombus size (p=0.00001) and decreased prevalence of mitral prosthesis (p=0.004) or mitral stenosis or prosthesis (p=0.00004). Mobile thrombus tended to be more common in patients

with LA appendage thrombus (p=0.059).

Multivariate analysis was performed to determine independent predictors of LA thrombus location, with gender, previous embolism, mitral stenosis or prosthesis, nonvalvular AF, LA dimension and LV dysfunction as variables. LA cavity thrombus was independently predicted by increased LA dimension (p=0.008, odds ratio 1.75 for 1 cm increment, 95% CI 1.2-2.6) while LA appendage thrombus was predicted by a history of embolism (p=0.03, odds ratio = 2.3, 95% CI 1.06-5.1).

Mitral valve disease

In patients with mitral stenosis or prosthesis, patients with cavity thrombus (38/109, 35%) had larger LA diameter (62 ±13 mm vs 56± 10 mm, p=0.01), larger mitral valve gradient (11.2±6.6 vs 8.2± 4.5 mm Hg, p=0.01), and trend to smaller mitral valve area (1.25± 0.7 cm^2 vs 1.52 ± 0.8 cm^2, p=0.09) compared to patients with appendage thrombus.

Spontaneous echo contrast

LA SEC was a frequent finding, present in 154 patients (80%). Patients with LA SEC had larger LA dimension (55 ±10 mm vs 51±10 mm, p=0.04), were less likely to have mitral regurgitation (22/154 (14%) vs 15/39 (38%), p=0.0006), and less likely to be in sinus rhythm (9/154 (6%) vs 8/39 (21%), p=0.004).

Mobile thrombus

Forty patients (21%) had mobile thrombus detected by TEE. Table 2 summarises clinical and echocardiographic variables related to the mobility of LA thrombus. Mobile thrombus was significantly associated with the absence of mitral stenosis or prosthesis (p=0.02) and the absence of mitral regurgitation (p=0.035), and with the presence of nonvalvular AF (p=0.005), recent (p=0.05) or previous (p=0.02) embolism, smaller thrombus size (p=0.006), and tended to occur in the LA appendage (p=0.059).

Table 1. Univariate Analysis of Clinical and Echocardiographic Factors Related to LA Thrombus Location.

	LA cavity n=46	LA appendage n=147	p
Clinical			
Nonvalvular AF	7 (15%)	67 (46%)	0.0002
Male gender	13 (28%)	78(53%)	0.003
Recent embolism	7 (15%)	55 (37%)	0.005
Previous embolism	14 (30%)	76 (52%)	0.01
AF < 1 month	5/38 (13%)	28/114 (25%)	0.14
Age (years)	63.0 ± 13.4	64.8 ± 11.5	NS
Anticoagulation	27 (59%)	77 (52%)	NS
AF (total)	44 (96%)	132 (90%)	NS
Echocardiographic			
Thrombus Area (cm2)	6.3 ± 5.2	1.8± 2.0	0.00001
LA dimension (cm)	6.0 ± 1.3	5.3 ± 0.9	0.00003
Mitral stenosis or prosthesis	38 (83%)	71 (48%)	0.00004
Mitral prosthesis	15 (33%)	20 (14%)	0.004
LV dysfunction	7 (15%)	44 (30%)	0.048
Mobile thrombus	5 (11%)	35 (24%)	0.059
Mitral stenosis	23 (50%)	51 (35%)	0.06
Mitral regurgitation	10 (22%)	27 (18%)	NS
LA SEC	37 (80%)	117 (80%)	NS
LV hypertrophy	14 (30%)	47 (32%)	NS

Table 2. Univariate Analysis of Clinical and Echocardiographic Factors Related to LA Thrombus Mobility.

	Mobile (n=40)	Fixed (n=153)	p
Clinical			
Nonvalvular AF	23 (57%)	51 (33%)	0.005
Previous embolism	25 (62%)	65 (42%)	0.02
Recent embolism	18 (45%)	44 (29%)	0.050
AF < 1 month	9/31(29%)	24/121 (20%)	NS
Age (years)	65.4±12.2	64.1 ± 11.9	NS
Anticoagulation	23 (57%)	81 (53%)	NS
AF (total)	37 (92%)	139 (91%)	NS
Male gender	24 (60%)	67 (44%)	NS
Echocardiographic			
Thrombus Area (cm2)	1.9 ±1.7	3.1± 3.9	0.006
MS or prosthesis	16 (40%)	93 (61%)	0.02
Mitral regurgitation	3 (7%)	34 (22%)	0.035
LA cavity location	5 (13%)	41 (27%)	0.059
Mitral stenosis	12 (30%)	62 (41%)	NS
Mitral prosthesis	4 (10%)	31 (20%)	NS
LV dysfunction	12 (30%)	39 (25%)	NS
LA SEC	35 (87%)	119 (78%)	NS
LV hypertrophy	17 (42%)	44 (29%)	NS
LA dimension (cm)	5.2 ± 0.9	5.5 ± 1.1	NS

DISCUSSION

LA thrombus has long been recognised as an important complication of rheumatic mitral valve disease (Daley et al 1951, Jordan et al 1951, Wallach et al 1953, Ellis and Harken 1961, Szekely 1964, Aberg 1969, Coulshed et al 1970, Hinton et al 1977, Wolf et al 1978, Davison and Greenland 1991). Interest in LA thrombus has been renewed by their recognition as the predominant cause of embolic events in patients with nonvalvular AF, the major cause of cardioembolic stroke (Sherman et al 1995). The advent of TEE has further increased interest in LA thrombus. Consistent with previous reports (Bansal et al 1989, Shrestha et al 1983, Schweizer et al 1981), this study found that TTE has poor sensitivity for LA thrombus, particularly if located in the LA appendage. In contrast, TEE shows high sensitivity and specificity for both LA cavity and appendage thrombus (Aschenberg et al 1986, Bleifeld et al 1986, Matsumura et al 1989, Acar et al 1991, Hwang et al 1992, Lin et al 1992, Olson et al 1992, Manning et al 1995, Fatkin et al 1996). The high correlation between TEE and surgical findings was confirmed in the present study.

This is the largest series of patients with LA thrombus assessed by TEE, and the first to specifically examine determinants of the location and mobility of thrombus. The principal finding is that the location and mobility of LA thrombus are dependent on the associated cardiac disease and other clinical and echocardiographic variables. LA cavity thrombus is associated with mitral stenosis or prosthesis and greater LA dilatation. In contrast, LA appendage thrombus is associated with nonvalvular AF, previous embolism and LV dysfunction. Mobile LA thrombus was associated with previous embolism, location in the appendage, nonvalvular AF and the absence of mitral valve disease. These findings give new insight into the pathogenesis of LA thrombus, and have implications for the clinical management of patients with risk factors for LA thrombus.

Determinants of thrombus location

186

The LA cavity and appendage have distinct anatomic, functional and pathophysiologic properties which may affect their predisposition to thrombus. The LA appendage is a blind-ended pouch with distinct trabeculations known as pectinate muscles, and arises from the embryonic LA (Sadler 1985). Circulation of blood within the LA appendage relies on the function of the LA appendage itself. In contrast, the LA cavity is smooth walled and is embryologically derived from the pulmonary veins (Sadler 1985), which channel blood into the LA chamber even in the absence of LA cavity function. These factors, particularly the blind-ended nature of the appendage, likely account for the predilection of thrombus for that location, as confirmed in the present study.

The varying distribution of LA thrombus location in different associated cardiac diseases suggests that the pathophysiologic determinants of atrial thrombosis also vary with associated cardiac disease. The determinants include Virchow's triad of blood stasis (eg atrial mechanical dysfunction, isolation of the LA appendage) haematological factors (fibrinogen, erythrocyte aggregation), and endocardial damage (rheumatic mitral valve disease, chronic atrial enlargement). It has been recognised for many years that nonvalvular AF and mitral stenosis are the major risk factors for atrial thrombus. Patients with AF, mitral stenosis or prosthesis accounted for almost all patients in this series. However, the current series extends previous observations by showing that location varies between these conditions, suggesting that the pathophysiological determinants noted above also differ.

Atrial fibrillation

As in previous reports, AF was the most frequent factor predisposing to LA thrombus. AF produces an irregular LA appendage contraction pattern with reduced, although variable, flow velocities compared to sinus rhythm (Pollick et al 1991). AF results in LA cavity (Henry et al 1976, Sanfilippo et al 1990) and appendage (Pollick et al 1991) dilatation, and reduced LA appendage flow velocity (Fatkin et al 1994), both of which reduces the shear rate, a measure of stasis,

derived from blood velocity divided by chamber dimension (Beppu et al 1985). AF also affects pulmonary vein flow (Klein and Tajik 1991), with a reduction in the systolic component.

The finding in this study that LA thrombus in patients with nonvalvular AF almost always occurs in the appendage suggests that the predominant haemodynamic effect of nonvalvular AF is an increase in LA appendage rather than cavity stasis. This finding is consistent with observations that LA SEC in patients with AF is frequently more severe in the appendage (Fatkin et al 1994).

Left ventricular dysfunction

The present series suggests an association between LV dysfunction and LA thrombus, particularly appendage thrombus. Several patients had LV dysfunction as the only risk factor for thrombus, and this factor was significantly associated with appendage thrombus. This may reflect the finding that LV dysfunction is frequently associated with nonvalvular AF (Cairns and Connolly 1991). LA cavity thrombus may occur in patients with dilated cardiomyopathy, even in the absence of AF (Roberts et al 1987). Black et al (1993) found that LV dysfunction was a predictor of the presence of LA appendage thrombus in patients with nonvalvular AF scheduled for cardioversion. LV dysfunction was a risk factor for thromboembolism in nonvalvular AF in the SPAF study (Stroke Prevention in Atrial Fibrillation Investigators, 1990 and 1991).

In the present series LA appendage thrombus was also found in patients with restrictive cardiomyopathy or constrictive pericarditis. Both systolic and diastolic LV dysfunction may lead to increased LA pressure and volume, and reduced cardiac output, potentially resulting in stasis in both the cavity and appendage. Etiologies of LV dysfunction such as coronary artery disease and amyloid may also directly impair LA function. Thrombus in patients with LV dysfunction was more frequent in the LA appendage. This may result in part from the lower threshold for thrombus in the appendage. In addition, Pollick et al (1991) noted

that in patients with AF, compression from the adjacent LV onto the medial LA appendage wall results in emptying of the LA appendage, and noted the predilection of LA appendage thrombus to form on the relatively immobile lateral wall. Hoit et al (1994) have shown that LV function is a major determinant of LA appendage function.

Mitral stenosis

The association between mitral stenosis and LA thrombus has long been recognised. The mechanical obstruction to LA outflow leads to LA dilatation and reduced cardiac output, both contributing to reduced LA shear rate. Mitral stenosis is also frequently accompanied by AF, with additional effects on LA size and function, as noted above. Even in the absence of AF, chronic mitral stenosis promotes structural and functional changes in the LA which result in LA dysfunction (Unverferth et al 1984, Jaffe et al 1987, Triposkiadis et al 1990, Keren et al 1987, Roberts et al 1978, Kuschner et al 1991). Both the cavity and appendage may be dilated in mitral stenosis, although as demonstrated in this study the cavity enlargement is typically greater than found in AF alone. Thrombus in patients with mitral stenosis or prosthesis was more frequent in the appendage than cavity, but with significantly less preponderance than in patients with nonvalvular AF or LV dysfunction. Patients with cavity thrombus had more severe mitral valve disease, with smaller mitral valve area, larger transmitral gradient and larger LA diameter. These findings suggest that in patients with mild mitral stenosis the presence of AF may be the major contributor to thrombus. More severe mitral stenosis is associated with progressive LA cavity dilatation and dysfunction which promotes thrombus in that location.

Spontaneous echo contrast

As reported previously (Black et al 1991a), both LA cavity and appendage thrombi are usually accompanied by LA SEC. This echocardiographic phenomenon reflects both atrial stasis and altered systemic haematological parameters (Black

et al 1993), thereby reflecting two arms of Virchow's triad of factors influencing thrombosis, and is a marker of LA thrombus and embolic risk in patients with mitral valve disease and with nonvalvular AF. (Black et al 1991a, Leung et al 1994). As shown previously (Black et al 1991a), LA SEC was associated with AF, LA dilatation and the absence of mitral regurgitation.

LA size

The effects of mitral regurgitation, which increases LA size while decreasing SEC, a marker of embolic risk, highlights the complex interaction between measurements of LA cavity size and the risk of thrombus. Several studies (Cabin et al 1990, Corbalan et al 1992, (The Stroke Prevention in Atrial Fibrillation Investigators 1992, Aronow et al 1989, Caplan et al 1986) have reported that LA cavity size was a risk factor for embolic events in AF. Black et al (1993) reported a significant but small increase in LA dimension in patients with LA appendage thrombus secondary to nonvalvular AF. The relatively poor correlation between thromboembolic risk and LA size may reflect the imperfect correlation between LA cavity and appendage size (Pollick et al 1991) and function (Klein et al 1993), the inaccuracies of M-mode measurement, and confounding factors such as mitral regurgitation.

Other factors

Although less well characterised than the haemodynamic factors discussed above, the remaining two arms of Virchow's triad may also contribute to the different pathogenesis of LA cavity and appendage thrombus. There is increasing evidence of abnormal systemic and local coagulation and platelet function parameters in patients with AF (Black et al 1993, Kumagai et al 1990, Gustafsson et al 1990, Fatkin et al 1994, Lip et al 1995, Lip et al 1996, Lip et al 1996, Mitusch et al 1996) and mitral stenosis (Kataoka et al 1993, Yasaka et al 1991, Jafri et al 1992, Yamamoto et al 1993). We have shown previously that patients with LA SEC associated with nonvalvular AF have significantly higher haematocrit and fibrinogen (Black et al 1993), with a trend to higher fibrinogen levels in patients

with LA thrombus. However, it is unclear how altered systemic parameters would influence the location of thrombus. Of more interest is recent evidence of local coagulation abnormalities, occurring in the LA cavity, in patients with mitral stenosis (Yamamoto et al 1993) The role of haematological factors has not been directly compared between LA cavity and appendage thrombus. However, Fatkin et al (1994) suggested that haematological factors were less important in mitral stenosis.

The role of endocardial factors in LA thrombosis is not well defined. Rheumatic carditis in patients with mitral stenosis may involve both the appendage and cavity and may predispose to thrombus. Patients with AF may also have abnormal endocardium (Unverferth et al 1984). Although endocardial function cannot be directly assessed by echocardiography, both LA dilatation and LA systolic failure are likely to represent a marker of abnormal endocardial structure and function.

In summary, these data suggest that the pathogenesis of LA thrombus in a particular location reflects a complex interplay of multiple factors including LA cavity and appendage anatomy, size and function, cardiac rhythm, mitral valve disease, pulmonary vein flow, LV systolic and diastolic function, haematological and endocardial factors.

Thrombus mobility and embolism

Despite the association between LA thrombus and embolism, thrombus characteristics increasing the risk for embolism remain poorly defined. This is the first study to examine correlates of the mobility of LA thrombus. Mobile LA thrombus was associated with an higher incidence of embolism, location in the appendage, nonvalvular AF and the absence of mitral valve disease. These findings suggest that as for the LV (Judgutt and Sivaram 1989), mobility is an important determinant of the embolic risk of LA thrombus. These results also provide clinical support to the hypothesis (Goldman 1960) that emboli are more likely to arise from recently formed, loosely adherent thrombus. The finding that

mobility was more likely in patients with appendage than cavity thrombus raises the possibility that appendage thrombus has greater embolic potential. This particular result should be interpreted with caution due to the selected population and potential bias, and requires assessment in future studies. Leung et al (1997) found that mobile thrombus was associated with increased thromboembolic risk on follow-up. The complex relation between LA thrombus and embolism is demonstrated by observations (Black et al 1993) that only a minority of patients with known LA thrombus develop clinical embolisation after reversion from AF. Even mobile thrombus may not result in clinical embolism. Finally, embolism reflects a balance between factors favouring stasis and the dynamic forces of the circulation that project thrombotic material into the circulation (Halperin and Fuster 1989).

Clinical issues

These findings have implications for the diagnostic evaluation of patients with risk factors for LA thromboembolism. In particular, these data highlight the role of TEE in addition to TTE in patients with nonvalvular AF, in whom the LA appendage is the predominant site of thrombus formation. TEE is finding increasingly clinical applicability in patients with AF; before cardioversion (Black et al 1991b, Klein et al 1997), as a predictor of future embolism (Leung et al 1994, Leung et al 1997, Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography 1998), and following embolic events (Black et al 1991b, Leung et al 1995). TEE is also used to detect LA thrombus in patients with mitral stenosis undergoing percutaneous valvuloplasty (Leung et al 1995). It remains uncertain whether TEE is always required in addition to TTE in patients undergoing percutaneous valvuloplasty, reflecting the greater utility of TTE in detecting LA cavity thrombus which is more frequently found in mitral stenosis. Important areas for future work include the differential prognostic importance and effect of anticoagulation on LA cavity and appendage thrombi. Firm clinical guidelines regarding the indications for TEE to detect LA thrombus are still evolving, and must await the final result of studies such as the Assessment of Cardioversion

Using Transoesophageal Echocardiography Study (Klein et al 1997). However, the SPAF-III TEE substudy (Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography 1998) has shown the prognostic implications of LA thrombus and other LA abnormalities, as well as aortic atheroma detected by TEE. Commenting on this study, Manning and Douglas (1998) concluded that TEE "added value" and was not merely an "expensive toy".

Limitations

Limitations of the study largely reflect its retrospective nature. Several potentially important variables were not measured, including LA appendage size and flow velocity, and haematological variables. The study population was a highly selected group, including a high proportion of patients with recent embolic events or mitral stenosis. The relatively increased utility of TTE for cavity thrombus may have resulted in fewer patients with cavity thrombus undergoing TEE. Although the study population was assessed in detail, information is lacking on the remaining >10,000 patients without LA thrombus. Measurement of interobserver agreement was not assessed in this study. Kronik et al (1995) reported 90% interobserver agreement for left atrial cavity thrombus and 94% interobserver agreement for left atrial appendage thrombus.

CONCLUSIONS

This study shows that LA cavity and appendage thrombus are distinct entities which are associated with different clinical and echocardiographic parameters. The study also identified mobile thrombus, a finding more common with appendage thrombus, as a potential marker of increased embolic risk. These findings provide new insights into the pathogenesis of LA thrombus, and have implications for the clinical management of patients at risk for LA thrombus. Future studies are required to further assess the implications of LA thrombus location and mobility.

CHAPTER 8

Embolisation of A Left Atrial Ball Thrombus During Transoesophageal Echocardiography

ABSTRACT

This case report describes systemic embolisation of a LA ball thrombus during TEE. A 49 year old man with rheumatic mitral stenosis and AF underwent TEE to evaluate a transient cerebral ischaemic attack. TEE demonstrated a free-floating LA thrombus. Disappearance of the thrombus during the study occurred following tachycardia, and was associated with acute hemiplegic stroke and an absent radial pulse. The possible mechanism of embolisation and the implications for the selection and management of patients undergoing TEE are discussed.

INTRODUCTION

TEE provides high resolution, close range imaging of the LA cavity and appendage, and is more sensitive than TTE for detecting LA thrombi (Bleifeld 1986, Acaret al 1991) and LA myxoma (Obeid et al 1989). Complications of the technique have been rare (Daniel et al 1991). We report a case of systemic embolisation of a mobile LA thrombus during TEE.

CASE REPORT

A 49 year old man with known rheumatic mitral stenosis presented with transient right hemiplegia and dysphasia. The patient had been prescribed warfarin following a cerebrovascular accident with mild left hemiplegia at age 26, but was not compliant and was not anticoagulated at the time of admission (INR 1.0). Physical examination revealed AF, accentuation of the first heart sound, no opening snap, and a rumbling mid-diastolic murmur at the apex which did not vary in intensity. There were no carotid bruits and the peripheral pulses were normal. Cerebral computed tomography showed right parietal infarction. Intravenous heparin and digoxin were commenced and the patient was referred for TEE to determine the presence of LA thrombi.

TTE performed immediately prior to TEE showed severe mitral stenosis (mitral valve area 0.7 cm^2), and a severely dilated LA (M-mode dimension 85 mm) which contained a 3 cm diameter mass, freely mobile within the atrial cavity. After intravenous sedation with midazolam and fentanyl and pharyngeal anaesthesia with lignocaine, a 5 MHz biplane TEE transducer (HP 21363A) was inserted without difficulty. The LA mass was seen to consist of an internal echo-dense core with a less dense surface layer, consistent with laminated thrombus. No attachment of the thrombus to the atrial wall could be detected. At times the thrombus rested transiently against the mitral valve orifice in diastole, appearing

to occlude the orifice (Figure), before careening off during systole with a ping-pong ball appearance. LA SEC was present, and the LA appendage was free of thrombus.

Several minutes after the commencement of the study the patient became restless and tachycardic (AF with ventricular rate 130/min), and required further sedation. Pulse oximetry did not reveal hypoxia, and the appearance of the thrombus was unchanged. Two minutes later the patient became acutely obtunded and was found to have left hemiplegia and an absent right radial pulse. The previously noted thrombus could no longer be visualised except for a 0.5 cm diameter mobile remnant which was observed transiently. The mitral valve orifice was not being imaged at the presumed time of embolisation. An urgent cerebral computed tomogram was unchanged from the previous scan. Intravenous heparin was continued, and the right radial pulse returned several hours later. There was little long-term improvement in the left hemiplegia and left sided sensory deficit. After a repeat TEE confirming the absence of residual thrombus, the patient subsequently underwent successful percutaneous mitral valvuloplasty with an increase in mitral valve area to 2.1 cm^2.
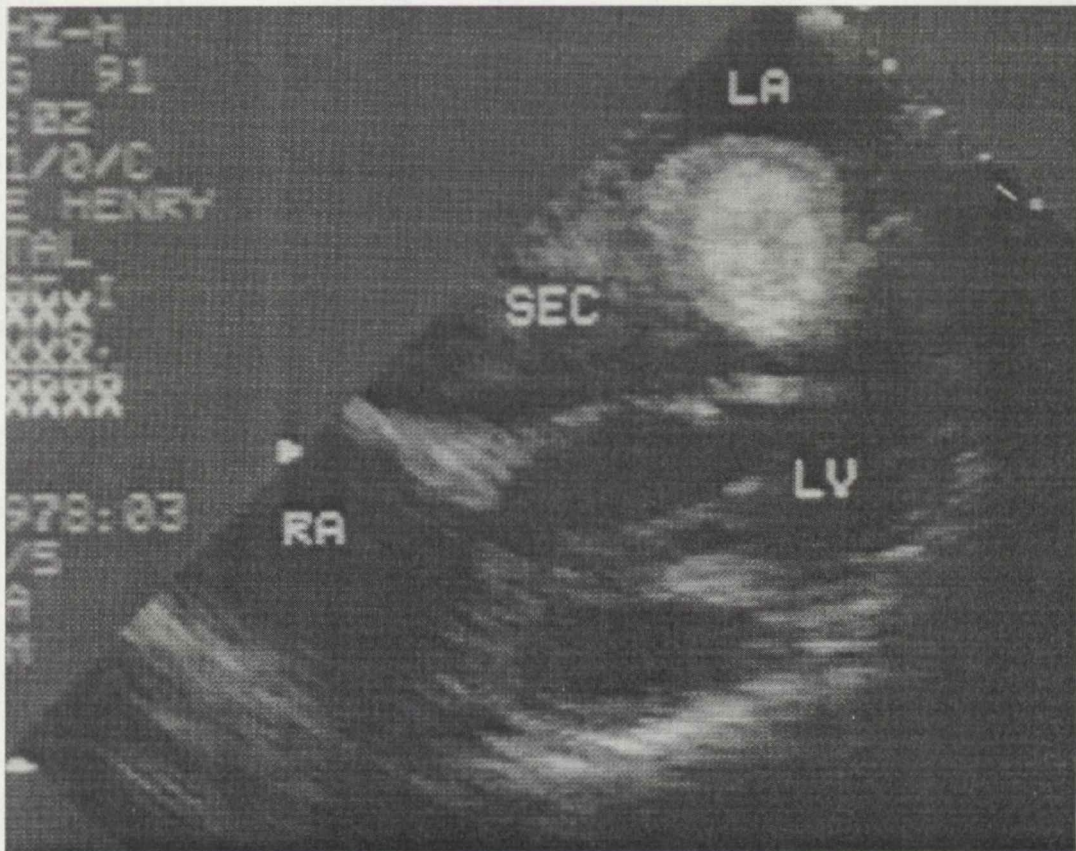
Figure. TEE Four-Chamber View Showing the Laminated Thrombus in the Left Atrium. LA=left atrium, LV=left ventricle, RA=right atrium, SEC=spontaneous echo contrast.

DISCUSSION

Free-floating thrombus within the LA, known as LA ball thrombus, is a rare complication of rheumatic mitral stenosis. Previous studies, reviewed by Wrisley et al (1991), have highlighted the importance of accurate diagnosis and prompt surgical removal of such thrombi, due to the frequent and unpredictable occurrence of systemic embolism or sudden death due to mitral valve occlusion. The present patient was referred for TEE to evaluate suspected LA thrombus as the cause of a cerebral embolic episode. Although TTE demonstrated a mobile atrial mass, TEE was performed for further assessment prior to definitive therapy. TEE was able to define the internal characteristics of the thrombus, exclude other thrombi, and confirm the lack of attachment to the atrial wall. However, cerebral and limb embolism occurred during the procedure, associated with disappearance of the thrombus.

Although the occurrence of embolism may have been coincidental, the mechanisms by which TEE may have precipitated this event should be considered. Sherman et al (1985) postulated that embolisation of free-floating LA thrombi might result from detachment of the entire thrombus, fragmentation of the thrombus as it is traumatised by the mitral valve in systole, or embolisation of a second atrial thrombus. The actual moment of embolism of LA thrombus was not visualised in the present case, and has not been visualised in any previous report.

Embolisation in the present case occurred several minutes after the onset of tachycardia associated with restlessness. Embolisation to both the right brachial and right carotid arteries may have resulted from fragmentation of the thrombus in the brachiocephalic artery. However, the transient presence of a thrombus remnant and the large size of the thrombus compared to the mitral orifice imply that the thrombus became fragmented before or during passage through the mitral valve. Tachycardia may have elevated the transmitral gradient (Arani and Carleton 1967) and increased the frequency and force of thrombus collision with the mitral

valve, resulting in passage of the thrombus through the mitral orifice. However, tachycardia as a consequence of an otherwise occult initial embolism cannot be excluded.

There are no previous reports of embolism during TEE. However, a recent report of rupture of an aortic dissection associated with retching during TEE (Silvey et al 1991) highlights the potential danger of haemodynamic and mechanical changes during the procedure. The present case may also be relevant to cases of mobile LA myxoma, in which tachycardia during TEE may increase the likelihood of fragmentation and subsequent embolisation.

CONCLUSION

This case illustrates the potential risk of TEE in patients with mobile LA masses, although the precise mechanism of embolisation is uncertain. When TEE is considered necessary in these patients, it should be performed with adequate sedation and close attention to haemodynamic and electrocardiographic monitoring.

This was the only major complication of TEE during approximately 2,000 TEE studies performed or observed during the period of this thesis. The low major complication rate of TEE was documented by Daniel et al (1991).

Part 4

Transoesophageal Echocardiography

Following Embolism

CHAPTER 9

Selection of Patients for Transoesophageal Echocardiography After Stroke and Systemic Embolic Events: Role of Transthoracic Echocardiography

ABSTRACT

Background and Objectives. Indications for TEE following embolic events are not well defined. This study examined whether patients with stroke or systemic embolism may be selected for TEE on the basis of clinical and TTE findings.

Methods. TTE and TEE were performed on 824 patients after stroke and other suspected embolic events. Patients were classified into group A if they were in sinus rhythm and had a normal TTE. Group B consisted of all other patients. TEE findings of LA SEC, LA thrombus, complex aortic atheroma, and interatrial septal anomalies were correlated with clinical and TTE results.

Results. TEE detected at least one potential source of embolism in 399 patients (49%): LA SEC in 214 patients (26%), LA thrombus in 54 (7%), complex atheroma in 111 (13%), and interatrial septal anomalies in 126 (15%). In group A (n=236), only 3 (1%) had LA SEC, 11 (4.6%) had complex atheroma, and none had LA thrombus. In group B (n=588), 211 patients (36%, p<.001) had LA SEC, 54 (9.2%, p<.001) had atrial thrombus and 100 (17%), p<.001) had complex atheroma. Interatrial septal anomalies were detected in similar proportions of patients (18% in group A versus 14% in group B). LA SEC, thrombus, and complex atheroma were significantly more prevalent in older patients, but interatrial septal anomalies were more prevalent in younger patients irrespective of TTE findings. Multivariate analysis identified both an abnormal TTE and patient age to be independent predictors of TEE findings of LA SEC, LA thrombus, or complex atheroma.

Conclusions. TEE has a low yield for LA SEC, LA thrombus, or complex aortic atheroma in patients with normal TTE and sinus rhythm and in younger patients. Interatrial septal anomalies are more prevalent in younger patients. TEE is recommended for patients with abnormal TTE and in younger patients when the finding of atrial septal anomalies may contribute to patient management.

INTRODUCTION

TEE is useful in detecting potential intrathoracic sources of embolism (Black et al 1991b, Pearson et al 1991, Pop et al 1990, DeRook et al 1992, Vandenbogaerde et al 1992, Lee et al 1991, Albers et al 1994) and is often performed in patients who have suffered from stroke or other systemic embolic events. However, it is still controversial whether all such patients should undergo TEE, and there have been no established guidelines for patient selection.

TTE, though a powerful noninvasive tool for the assessment of cardiac chamber size, function, and valvular disease, is insensitive in detecting intrathoracic sources of embolism (Sansoy et al 1995). LA SEC, LA thrombus, and complex aortic atheroma, which are high risk factors for subsequent thromboembolism (Leung et al 1994, Tunick et al 1994), are usually not visualised by TTE (Pearson et al 1991, Black et al 1991a, Pop et al 1990, DeRook et al 1992, Vandenbogaerde et al 1992, Lee et al 1991, Albers et al 1994). However, the role of TTE in selecting patients for TEE after stroke or other embolic events has not been examined. The purpose of this study was to examine whether these patients can be selected for TEE on the basis of clinical and TTE findings.

METHODS

Patients

The study population comprised 824 consecutive patients referred for TEE at The Cleveland Clinic Foundation (Cleveland) and Prince Henry Hospital (Sydney) with a diagnosis of stroke, transient ischaemic attack, or systemic peripheral embolism from 1988 through 1993. The diagnoses of these events were made by referring physicians. Patients from Prince Henry Hospital (n=632) were identified prospectively; clinical data, including demographic data, cardiac rhythm, type of systemic embolic event, and interval between the index event and TEE, were obtained by patient interview and chart review at the time of TEE. The initial 63

patients were reported in part previously (Black et al 1991b). Patients from The Cleveland Clinic Foundation (n=192) were identified retrospectively from a computerised database, and clinical data were obtained by chart review.

Echocardiography

All patients underwent both TTE and TEE. Echocardiographic examinations were performed with commercially available systems (Hewlett-Packard Sonos 1000 or 1500, Acuson 128 XP) equipped with 2.5 and 3.5-MHz phased-array transthoracic transducers and 5-MHz transoesophageal transducers. TTE studies were performed from all standard echocardiographic windows. Global LV systolic function was assessed semiquantitatively from the parasternal and apical views and graded as normal or mild, moderate, or severe impairment. The mitral and aortic valves were assessed by colour, pulsed, and continuous-wave Doppler. Mitral and aortic regurgitation, if present, were graded as trivial, mild, moderate, or severe (Helmcke et al 1987, Perry et al 1987). LA dimension and LV wall thickness were measured according to standard M-mode criteria (Sahn et al 1978). The presence of LV hypertrophy was also assessed semiquantitatively. Patients were classified into two groups on the basis of clinical and TTE findings. Group A consisted of patients with normal TTE and normal sinus rhythm at the time of TEE. A TTE was considered normal when all of the following criteria were met: (1) normal LV systolic function with no LV hypertrophy, (2) no prosthetic valve, (3) no valvular stenosis and no more than mild mitral or aortic regurgitation, (4) LA dimension of ≤40 mm, and (5) no visualised valvular vegetation or intracardiac masses. Group B consisted of all other patients. These criteria were chosen to focus on the abilities of TTE while accepting its low sensitivity for LA SEC, thrombus, and aortic atheroma.

TEE was performed according to standard protocols (Seward et al 1988, 1990, 1993). All TEE examinations were performed within 48 to 72 hours of the corresponding TTE studies. Approximately 13% were monoplane, 43% biplane, and 44% multiplane studies. The presence of the following potential sources of

205

embolism was specifically examined: (1) LA SEC and thrombus; (2) atheroma in the thoracic aorta; (3) patent foramen ovale, atrial septal defect, and atrial septal aneurysm; and (4) others, including valvular vegetations and intracardiac masses. LA SEC was diagnosed by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artefact (Black et al 1991a). LA thrombus was diagnosed by the presence of an echodense mass in the LA or the LA appendage, distinct from the endocardium and the pectinate muscles of the LA appendage (Beppu et al 1984). The presence of atheroma in the thoracic aorta was examined. Atheroma that were mobile, pedunculated, or protruding ≥ 5 mm into the lumen were classified as complex atheroma (Katz et al 1991, Karalis et al 1991). All other atheroma were classified as simple atheroma. The interatrial septum was examined for patent foramen ovale, atrial septal defect, and atrial septal aneurysm. Bubble contrast study with agitated saline was performed in all patients to look for interatrial shunting. Bubbles appearing in the LA within 3 cardiac cycles or observed traversing the interatrial septum constituted a positive study for shunting. Atrial septal aneurysm was defined using the criteria of Hanley et al (1985), with a base of at least 15 mm and an excursion during the cardiac cycle of at least 15 mm.

Statistical analysis

Results are expressed as mean ±SD where appropriate. The chi-square test or Fisher's exact test was used to compare categorical variables. A multiple logistic regression model was used to examine the relative value of TTE and patient age (as a continuous variable) in predicting TEE findings of LA SEC, LA thrombus, or complex aortic atheroma. Odds rations were shown with 95% confidence intervals, and statistical significance was defined as two-tailed $p < 0.05$.

RESULTS

A total of 824 patients were studied. There were 463 men and 361 women with a

mean age of 63±15 years. Five hundred eighty-three patients (71%) were in sinus rhythm and 241 (29%) in AF. Five hundred twenty-three patients (64%) had suffered a stroke, 145 (18%) transient ischaemic attack, 114 (14%) acute embolism to an extremity, and 42 (4%) had visceral or other embolism. Ninety-eight percent of these events had occurred within 1 month of the echocardiographic studies. Twenty-five patients (3%) had an aortic valve prosthesis, another 23 patients (3%) had a mitral prosthesis, and 2 other patients had mitral valve repair.

TTE findings

One hundred forty-five patients (18%) had LV systolic dysfunction, which was mild in 56, moderate in 54, and severe in 35. TTE detected LV apical thrombus in 9 patients (1%). All 9 patients had impaired LV function. Three hundred thirteen patients (38%) had LV hypertrophy, which was considered mild in 245 and severe in 68. Twenty-nine patients had aortic stenosis or more than mild aortic regurgitation, and another 23 had mitral stenosis. Nineteen patients (2%) had moderate and 7 patients (0.8%) had severe mitral regurgitation. TTE detected aortic valve vegetations in 2 patients and mitral valve vegetations in another 3 patients. No other intracardiac masses were detected by TTE. The mean LA dimension was 41.5±9 mm, with 401 patients (48%) having a LA dimension of 40 mm. TTE was considered normal in 240 patients (29%), of whom 236 were in sinus rhythm. Group A comprised the latter 236 patients, whereas the remaining 588 patients (61%) constituted group B.

TEE findings

TEE detected at least one potential source of embolism in 399 patients (49%). LA SEC was detected in 214 patients (26%). Fifty-four patients (7%) had LA thrombus, of which 46 (6%) were in the LA appendage, 5 in the LA cavity, and 3 involved both the LA appendage and cavity. Two hundred and fifty-five patients (32%) were found to have simple aortic atheroma, and 111 patients (13%) had complex aortic atheroma. A patent foramen ovale was detected in 110 (13%),

atrial septal defect in 8 (1%), and atrial septal aneurysm in another 8 patients (1%). TEE confirmed TTE findings of valvular vegetations in the 5 patients and detected vegetations on an aortic prosthesis in 2 additional patients and vegetation on a mitral prosthesis in another. TEE also visualised strands on a native aortic or mitral valve in another 7 patients. No LA myxoma or other intracardiac masses were found.

Table 1 shows the clinical, TEE and TTE findings according to the preceding clinical events. Compared with patients who had suffered from either transient ischaemic attack or stroke, patients suffering from peripheral embolism were more likely to have LA enlargement and complex thoracic atheroma.

The Figure shows the results of the TEE in patient groups A and B. LA SEC was detected in only 3 patients (1%) in group A compared with 211 patients (36%) in group B (P<0.001). Two of the 3 patients with LA SEC in group A had a history of paroxysmal AF. All LA thrombi were found in patients in group B (*p*<0.001). Complex thoracic aortic atheroma was detected in 11 patients (4.6%) in group A compared with 100 patients (17%) in group B (p<0.001). An abnormal TTE according to the abovementioned criteria identified 95% of all patients with LA SEC or LA thrombus or complex atheroma. However, abnormalities of the interatrial septum including patent foramen ovale, atrial septal defect, or aneurysm, were found in similar proportions in both groups (18% versus 14%, p=NS). No patient in group A aged 50 years or less had LA SEC, LA thrombus, or complex aortic atheroma.

Sixty-five patients (8%) with AF were found to have LV systolic dysfunction. Eighteen of these 65 patients (28%) had LA thrombus, 52 (80%) had LA SEC, and 16 (25%) had complex aortic atheroma. TEE detected at least one of the above three potential sources of embolism in 57 of the 65 patients (90%).

Table 2 shows the results of the TEE when all study patients were subdivided

according to patient age, irrespective of the results of their TTE. Dividing ages of 40, 50, and 60 years were used. The prevalence of LA SEC, LA thrombus, and complex aortic atheroma were consistently lower in younger patients compared with older patients, irrespective of the dividing age. In contrast, the prevalence of interatrial septal anomalies was higher in the younger, except with a dividing age of 60 years.

Multiple logistic regression showed that both an abnormal TTE (odds ratio, 8.9; 95% CI, 6.7 to 12.1; p<0.0001) and patient age (odds ratio, 1.05; 95% CI, 1.04 to 1.06; p<0.0001) were independent predictors of TEE findings of LA SEC, LA thrombus, or complex atheroma.
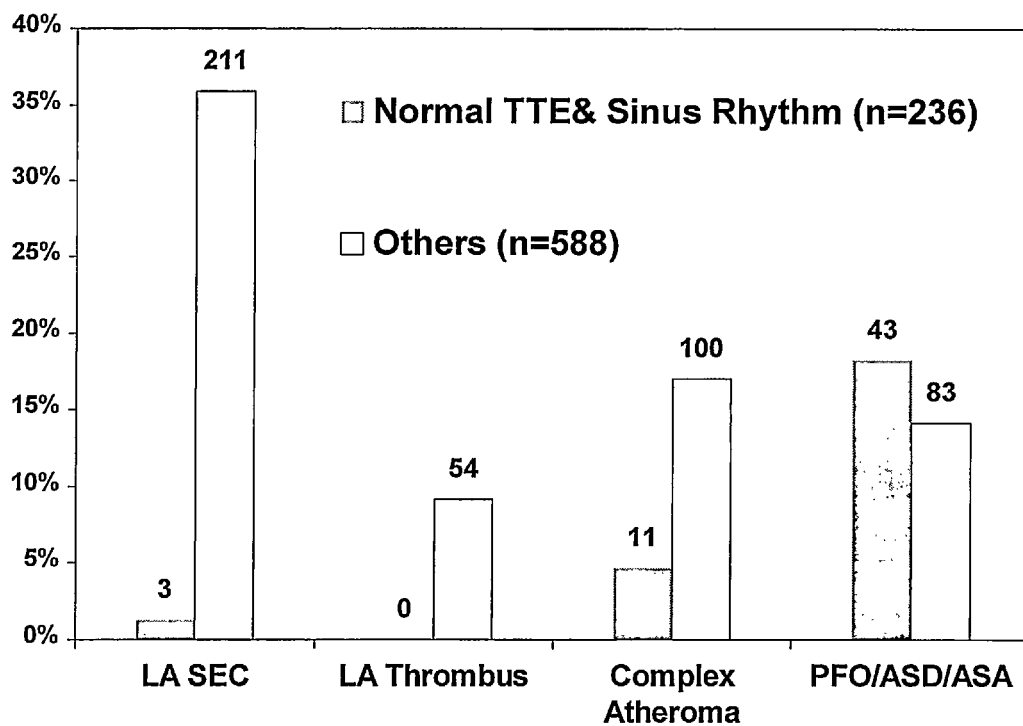
Figure. TEE Findings in Patient Group A (Normal Transthoracic Echocardiogram [TTE] and Sinus Rhythm) and in Group B (All Others).

Numbers above the bar refer to number of patients. Percentages refer to the frequency of the finding in the patient group. PFO=patent foramen ovale, ASD=atrial septal defect, ASA=atrial septal aneurysm.

Table 1. Clinical, TTE and TEE Findings According to Type of Embolism.

Finding	TIA (n=145)	Stroke (n=523)	Peripheral Embolism (n=114)	p
Complex atheroma, %	12	12	21	0.004
LA dilatation %	44	46	60	0.03
Male, %	57	58	47	NS
Age (yrs)	62±15	64±15	65±14	NS
AF,%	30	28	35	NS
LV dysfunction, %	13	18	24	NS
LV thrombus, %	0.7	1	1.8	NS
LA thrombus, %	5.5	6	8.8	NS
LA SEC %	25	25	30	NS
Interatrial anomalies, %	12	16	13	NS
Normal TTE, %	32	30	23	NS

TIA=transient ischaemic attack.

Table 2. TEE Findings of Patients Subdivided According to Age Irrespective of TTE Findings

	Age ≤ 40 (n=74)	Age >40 (n=750)	Age ≤ 50 (n=158)	Age >50 (n=666)	Age ≤ 60 (n=279)	Age > 60 (n=545)
LA SEC	2 (3%)	212 (28%)*	8 (5%)	206 (31%)*	24 (9%)	190 (35%)*
LA thrombus	0	54 (7%)*	3 (2%)	51 (8%)*	9 (3%)	45 (8%)*
Complex atheroma	0	111 (15%)*	1 (0.6%)	110 (17%)*	11 (4%)	100 (18%)*
PFO/ASD/ASA	18 (24%)	108(14%)†	36 (23%)	90 (13%)‡	48(17%)	78 (14%)§

*p<0.001, † p=0.02, ‡ p=0.001, § p=NS

DISCUSSION

This study is the largest reported series of patients referred for TEE after stroke or other suspected systemic embolic events. It confirms the utility of TEE in detecting potential intrathoracic sources of embolism in these patients. LA thrombus was detected in 7% of the patients, LA SEC in 26%, and complex thoracic aortic atheroma in 13%. The vast majority of the patients (95%) with these abnormalities had an abnormal TTE. Interatrial septal anomalies, detected in 15% of the patients, were more common in younger patients.

Role of TTE

This study systematically examined the value of clinical and TTE findings in selecting patients for TEE after stroke of systemic embolic events. TTE plays a complementary role in the noninvasive detection of LV dysfunction, hypertrophy, valvular disease, and LA enlargement and is often performed before TEE in these patients. Various investigators have suggested that the yield of TEE for potential intracardiac sources of embolism tended to be higher in patients with clinically suspected heart disease (Black et al 1991b, Pearson et al 1991, Pop et al 1990, Lee et al 1991, Cujec et al 1991). In the present study, 95% of all patients with LA SEC, LA thrombus or complex aortic atheroma had an abnormal TTE and/or AF. Ninety percent of all patients with impaired LV function and in AF were found to have at least one of the above abnormalities by TEE. In contrast, TEE had a very low yield for these abnormalities in patients with normal TTE. These findings are perhaps not surprising given the strong association between LA SEC, LA thrombus, LA enlargement, mitral valve disease and AF (Black et al 1991a). LA SEC has also been shown to be significantly associated with complex aortic atheroma (Leung et al 1994). The present study also showed that the value of a normal TTE in identifying patients with a very low prevalence of the above TEE findings was independent of patient age. A role for TTE in selecting patients for TEE has been subsequently confirmed by other investigators (Shiran et al 1988).

Patient age

Older patients had a higher prevalence of LA spontaneous echo contrast, thrombus, and complex atheroma, irrespective of the dividing age and results of their TTEs. The prevalences of heart disease and AF, and hence the potential sources of embolism, increase with age. These findings are consistent with the results of the Stroke Prevention in Atrial Fibrillation II Study (Stroke Prevention in Atrial Fibrillation II Study 1994 and 1996), which suggested that older patients had a higher thromboembolic risk reduction with anticoagulation, although at the expense of an increased bleeding risk. The risk-benefit ratio of anticoagulation may be further improved by TEE by allowing selective treatment of those patients with these abnormalities. While this study suggests that the prevalence of interatrial septal anomalies is not significantly affected by the presence of other structural heart diseases, their prevalence was significantly higher in young patients. Although this finding could represent an age-related decrease in the prevalence of these anomalies (Hagen et al 1984), it may also suggest that these anomalies could be related to embolic events and therefore that their detection may be potentially more important in the younger age group.

Impact of TEE findings

The decision to perform TEE in patients after stroke or other embolic events should be based on the likelihood of the findings contributing to patient management. The presence of LA thrombus increases the risk of subsequent thromboembolism. In the absence of contraindications, warfarin therapy may be considered on their detection. LA SEC may represent a hypercoagulable state (Black et al 1993a) and increases the risk of future thromboembolic events, with the risk reduced by warfarin therapy (Leung et al 1994). Complex aortic atheroma seen on TEE have been shown to predispose to future vascular events (Tunick et al 1994) and are associated with a higher rate of perioperative stroke in patients undergoing cardiopulmonary bypass (Katz et al 1991). Although warfarin or antiplatelet therapy for complex aortic atheroma is empirical with no proven efficacy, the detection of such atheroma by TEE may still be worthwhile for pre-

operative assessment because invasive intravascular procedures can be avoided and aortic cannulation during cardiopulmonary bypass modified (Black et al 1993a).

Interatrial septal anomalies

Paradoxical embolism through a patent foramen ovale, atrial septal defect, and aneurysm is a well-recognised mechanism for systemic thromboembolism, with isolated case reports showing thrombus straddling a patent forman ovale (Nellessen et al 1985, Nagelhout et al 1991, Speechley-Dick et al 1991). Although several studies have suggested that interatrial septal anomalies were more prevalent in patients with unexplained stroke than in control subjects (Lechat et al 1988, Webster et al 1988), others failed to demonstrate such an association (Ranoux et al 1993, Jones et al 1994). Moreover, patent foramen ovale is a common finding in the general population. Up to 20% of the control subjects in these studies were found to have a patent foramen ovale (Lechat et al 1988), and autopsy studies (Hagen et al 1984) have shown that patent foramen ovale was detected in up to 27% of otherwise normal hearts. The risk of recurrent stroke related to patent foramen ovale has been reported to be only 1.9%/yr (Bogousslavsky et al 1996). The causal relationship between the detection of interatrial septal anomalies and embolism may be difficult to establish in a given patient, especially if a venous source of embolism has not been identified. As the results of this study suggest, detection of these anomalies may be more important in younger patients in whom the prevalence of these anomalies is higher and other detectable sources of embolism less frequent. It is anticipated that forthcoming studies, such as the Patent foramen ovale in Cryptogenic Stroke Study (PICCS), will provide further information on the significance and management of these disorders.

Limitations

The study patients were a selected group who were referred for TEE and were note true consecutive patients admitted with stroke or other systemic embolic

events. The true prevalence of the various sources of embolism might have been lower had all such patients been included. There was no control group of patients without embolism. However, this is unlikely to affect the validity of the observations, which were made from comparisons of the results of TTE and TEE of the study patients. The reported prevalence of patent foramen ovale ranged from 3% to 47% (Lee et al 1991, Cujec et al 1991, Lechat et al 1988, Ranoux et al 1993, Jones et al 1994, Hausmann et al 1992, Movsowitz et al 1991) and that for atrial septal aneurysm ranges from 1% in autopsy series (Silver et al 1978) to 3% to 16% in TEE series (Pearson et al 1991, Cujec et al 1991, Pearson et al 1991, Zabalgoitia et al 1994), depending on the patient population and diagnostic criteria used. Pearson et al (1991) reported a 21% prevalence of atrial septal aneurysm in a selected population with no cardiac disease, stroke, or transient ischaemic attack. The relatively low 13% prevalence of patent foramen ovale in the present study may have been due to the fact that the patients belonged to a more elderly population and that multiple contrast injections were not routinely performed. The low 1% prevalence of atrial septal aneurysm may have been due to the use of strict diagnostic criteria. The classification system of normal TTE is not perfect (sensitivity 95%); 3 patients with LA SEC and 11 patients with complex aortic atheroma had a normal TTE. Therefore, these diagnostic guidelines should be used in conjunction with clinical judgement in each individual case.

CONCLUSIONS

In addition to being a noninvasive screening tool for patients after stroke or systemic embolic events, TTE may assist in the selection of patients for TEE. The results of the present study suggest that the type of embolic source detectable by TEE may reasonably be predicted on the basis of clinical and TTE findings, so that the clinician can decide whether TEE is indicated in a given patient. We recommend TEE in patients with abnormal TTE, especially when the decision to give long-term systemic anticoagulation is being considered. The prevalences of LA thrombus, SEC, and complex aortic atheroma are higher in this subset of

patients and the detection of these abnormalities may help guide further therapy. The SPAF-III TEE Study (Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography 1998) has recently shown a benefit for warfarin for patients with LA SEC and with aortic atheroma. Patients with LA thrombus in that study had a high risk of stroke despite warfarin, suggesting that more intensive anticoagulation might be required. In patients with normal TTE, the decision to perform TEE should be based on the perceived importance of possible findings of interatrial septal anomalies. TEE may be recommended in younger patients with otherwise unexplained events in whom patent foramen ovale is more prevalent and is potentially of higher importance. Whether the overall cost-effectiveness of TEE can be improved by this approach needs to be examined by future studies regarding the clinical relevance of various TEE findings and the impact of therapy.

PART 5

Cardioversion of Atrial Fibrillation and Flutter

CHAPTER 10

Evaluation of Transoesophageal Echocardiography Prior to Cardioversion of Atrial Fibrillation and Flutter in Non-anticoagulated Patients

ABSTRACT

Background and Objectives. Electrical cardioversion of AF may result in systemic embolism due to atrial thrombus. This study prospectively evaluated the role of TEE in screening for atrial thrombi prior to elective cardioversion in 40 non-anticoagulated patients with nonvalvular AF (n=33) or atrial flutter (n=7).

Results. TTE did not detect atrial thrombus in any patient. TEE detected LA appendage thrombi in 5 patients (12%, p=0.03 compared to TTE), significantly associated with LV systolic dysfunction (p=0.02) and with LA SEC (p=0.04). Cardioversion was cancelled in the 5 patients with thrombi and in 2 patients with spontaneous reversion prior to planned cardioversion. Cardioversion was successful in 25 (76%) of the 33 remaining patients. Cerebral embolism occurred 24 hours following successful cardioversion in 1 patient with AF and LV dysfunction, who had LA SEC but no thrombus detected by TEE prior to cardioversion. Repeat TEE following embolism showed a fresh LA appendage thrombus and increased LA SEC.

Conclusions. TEE improves the detection of LA appendage thrombi in cardioversion candidates, in whom the procedure may be deferred. However, the exclusion by TEE of pre-existing atrial thrombi prior to cardioversion does not eliminate the risk of embolism after cardioversion, due to persistent atrial stasis and de novo thrombosis.

220

INTRODUCTION

Electrical cardioversion of AF and atrial flutter is performed to relieve symptoms, improve cardiac function and reduce the potential for subsequent thromboembolism. Cardioversion itself may be complicated by cerebral, systemic and pulmonary embolism, occurring in 0-5.6% of patients (De Silva et al 1980, Mancini et al 1982, Stein et al 1990). Despite the lack of randomised controlled trials, some studies (Bjerkelund et al 1969, Weinberg et al 1989, Lown et al 1967, Arnold et al 1992) suggest a reduction in the incidence of embolism following cardioversion in patients receiving anticoagulant therapy. However, prophylactic anticoagulation does not eliminate the risk of embolism (Bjerkelund et al 1969, Resnekov et al 1967, Aberg et al 1968, Henry et al 1976, Lesser 1990) may be associated with delay in cardioversion, additional cost and potential morbidity, and consequently is not always used.

Embolism following cardioversion is assumed to result from dislodgment of atrial thrombi following the return of atrial mechanical activity (Mancini et al 1982, Stein et al 1990, Goldman 1960). TEE is sensitive and specific for the detection of LA thrombi (Aschenberg et al 1986, Bleifeld et al 1986, Matsumura et al 1989, Acar et al 1991, Hwang et al 1992, Lin et al 1992, Olson et al 1992, Manning et al 1995, Fatkin et al 1996). The purpose of this study was to determine whether screening patients for atrial thrombi by TEE may allow cardioversion to be performed safely in patients not receiving anticoagulation. This study prospectively evaluated the echocardiographic findings and clinical outcome in a consecutive series of non-anticoagulated patients screened by TEE prior to cardioversion of nonvalvular AF or flutter.

METHODS

Patients

Inclusion and exclusion criteria for the study patients were 1) nonvalvular AF or

221

atrial flutter, 2) referral for elective electrical cardioversion, 3) not receiving anticoagulant therapy, and 4) no history of embolism. The decision not to prescribe anticoagulant therapy was determined by the referring physician so that patient allocation was not randomised. The baseline characteristics of the 40 patients meeting the study criteria are shown in Table 1.

Protocol

No patient was receiving anticoagulant therapy prior to the study. Following initial TTE, all patients underwent TEE. Patients in whom atrial thrombi were not detected proceeded to cardioversion. Patients in whom cardioversion was successful did not receive anticoagulant therapy following the procedure, while patients who had unsuccessful cardioversion received anticoagulant therapy subsequently at the discretion of the referring physician. If atrial thrombi were detected by TEE, cardioversion was not performed and the patients were commenced on anticoagulant therapy.

Echocardiography

Two-dimensional and Doppler TTE, using 2.5 MHz or 3.5 MHz imaging transducers (HP 77020A), was performed immediately before TEE. LA dimension and LV diastolic dimension were determined by standard criteria (Sahn et al 1978). LV systolic function was assessed by TTE (Feigenbaum 1986) and graded qualitatively as normal or mild, moderate or severe overall impairment. TEE was performed with a 5 MHz single plane (n=27) or biplane (n=13) transducer using standard techniques (Seward et al 1988, 1990). Written informed consent was obtained. The presence of atrial thrombus and SEC were specifically assessed. Atrial thrombus was diagnosed by the presence of a clearly defined intracavitary mass, acoustically distinct from underlying endocardium and not due to the pectinate ridges of the atrial appendage (Beppu et al 1984). LA SEC was diagnosed by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artefact (Black et al 1991a). Technically adequate TEE images were obtained in all patients.

Echocardiographic findings were recorded immediately and were therefore blinded to the results of cardioversion. There were no complications of TEE.

Cardioversion

Cardioversion was performed in the coronary care unit following sedation with intravenous thiopentone or propofol. Either the anterolateral or anteroposterior paddle positions were used. Synchronised direct current shocks were administered with increasing discharge energy until either cardioversion was successful or failure to convert, at a maximum of 360 J. Following the procedure, patients were monitored for at least 4 hours prior to discharge from the coronary care unit, and assessed clinically for evidence of embolism. Successful cardioversion was defined as the presence of sinus rhythm at discharge from the coronary care unit. All patients were followed up 1 month after cardioversion. Cardioversion-related embolism was prospectively defined as any clinically evident acute cerebral or systemic ischaemic event or pulmonary embolism during the 1 month following cardioversion.

Data collection and statistical analysis

All clinical and echocardiographic data were recorded prospectively. Clinical data were determined from patient and physician interview and chart review . TTE and TEE studies were performed and interpreted independently by experienced echocardiographers. Categorical variables were compared with the chi-square test or Fisher's exact test, and continuous variables were compared with the unpaired t test, with statistical significance defined as two-tailed $p<0.05$. Continuous variables are reported as mean $\pm$ 1 SD.

RESULTS

Echocardiographic findings prior to cardioversion

TTE did not detect atrial thrombus in any patient. In contrast, TEE demonstrated atrial thrombi in 5 (12%) of the 40 patients (p=0.03 compared to TTE), all in the LA

223

appendage (Figure 1). The clinical and echocardiographic characteristics of these 5 patients are shown in Table 2. LA thrombi were found in 4 (12%) of the 33 patients with AF and in 1 (14%) of the 7 patients with atrial flutter (p=NS). None of the LA thrombi were mobile. The single patient with LA thrombus and atrial flutter had undergone continuous electrocardiographic monitoring for 7 days prior to TEE, and did not have AF recorded at any time.

TTE did not detect atrial SEC in any patient. TEE detected LA SEC in 14 (35%) of the 40 patients (p<0.001), including 11 (33%) of 33 patients with AF and 3 (43%) of 7 patients with atrial flutter (p=NS). TEE also detected right atrial SEC in 1 (2%) of the 40 patients.

The characteristics of patients with and without LA thrombi are shown in Table 3. There was no significant difference between the two groups with regard to age, duration or type of arrhythmia, or cardiac dimensions. However, patients with LA thrombus were more likely to have moderate or severe LV dysfunction (p=0.02) and LA SEC (p=0.04).

Cardioversion

Cardioversion was cancelled and anticoagulant therapy was commenced in the 5 patients with atrial thrombi. Two other patients with post-operative AF (mean duration 6 days) in whom atrial thrombi were not detected reverted spontaneously to sinus rhythm without embolic complications within 12 hours after TEE, prior to scheduled cardioversion.

Cardioversion was performed within 1 hour after TEE in 25 of the 33 remaining patients. Eight patients early in the study underwent cardioversion 1 day following TEE. Cardioversion was successful in 25 (76%) of the 33 patients, including 19 (70%) of 27 patients with AF and all 6 patients with atrial flutter.

Follow up

Two of the 5 patients with LA thrombi detected by TEE, in whom cardioversion was cancelled, reverted spontaneously to sinus rhythm without embolic complications 1 and 10 days respectively after the TEE study, while receiving anticoagulant therapy. Repeat TEE in the latter patient 5 days after reversion, and after 3 months in 2 of the 3 other patients with thrombi, showed no change in the appearance of the thrombi.

One patient suffered a cerebral embolism after cardioversion. This 75-year old male with AF of 4 weeks duration had a history of remote myocardial infarction and congestive heart failure, without previous embolism. TTE showed LV dilatation (diastolic dimension 62 mm) and severe LV systolic dysfunction, without LV thrombus or aneurysm. The LA dimension was 54 mm. Biplane TEE clearly visualised the LA and appendage, and showed mild LA SEC but no thrombus (Figure 2). Cardioversion was successfully performed 1 hour after TEE. Twenty-four hours after cardioversion the patient suddenly developed dysphasia and right hemiplegia. An electrocardiogram showed sinus rhythm, and cerebral computed tomography 2 hours after embolism showed no haemorrhage or infarction. Intravenous heparin was commenced, and TTE and TEE were repeated 4 days later. TEE showed a fresh thrombus attached to the lateral wall of the LA appendage (Figure 2), associated with marked LA SEC. There was no evidence of LV thrombus, patent foramen ovale, or significant aortic atheroma. Carotid ultrasonography was normal. This patient died 12 days after the stroke.

There were no embolic events in the other 39 patients during the 1 month following cardioversion.

225

Table 1. Patient Characteristics.

Age (yrs) (range)	62±13 (28-79)
Male/Female (n)	29/11
Atrial fibrillation/flutter (n)	33/7
Arrhythmia aetiology (n)	
Systemic hypertension	7
Idiopathic dilated cardiomyopathy	4
Alcohol ingestion	6
Post-operative	6
Lone arrhythmia	4
Ischaemic heart disease	6
Hypertrophic cardiomyopathy	1
Other	6
Arrhythmia duration (n)	
0-1 month	21
1-12 months	16
1-5 years	3
Previous cardioversion (n)	3
Left ventricular function (n)	
Normal	28
Mild dysfunction	6
Moderate dysfunction	2
Severe dysfunction	4

Table 2. Findings in 5 Patients with Atrial Thrombus Prior to Cardioversion.

Age(yr)/ Gender	Rhythm	Aetiology	Duration	LA mm	LV mm	LV Dysfunction	Thrombus	LA SEC
28/F	AFB.	HCM	7d	50	36	Normal	LAA	+
62/M	AFib.	IDC	15d	56	69	Severe	LAA	+
79/M	AFlutter	IHD	14d	49	61	Severe	LAA	+
48/M	AFib.	HT	6w	56	58	Moderate	LAA	+
71/M	AFib.	Postop.	7d	41	57	Normal	LAA	-

AFlutter = atrial flutter, HCM = hypertrophic cardiomyopathy, IDC = idiopathic dilated cardiomyopathy, IHD = ischaemic heart disease, Postop = postoperative, HT = hypertension.

Table 3: Characteristics of Patients With and Without LA Thrombus.

Characteristics	LA thrombus (n=5)	No LA thrombus (n=35)	p
LA SEC	4 (80%)	10 (29%)	0.04
≥Moderate LV dysfunction	3 (60%)	3 (9%)	0.02
Age (yrs)	58 ± 20	63 ± 12	NS
Arrhythmia duration <1 month	4 (80%)	17 (49%)	NS
Atrial flutter	1 (20%)	6 (17%)	NS
LA dimension (mm)	50 ± 6	46 ± 8	NS
LV diastolic dimension (mm)	56 ± 12	52 ± 7	NS

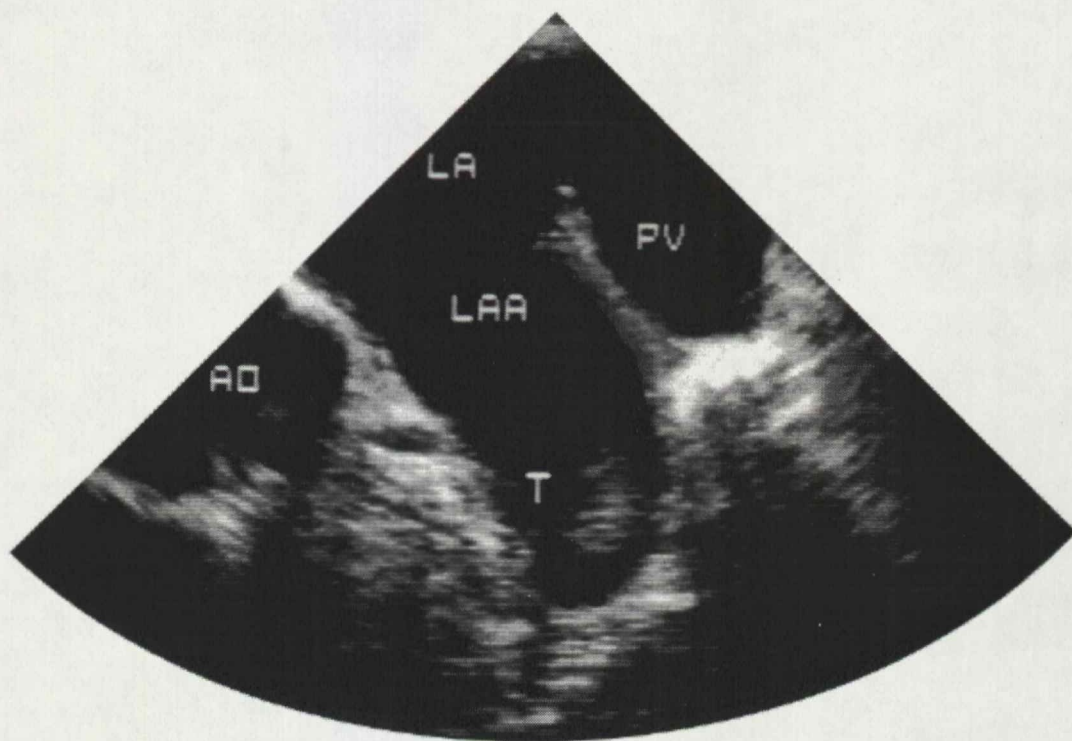**Figure 1. TEE in a Candidate for Cardioversion Showing Thrombus (T) at Apex of Left Atrial Appendage (LAA).**

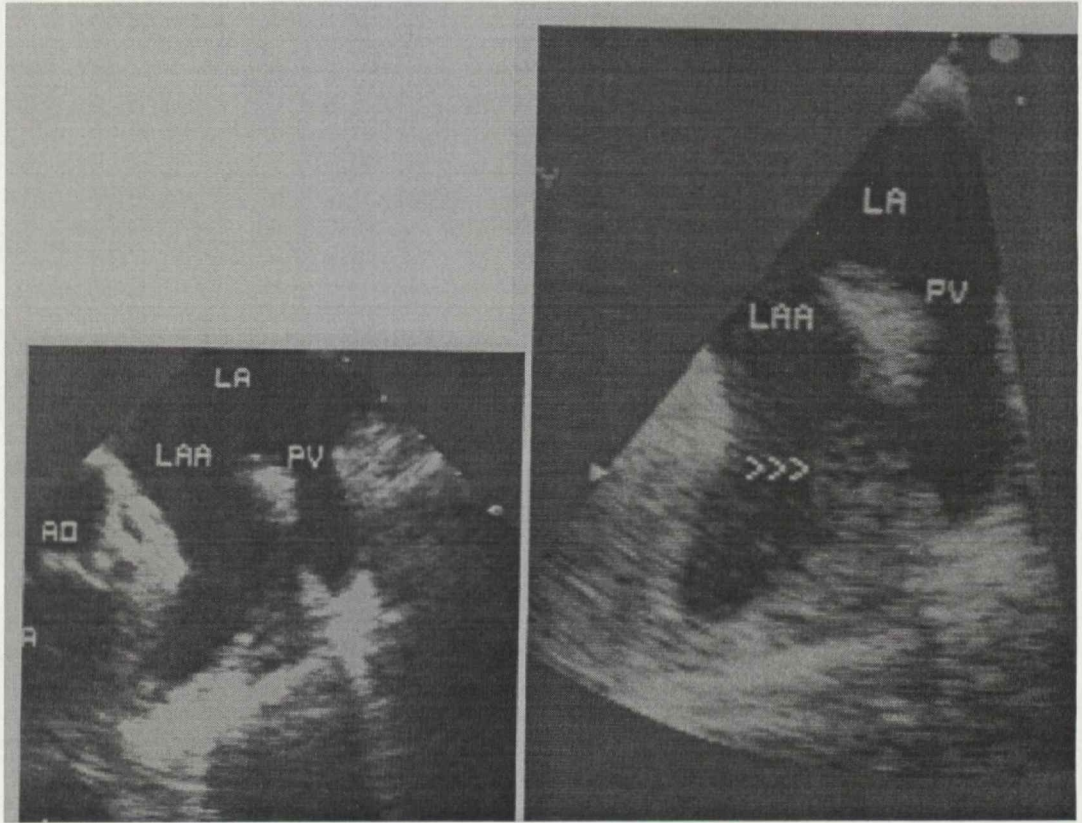AO=aorta, LA=left atrium, PV=pulmonary vein.

Figure 2. TEE in Patient with Cerebral Embolism After Cardioversion.

A, Before cardioversion. Left atrial appendage is clear of thrombus. B, After embolism. Thrombus (arrows) is present on lateral wall of left atrial appendage. Abbreviations as in Figure 1.

DISCUSSION

Recent clinical trials have highlighted the risk of embolism in patients with nonvalvular AF (Cairns and Connolly 1991). These trials have stimulated interest in cardioversion, which is also associated with a risk of embolism from atrial thrombi (De Silva et al 1980, Mancini et al 1982, Stein et al 1990) Although non-randomised case series suggest that the incidence of embolism following cardioversion may be reduced in patients receiving anticoagulant therapy (Bjerkelund et al 1969, Weinberg et al 1989, Lown et al 1967, Arnold et al 1992), there remains concern about the risk of bleeding, especially in the elderly (Kutner et al 1991, Stroke Prevention in Atrial Fibrillation Investigators 1996). In the recent AF trials (Cairns and Connolly 1991) the incidence of major bleeding including cerebral haemorrhage ranged up to 3.5% per year in patients receiving warfarin. Furthermore, these studies excluded patients considered to have an increased bleeding risk. Therefore there remains a significant number of patients with AF or flutter who are not anticoagulated and in whom cardioversion without the need for several weeks of anticoagulant therapy would be desirable.

This is the first study to evaluate the role of TEE in screening non-anticoagulated patients for atrial thrombi prior to cardioversion of nonvalvular AF and flutter. TEE improved the identification of patients with LA appendage thrombi, in whom cardioversion was deferred. However, this study has shown that embolism may still occur following cardioversion in non-anticoagulated patients despite screening by TEE.

Detection and risk factors for LA thrombi

TTE did not detect LA thrombus in any patient in the present study. There are no reports of LA thrombus detected by TTE in candidates for cardioversion, despite use of the technique in several studies (Weinberg et al 1989, Lesser 1990). In contrast, LA appendage thrombi were detected by TEE in 5 (12%) of the 40 patients, consistent with previous reports (Aschenberg et al 1986, Bleifeld et al

231

1986, Matsumura et al 1989, Acar et al 1991, Hwang et al 1992, Lin et al 1992, Olson et al 1992, Manning et al 1995, Fatkin et al 1996). Careful retrospective review of the TEE study in the patient with cerebral embolism, in whom the LA and appendage were clearly visualised, did not reveal any suggestion of pre-existing thrombus. Nevertheless the LA appendage is not optimally visualised in all patients, and it may be difficult to distinguish the pectinate ridges of the appendage from small or recently formed thrombi.

TEE may also be used to monitor patients in whom LA thrombi have been detected. Although no change in thrombus appearance following anticoagulation was observed in the present study, the utility of TEE in demonstrating resolution of LA appendage thrombi has been previously described (Tsai et al 1991).

LV dysfunction and LA SEC detected by TEE were significantly associated with the presence of LA thrombus in this series. The patient in whom thromboembolism occurred following cardioversion had both these risk factors. Although LV systolic dysfunction has not emerged as a risk factor for embolism in previous cardioversion series, LV dysfunction in patients with AF was associated with increased embolic risk in the SPAF study (The Stroke Prevention in Atrial Fibrillation Investigators 1992). As in the SPAF study, LV dysfunction in the present study was assessed qualitatively. The single patient in this series with hypertrophic cardiomyopathy was also found to have a LA thrombus. The increased embolic risk of cardioversion in these patients has been noted previously (Henry et al 1976). The criteria for this study excluded patients with rheumatic heart disease or previous embolism, also associated with increased thromboembolic risk (The Stroke Prevention in Atrial Fibrillation Investigators 1992, Wolf et al 1978).

The primary purpose of TEE prior to cardioversion is the detection of formed LA thrombi. However, TEE also improved the detection of LA SEC in the present series. We have previously reported the association between LA SEC and

232

thromboembolism in patients with nonvalvular AF (Black et al 1991a). We have also shown (Black et al 1993a) that LA SEC in patients with nonvalvular AF is associated with altered haematological parameters, indicating a hypercoaguable state in addition to stasis. Thus, the detection of LA thrombi and/or SEC by TEE may identify patients at increased risk of embolism following cardioversion.

Embolism following cardioversion

Embolism following cardioversion of AF and flutter is usually attributed to dislodgment of pre-existing atrial thrombus following the return of atrial mechanical activity (Mancini et al 1982, Stein et al 1990, Goldman 1960). However, return of mechanical function of the atrial cavity may be delayed several days to weeks after restoration of electrical sinus rhythm (Shapiro et al 1988, Manning et al 1989). Recently, Grimm et al (1992) reported that LA SEC may be generated or intensified immediately following successful cardioversion. Grimm et al (1992) also reported that LA appendage flow velocities are decreased immediately following cardioversion despite conversion from AF to sinus rhythm. These findings suggest that persistent or increased atrial stasis early after cardioversion may favour de novo thrombosis and potential embolism. The relevance of this mechanism of thromboembolism is supported by the occurrence of embolism several days after successful cardioversion (Bjerkelund et al 1969, Arnold et al 1992) and by the increased risk of embolism attributed to recently formed atrial thrombi (Goldman 1960).

This mechanism may account for the cerebral embolism in 1 patient following cardioversion despite screening by TEE in the present series. No source of embolism other than de novo LA appendage thrombus after cardioversion was detected in this patient. The thrombus was attached to the lateral wall of the appendage, a frequent location of LA appendage thrombi due to relative immobility (Pollick et al 1991). The increased intensity of LA SEC after successful cardioversion in this patient is also consistent with increased stasis and risk of thrombosis. Subsequent to the publication of the present study, Stoddard et al

233

(1995) also reported a patient with new LA appendage thrombus formation early after cardioversion.

The results of the present study and those of Grimm et al (1992) therefore suggest that the exclusion by TEE of pre-existing atrial thrombus before cardioversion does not preclude embolism after cardioversion, due to persistent atrial stasis and de novo thrombosis. Further studies will be required to determine whether anticoagulation after cardioversion can prevent LA thrombosis during this period.

It is of interest that embolism did not occur in 2 patients with documented atrial thrombi in the present series who reverted to sinus rhythm 1 and 10 days respectively after commencing anticoagulant therapy. The latter case is consistent with Goldman's hypothesis (1960) that anticoagulant therapy given for 2 weeks prior to cardioversion may stabilise a pre-existing thrombus and thereby reduce the likelihood of embolism at the time of reversion. The incidence of embolism after cardioversion is 1-5% and the prevalence of LA thrombi in nonvalvular AF is approximately 10%. Therefore the majority of LA thrombi, as in the former case, do not embolise following cardioversion. Risk factors for embolisation of LA thrombi, such as mobility, site, duration and morphology, require further study.

Embolism following cardioversion of atrial flutter is well recognised (Roy et al 1986), although considered as lower risk than AF. Three (43%) of the 7 patients with atrial flutter in the present series had LA SEC, including 1 patient with LV dysfunction in whom a thrombus was found. Black et al (1992) reported that both LA SEC and LA thrombi may occur in patients with atrial flutter, with a lesser incidence than in patients with AF. Prolonged atrial dysfunction after cardioversion of atrial flutter has also been reported (Jordaens 1991). These data suggest that patients with atrial flutter as well as fibrillation may have impaired atrial function and also merit screening for atrial thrombi prior to cardioversion.

Limitations

The present study comprised non-anticoagulated patients only, and did not directly address the risks and benefits of anticoagulant therapy in patients undergoing cardioversion. Since the risk of embolism is small, a much larger study would be required to precisely determine the risk of embolism in non-anticoagulated patients screened by TEE. LA appendage flow velocities, which provide an additional assessment of atrial mechanical function (Pollick et al 1991), were not measured.

CONCLUSIONS

This study has shown that TEE improves the detection of LA appendage thrombi in cardioversion candidates, in whom the procedure may be deferred. TEE also enabled serial monitoring of the effect of anticoagulant therapy on LA thrombi, and improved detection of LA SEC. However, the study shows that there remains a risk of embolism in non-anticoagulated patients despite screening for atrial thrombi by TEE. This finding and other recent studies suggest that the absence of detectable atrial thrombus prior to cardioversion does not preclude de novo thrombosis due to persistent or increased atrial stasis following return to sinus rhythm. A randomised, controlled clinical trial is required to determine the relative risk of embolism after cardioversion in patients conventionally managed with anticoagulant therapy compared to patients screened by TEE.

CHAPTER 11

Exclusion of Atrial Thrombus by Transoesophageal Echocardiography Does Not Preclude Embolism After Cardioversion of Atrial Fibrillation: A Multicenter Study

ABSTRACT

Background and Objectives. TEE has been used recently to detect atrial thrombi before cardioversion of atrial arrhythmias. It has been assumed that embolic events after cardioversion result from embolism of pre-existing atrial thrombi which are accurately detected by TEE. This study examined the clinical and echocardiographic findings in patients with embolism after cardioversion of AF despite exclusion of atrial thrombi by TEE.

Methods and Results. Clinical and echocardiographic data in 17 patients with embolic events after TEE-guided electrical (n=16) or pharmacologic (n=1) cardioversion were analysed. All 17 patients had nonvalvular AF, including 4 patients with lone AF. TEE before cardioversion showed LA SEC in 5 patients and did not show atrial thrombus in any patient. Cardioversion resulted in return to sinus rhythm without immediate complication in all patients. Thirteen patients had cerebral embolic events and 4 patients had peripheral embolism, occurring 2 hours-7 days after cardioversion. None of the patients were therapeutically anticoagulated at the time of embolism. New or increased LA SEC was detected in 4 of the 5 patients undergoing repeat TEE after cardioversion, including 1 patient with a new LA appendage thrombus.

Conclusions. Embolism may occur after cardioversion of AF in inadequately anticoagulated patients despite apparent exclusion of pre-existing atrial thrombus by TEE. These findings suggest de novo atrial thrombosis after cardioversion, or imperfect sensitivity of TEE for atrial thrombi, and suggest that screening by TEE does not obviate the requirement for anticoagulant therapy at the time of and following cardioversion. A randomised clinical trial is needed to compare conventional anticoagulant management with a TEE-guided strategy including anticoagulation following cardioversion.

INTRODUCTION

Recent clinical trials have focussed attention on methods of reducing the thromboembolic risk of AF, including antithrombotic therapy and cardioversion (Cairns and Connolly 1991). However, cardioversion itself may result in embolism (Stein et al 1990, De Silva et al 1980, Mancini and Goldberger 1982). Although anticoagulant therapy is frequently employed in patients undergoing cardioversion (Bjerkelund and Orning 1969, Arnold et al 1992), such therapy does not eliminate the risk of embolism (Bjerkelund and Orning 1969, Resnekov and McDonald 1967, Aberg and Cullhed 1968, Henry et al 1976, Lesser 1990) and may result in additional cost, delay, and potential morbidity.

Recently, several investigators have proposed the use of TEE to screen patients for atrial thrombi before cardioversion (Black et al Circulation 1991, Black et al Br Heart J 1991, Manning et al 1993), potentially reducing the thromboembolic risk and requirement for anticoagulation. It has been suggested that cardioversion using TEE without prolonged anticoagulation may be safer than cardioversion using anticoagulation without TEE (Daniel 1993). However, we have identified 17 patients with embolism after cardioversion despite apparent exclusion of atrial thrombus by TEE. The purpose of this study was to analyse the clinical and echocardiographic characteristics of these patients, and examine the implications for the mechanism of post-cardioversion embolism and for the role of TEE in patients undergoing cardioversion.

METHODS

Investigators from hospitals performing TEE-guided cardioversion were requested to provide information regarding embolic events after electrical or pharmacologic cardioversion for AF or atrial flutter in patients screened by TEE. The investigators were identified at major scientific meetings. All the investigators agreed to contribute information to this study, and completed a standard questionnaire for

each patient. Seven of the patients were also reported in part elsewhere (Chapter 10, Fatkin et al 1994, Salka et al 1993).

Clinical data included demographic information; type, duration and aetiology of the atrial arrhythmia; previous cardioversion attempts; coexisting cardiac diseases; thromboembolic risk factors and previous embolic events; and antithrombotic and antiarrhythmic medication. Nonvalvular AF refers to the absence of mitral stenosis or any valve prosthesis (The Stroke Prevention in Atrial Fibrillation Investigators 1992a). Lone AF refers to the absence of a known predisposing cause, including cardiac disease, hypertension or diabetes (Kopecky et al 1987). Duration of arrhythmia refers to the current episode of arrhythmia. Antithrombotic therapy was determined by the treating physician and did not follow a uniform protocol. Therapeutic anticoagulation was defined as International Normalised Ratio (INR) ≥ 2.0 for patients receiving warfarin, activated partial thromboplastin time ≥ 1.5 x control for patients receiving heparin, and anti-Factor Xa ≥ 0.5 IU/ml for patients receiving low molecular weight heparin (dalteparin sodium, Fragmin).

Echocardiographic data comprised transducer type and frequency; LV systolic function; LA diameter; mitral valve stenosis and regurgitation; left and right atrial SEC and thrombus; and other potential cardiac sources of embolism. TTE was performed with commercially available 2.25-3.5 MHz transducers. TEE was performed with standard techniques (Seward et al 1988, 1990, 1993) using commercially available 5 MHz biplane (n=8), single plane (n=8) or multiplane (n=1) transducers. There were no complications of TEE. The LA cavity and appendage were visualised by TEE in all patients. LA SEC was diagnosed by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artefact (Black et al 1991a). LA SEC was graded as mild or severe (Beppu et al 1985). Atrial thrombus refers to the presence of a clearly defined intracavitary mass, acoustically distinct from underlying endocardium and not due to the pectinate ridges of the atrial appendage (Beppu et al 1984). LA appendage Doppler flow velocities were not routinely determined.

Cardioversion data collected included interval between TEE and cardioversion; cardioversion method; number and strength of direct current shocks; non-embolic complications; and recurrence of AF after cardioversion. Data regarding embolic events included interval between cardioversion and embolism; clinical description of event; results of investigations; clinical management and outcome. Cardioversion-related embolism was defined as any clinically evident acute cerebral or systemic ischaemic event or pulmonary embolism within 1 month following cardioversion.

RESULTS

Clinical Characteristics

Clinical and echocardiographic characteristics of all 17 patients with embolism after TEE-guided cardioversion are summarised in Table 1. The 17 patients represent 2.4% of the 712 patients screened by TEE prior to cardioversion at the centres at which the embolic events occurred. There were 11 men and 6 women, aged 68 ± 13 years. All patients had nonvalvular AF, including 4 patients with lone AF. The duration of arrhythmia was 2 days to 3 years. Seven patients had congestive heart failure, 7 patients had hypertension and 2 patients had diabetes mellitus. Four patients had undergone previous cardioversion, without embolism. Two patients had previous embolism. No patient had undergone previous cardiac surgery. Eleven patients were receiving class I or III antiarrhythmic therapy, comprising amiodarone (n=4), procainamide (n=3), sotalol (n=3), flecainide (n=2) and quinidine (n=1). Four patients were considered to have clinical contraindications to anticoagulant therapy.

Echocardiography

TTE did not detect mitral stenosis, intracardiac thrombus, SEC or other source of embolism in any patient. LV systolic function was normal in 11 patients and impaired in 6 patients. Two patients had LV hypertrophy. LA diameter was 47 ± 7 mm.

TEE did not detect left or right atrial thrombus or other intracardiac thrombus or masses in any patient. All videotapes were independently overread by an experienced echocardiographer, and all videotapes except one were also reviewed in a central reference laboratory. The absence of atrial thrombus was confirmed in all cases. LA SEC was detected in both the LA cavity and appendage in 4 patients and in the LA cavity alone in 1 patient; and was graded as mild intensity in all 5 patients. Other potential sources of embolism included patent foramen ovale (n=2), protruding aortic atheroma (n=1) and mitral annular calcification (n=1). Seven patients had at least mild mitral regurgitation.

Antithrombotic therapy at the time of TEE comprised aspirin (n=4); intravenous heparin (n=3) including 1 patient also receiving warfarin; subcutaneous dalteparin (low molecular weight heparin) (n=2) including 1 patient also receiving aspirin; and subcutaneous heparin (n=1). Seven patients were receiving no antithrombotic therapy at the time of TEE. The duration of anticoagulant therapy in the 6 patients receiving heparin and/or warfarin was 1-11 days. Only 3 of the 17 patients were therapeutically anticoagulated at the time of TEE.

Cardioversion

Sixteen patients underwent electrical cardioversion using synchronised direct current shocks. Electrical cardioversion was performed within 24 hours after TEE in 13 patients and 7-21 days after TEE in 3 patients. Patients received 2.2 ± 1.3 shocks (range 1-6) with a maximum single shock of 227 ± 100 joules (range 100-360) and cumulative 419 ± 356 joules (range 100-1420). All 16 patients were successfully cardioverted to sinus rhythm. The single patient receiving pharmacologic cardioversion commenced quinidine 3 hours after TEE and reverted to sinus rhythm 19 hours after TEE. There were no immediate complications of cardioversion in the 17 patients. Three patients reverted to AF within 24 hours after cardioversion.

Antithrombotic therapy at the time of cardioversion comprised aspirin (n=4);

intravenous heparin (n=3) including 1 patient also receiving warfarin; subcutaneous heparin (n=3); and subcutaneous dalteparin (n=2) including 1 patient also receiving aspirin. Five patients were receiving no antithrombotic therapy at the time of cardioversion. Only 2 of the 17 patients were therapeutically anticoagulated at the time of cardioversion.

Embolic events

Thirteen patients had cerebral embolic events after cardioversion, and 4 patients had brachial (n=2), femoral (n=1) or mesenteric (n=1) embolism. Embolism occurred 2 hours-7 days (mean 46 ± 42 hours) following cardioversion. Electrocardiography following embolism showed that 13 patients were in sinus rhythm and 4 patients had reverted to AF. The cerebral embolic events were classified as cerebrovascular accident in 9 patients and transient ischaemic attack in 4 patients. Cerebral CT scanning was performed in 12 of 13 patients with cerebral embolism, and showed cerebral infarction in 8 patients and normal findings in 4 patients. Carotid duplex scanning in 7 patients showed no significant (>50%) stenosis. The 13 patients with cerebral embolism were treated with intravenous heparin (n=9), aspirin (n=3) or no antithrombotic therapy (n=1). The 4 patients with limb or mesenteric embolism were treated with surgical thromboembolectomy (n=3) or intravenous heparin (n=1). Eleven of the 17 patients returned home, 4 patients were transferred to nursing homes, and 2 patients died.

Antithrombotic therapy at the time of embolism comprised no therapy (n=6); aspirin (n=5); intravenous heparin (n=3) including 1 patient also receiving warfarin; subcutaneous dalteparin (n=2) including 1 patient also receiving aspirin; and subcutaneous heparin (n=1). None of the 17 patients were therapeutically anticoagulated at the time of embolism.

Echocardiography after cardioversion

Five patients underwent repeat TEE 0-96 hours after cardioversion. LA SEC was

detected in 4 of the 5 patients. In all 4 patients SEC was not previously present (n=2) or showed markedly increased intensity (n=2) compared to the pre-cardioversion study. One patient, with mild LA SEC without thrombus at the pre-cardioversion study, had increased LA SEC and a fresh thrombus adjacent to the lateral wall of the LA appendage detected by TEE 4 days after embolism. This patients was also reported in Chapter 10.

Table 1. Selected Characteristics of 17 patients with Embolism After Cardioversion of Atrial Fibrillation.

Pt	Age/ Sex	Arrhythmia Duration	Aetiology	Antithrombotic Therapy	LA (mm)	LV Dysfunction	LA SEC	Cardioversion Method	Interval CV-Embolism (hrs)	Deficit
1	37/M	1 yr	Lone	None	40	Normal	No	Quinidine	2	R hemiplegia, dysphasia
2	57/M	4 w	Lone	Aspirin	43	Normal	No	DC	48	Hemianopia
3	59/M	3 yrs	CAD	SC Hep./Asp.	48	Mild	No	DC	99	Brachial embolism
4	61/M	2 w	HT	SC Heparin	49	Normal	No	DC	48	Dysphasia
5	62/M	13 d	ETOH	IV Heparin	42	Moderate	Yes	DC	4	Dysphasia
6	63/M	7 d	DCM	Aspirin	NA	Moderate	Yes	DC	24	Femoral embolism
7	64/M	5 d	ETOH	None	45	Normal	No	DC	45	R hemiplegia, dysphasia
8	65/F	11 d	HT	IV Hep./Warf.	42	Normal	No	DC	36	R hemiplegia, dysphasia
9	66/F	3 w	Lone	IV Heparin	49	Mild	No	DC	24	L hemiparesis
10	68/M	2 w	ETOH	Aspirin	48	Normal	No	DC	30	L hemiparesis
11	69/F	2 d	HT	None	NA	Moderate	Yes	DC	48	Cerebellar syndrome
12	77/M	6 w	DCM	Aspirin	54	Severe	Yes	DC	28	R hemiplegia, dysphasia
13	77/M	2 w	Postop	SC Heparin	58	Normal	Yes	DC	168	L hemiparesis
14	77/M	4 w	COPD	None	45	Normal	No	DC	39	Brachial embolism
15	84/F	6 w	Lone	SC Heparin	33	Normal	No	DC	24	L monoplegia
16	87/F	12 d	HT	None	55	Normal	No	DC	9	L hemiparesis
17	88/F	8 d	COPD	SC Heparin	58	Normal	No	DC	98	Mesenteric embolism

Antithrombotic therapy refers to the time of cardioversion. CAD= coronary artery disease, COPD= chronic obstructive pulmonary disease, CV= cardioversion, d=day, DC=direct current, DCM=dilated cardiomyopathy, ETOH=alcohol, HT=hypertension, IV=intravenous, NA=not available, Postop- postoperative, SC=subcutaneous, w=week.

DISCUSSION

Embolism represents an uncommon but feared complication after cardioversion of atrial arrhythmias. Although prolonged anticoagulation before and after cardioversion has been recommended (Laupacis et al 1992, 1995), such therapy is not universally employed, particularly in patients with recent onset or post-operative AF. This may reflect the absence of randomised trials, the occurrence of embolism despite anticoagulation, (Bjerkelund and Orning 1969, Resnekov and McDonald1967, Aberg and Cullhed 1968, Henry et al 1976, Lesser 1990) the risk of bleeding (Stroke Prevention in Atrial Fibrillation Investigators 1996), and additional cost, inconvenience and delay.

Recently, investigators have used TEE to screen for atrial thrombi prior to cardioversion of atrial arrhythmias (Black et al Circulation 1991, Black et al Br Heart J 1991, Manning et al 1993) The rationale for TEE was based on two assumptions. Embolism after cardioversion has been assumed to result from propulsion of pre-existing atrial thrombus into the circulation (Stein et al 1990, Mancini and Goldberger 1982, Goldman 1960). It has also been assumed that TEE is a highly sensitive method of detecting atrial thrombi. The finding in the present study that embolism may occur despite apparent exclusion of pre-existing atrial thrombus by TEE requires that these assumptions be reassessed.

Characteristics of patients with embolism

Patients in the present series featured a spectrum of risk factors for embolism. The Stroke Prevention in Atrial Fibrillation (SPAF) investigators identified five clinical or echocardiographic predictors of increased thromboembolic risk in nonvalvular AF, (The Stroke Prevention in Atrial Fibrillation Investigators 1992a and 1992b) the arrhythmia present in all patients in the present series. The clinical risk factors, comprising congestive heart failure, previous embolism and hypertension, were present in 11 patients in the present series. Six patients in this series had LV dysfunction, and most patients had LA dilatation. However, the series included 4

245

patients with lone AF, associated with low embolic risk (Kopecky et al 1987). We also assessed the presence of LA SEC detected by TEE. This echocardiographic phenomenon reflects atrial stasis and altered systemic haematological parameters, thereby reflecting two arms of Virchow's triad of factors influencing thrombosis, and is a marker of LA thrombus and previous embolism in patients with nonvalvular AF (Black et al JACC 1991, Black et al 1993a). The limited predictive value for embolism of pre-cardioversion LA SEC in this series suggests that atrial function in the post-cardioversion period is a more important determinant of embolic risk.

The most characteristic feature of patients in this series is inadequate anticoagulation. No patient was therapeutically anticoagulated at the time of embolism, and no patient received prolonged anticoagulation before cardioversion. Manning et al recently utilised TEE to avoid prolonged anticoagulation prior to cardioversion (Manning et al 1993). Although not all patients in that study received anticoagulants at the time of and following cardioversion, no embolic events were detected (95% CI 0-4.6%). It was suggested that cardioversion using TEE without prolonged anticoagulation may be safer than cardioversion using anticoagulation without TEE (Daniel 1993). The present series shows that screening by TEE without adequate anticoagulation does not preclude the risk of embolism, and supports the use of anticoagulant therapy at the time of and for a period after cardioversion. This series also suggests that aspirin and/or subcutaneous heparin may not provide adequate protection against embolism in the cardioversion setting.

Detection of LA thrombus by TEE

The rationale for TEE-guided cardioversion assumes that TEE is an accurate method for the detection of LA thrombus. Could TEE have missed pre-existing LA thrombi in the present series? Multiple studies (Aschenberg et al 1986, Bleifeld et al 1986, Matsumura et al 1989, Acar et al 1991, Hwang et al 1992, Lin et al 1992, Olson et al 1992, Manning et al 1995, Fatkin et al 1996) have shown

246

approximately 95% sensitivity and specificity, compared with surgical findings, for detection of LA thrombi by TEE in patients with mitral valve disease. The imperfect sensitivity of TEE may reflect the complex three-dimensional structure of the LA appendage (Ernst et al 1993, Veinot et al 1997). The sensitivity of TEE may be further reduced in patients with nonvalvular aetiology, in whom thrombi are typically smaller and located in the LA appendage rather than the main atrial cavity (Matsumura et al 1989). Several patients in the present series had single plane TEE imaging only. Biplane or multiplane imaging improves visualisation of the atrial appendage (Seward et al 1990) and may improve the diagnostic accuracy of TEE for thrombus (Manning et al 1993). Although most patients in the present series underwent cardioversion shortly after TEE, intervals up to 21 days occurred. Thrombus may have formed in these patients between TEE and cardioversion.

Although missed thrombi may in part account for the embolic events observed, several factors suggest that this is an incomplete explanation. The LA appendage and cavity were visualised in all patients and were assessed by echocardiographers with considerable expertise in TEE. The majority of patients were studied shortly before cardioversion by biplane or multiplane TEE imaging. LA SEC and other risk factors for thrombus were uncommon before cardioversion. Nevertheless, this series highlights both the potential limitations and the importance of diagnostic accuracy when TEE is used to screen patients for atrial thrombi.

Mechanisms of embolism after cardioversion

It has been assumed that post-cardioversion embolism results from dislodgment of pre-existing atrial thrombus following the return of mechanical atrial contraction (Goldman 1960). However, recent studies have suggested an alternate mechanism for thromboembolism. Grimm et al (1993) performed TEE immediately before and after successful electrical cardioversion of AF. LA SEC developed de novo or increased after cardioversion in 35% of the patients, associated with a decrease in blood flow velocity in the LA appendage. Fatkin et al (1994) reported

247

new or increased LA SEC after cardioversion in 40% of patients studied. The pathogenesis of this apparently paradoxical deterioration in atrial appendage mechanical function after cardioversion despite reversion to sinus rhythm is not well understood. Nevertheless, these recent studies suggest an alternate mechanism for embolism, in which persistent or increased atrial stasis after cardioversion results in the formation of fresh, loosely adherent thrombus and subsequent embolism.

The findings of the present study support the hypothesis that cardioversion may result in a thrombogenic milieu. New or increased LA SEC after cardioversion was found in 4 of the 5 patients in whom it was assessed, including 1 patient with de novo thrombosis documented by TEE. It is apparent that even if TEE were a perfect test for atrial thrombus, screening prior to cardioversion would not preclude all cases of post-cardioversion embolism. The finding of residual thrombus in only 1 of 5 patients is consistent with previous reports (Black et al 1993a), and presumably reflects complete embolisation of loosely adherent thrombus. The remaining 12 patients were not re-studied following embolism, leaving it uncertain as to whether de novo atrial thrombosis occurred.

Conversely, these findings do not preclude a role for pre-existing atrial thrombus in the pathogenesis of post-cardioversion embolism. Detection of preexisting atrial thrombus by TEE presumably identifies a subgroup of patients with increased risk for embolism; in whom cardioversion can be deferred and antithrombotic therapy can be commenced or continued.

Although not all embolic events during AF result from LA thrombi (Bogousslavsky et al 1990), only 4 patients in the present series had a potential source of embolism other than the LA. The 4 patients with recurrent AF also illustrate the probable heterogeneity of embolism related to cardioversion. One patient had embolism after quinidine cardioversion. Previous reports suggest that the risk of embolism after pharmacologic and electrical cardioversion is similar (Stein et al

248

1990, Goldman 1960).

Limitations

The precise incidence of embolism after TEE-guided cardioversion cannot be determined from the present study, which comprises a selected patient population. Nevertheless, the study demonstrates that embolic events may still occur despite screening by TEE. Detailed LA and appendage mechanics were not assessed, and not all patients underwent repeat TEE after cardioversion. We cannot therefore be certain whether emboli occurred due to pre-existing thrombi missed by TEE or de novo atrial thrombosis resulting from atrial stasis after cardioversion.

CONCLUSIONS

This study has shown that exclusion of pre-existing atrial thrombus by TEE in inadequately anticoagulated patients does not abolish the risk of embolism after cardioversion of AF. The study provides clinical correlation for recent studies of mechanism suggesting that persistent or increased LA stasis after cardioversion may result in a thrombogenic milieu. These findings suggest that a negative TEE for thrombus may not obviate the requirement for anticoagulant therapy during and after cardioversion. Subsequent to the publication of this study, four other non-anticoagulated patients with embolism after cardioversion despite TEE have been reported (Missault et al 1994, Mehta et al 1996). Small LA appendage thrombi missed by TEE may have also contributed to the embolic events observed. It therefore remains to be determined whether screening by TEE removes the need for pre-cardioversion anticoagulation, and whether screening by TEE decreases the embolic risk in patients receiving conventional anticoagulant therapy. A randomised clinical trial, the Assessment of Cardioversion Utilizing Transesophageal Echocardiography (ACUTE) study, is underway to assess the potential benefits and limitations of TEE in preventing thromboembolism associated with cardioversion.

CHAPTER 12

Left Atrial Appendage "Stunning" After Spontaneous Conversion of Atrial Fibrillation

ABSTRACT

Two patients with spontaneous conversion from AF to sinus rhythm during TEE are reported. A reduction in LA appendage function, manifested by decreased LA appendage flow velocity and increased SEC, was observed. This finding suggests that the return to sinus rhythm per se, and not the electrical discharge, may precipitate atrial "stunning" after cardioversion.

INTRODUCTION

LA appendage function as assessed by TEE worsens immediately after electric cardioversion of AF to sinus rhythm (Grimm et al 1993), manifested by decreased LA appendage flow velocity and increased LA SEC. These findings represent a mechanism for thrombogenesis and thromboembolism after cardioversion. However, the mechanism of this atrial "stunning" is uncertain. All patients in the study of Grimm et al (1993) had electric cardioversion, and this therapy itself has been the leading candidate for the cause of LA appendage "stunning" which, if proved correct, could be detrimental to this traditional method of cardioversion. This report summarises the results of 2 patients who underwent TEE before a scheduled electric cardioversion and who spontaneously converted to sinus rhythm during the TEE. In both cases lower LA appendage pulsed Doppler flow velocities were demonstrated after the conversion to sinus rhythm than were measured in AF. In 1 of the 2 cases SEC was also found to increase in intensity after conversion to sinus rhythm. These cases suggest that it is merely the reversion to sinus rhythm that results in worsening LA appendage function rather than the electric shock applied during direct-current cardioversion.

CASE REPORTS

Case 1. A 32 year old, previously healthy man had new onset AF 2 weeks after the onset of an upper respiratory tract infection. After being hospitalised for ventricular rate control and receiving intravenous heparin, the patient underwent TEE to rule out LA thrombus to allow early cardioversion. The TEE revealed normal LA size, no LA SEC or thrombus, a small patent foramen ovale, and normal ventricular function. No other disease was detected. Pulsed Doppler interrogation of the LA appendage demonstrated a fibrillatory pattern with peak emptying flow velocities averaging 0.56 m/sec. During the TEE examination the patient had spontaneous conversion to sinus rhythm, and new SEC was seen in the atrial cavity. Pulsed

Doppler evaluation of the LA appendage revealed a sinus pattern with late diastolic peak emptying velocities of 0.25 m/sec as compared to the 0.56 m/sec peak velocity exhibited in AF (Figure 1). The patient was discharged 2 days later receiving warfarin, procainamide, and digoxin. No evidence for systemic embolisation was uncovered at follow-up 4 weeks later, although the AF recurred.

Case 2. A 68 year old man with severe aortic stenosis, coronary artery disease and hypertension had atrial flutter 4 days after cardiac surgery. The surgical procedure, which involved an aortic valve replacement, ascending aorta repair, and three-vessel coronary artery bypass graft surgery, was complicated by postoperative pseudomonas pneumonia that resulted in prolonged mechanical ventilation. Three weeks after surgery a TEE was performed to exclude LA thrombus prior to planned electric cardioversion. At the time of the TEE examination, the ventricular rate was controlled with verapamil. TEE revealed no LA SEC or thrombus, and pulsed Doppler evaluation of the LA appendage demonstrated emptying and filling flows in the pattern typically seen in atrial flutter. During the study the patient had spontaneous conversion to sinus rhythm, and Doppler interrogation of the LA appendage revealed an LA appendage A-wave peak velocity of 0.40 m/sec, significantly lower than the 0.67 m/sec peak velocity obtained before conversion and while in atrial flutter (Figure 2). Although the patient received heparin anticoagulation therapy at the time of conversion and for 24 hours after, anticoagulants were not instituted long term and the patient was discharged 6 days later receiving verapamil and aspirin alone. At follow-up 5 weeks later the patient was doing well, with no clinical evidence of embolism and in sinus rhythm.

Figure 1. Pulsed Doppler Flow Profiles From Patient 1 in Atrial Fibrillation (A) and in Sinus Rhythm (B) Immediately After Spontaneous Conversion.

Peak emptying flow velocities were greater in atrial fibrillation (0.60 m/sec) than in sinus rhythm (0.25 m/sec). Cal=calibration.
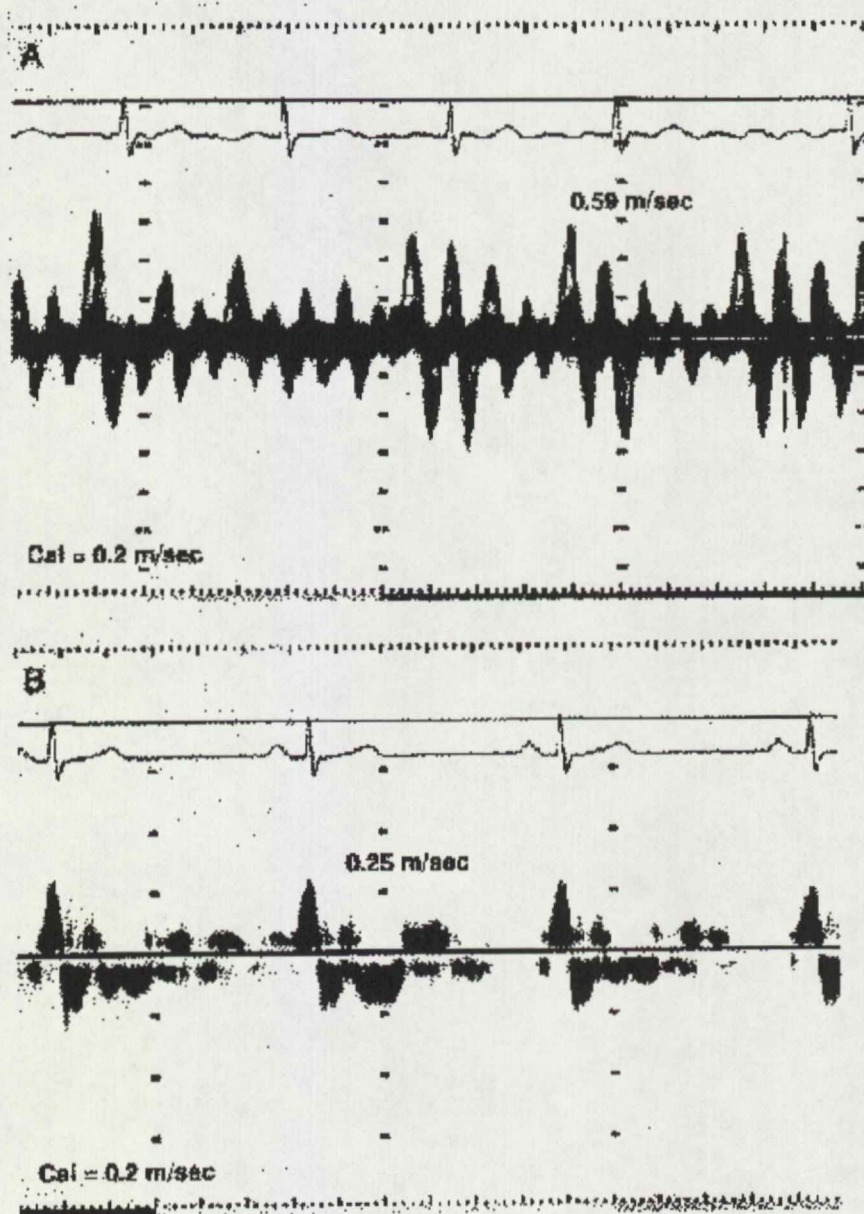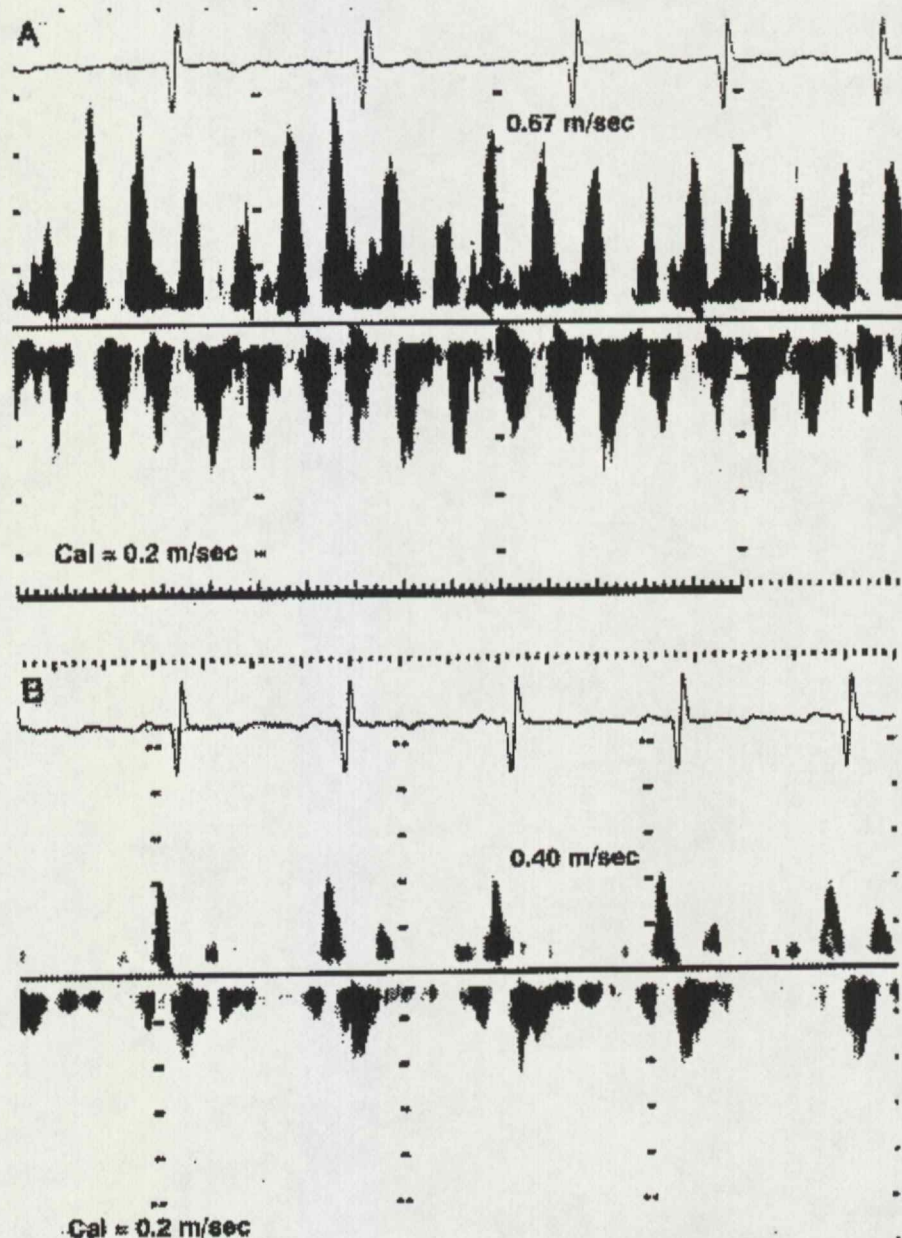
Figure 2. Pulsed Doppler Flow Profiles From Patient 2 in Atrial Flutter (A) and in Sinus Rhythm (B) Immediately After Spontaneous Conversion.

Peak emptying flow velocities were greater in atrial flutter (0.72 m/sec) than in sinus rhythm (0.40 m/sec). Cal=calibration.

DISCUSSION

The results of the two case studies reported here demonstrate that worsening LA appendage function occurs after *spontaneous* conversion from AF and flutter to sinus rhythm, independent of electric or chemical therapeutic interventions. Therefore, it appears as though the mere conversion to sinus rhythm may be sufficient to predispose the LA appendage to thrombogenesis and thromboembolism. Subsequent to the publication of the study presented in this Chapter, Falcone et al (1996) reported that atrial "stunning" occurred after successful reversion to sinus rhythm, but not after ineffective electrical or chemical cardioversion attempts.

The mechanism of embolism as a complication of cardioversion of AF remains incompletely defined. In 1960, Goldman theorised that embolic complications after cardioversion resulted from pre-existing left atrial thrombi dislodged and expelled into the systemic circulation after conversion to sinus rhythm. Although seemingly reasonable, this theory has not been validated and clinical observations imply that the theory as proposed by Goldman is not the sole mechanism of embolism after cardioversion. Echocardiographic studies in patients with AF suggest that most thrombi that exist in these patients do not embolise (Black et al 1993b). Furthermore, Black et al (1994) reported that postcardioversion thromboembolic complications can occur despite the exclusion of atrial thrombus by TEE performed before cardioversion.

Grimm et al (1993) studied 20 patients with TEE before and immediately after electric cardioversion of AF. LA appendage function was assessed with pulsed Doppler echocardiography, and the presence or absence of SEC and/or thrombus was noted. This study demonstrated new or increased SEC in the LA or LA appendage in 35% of patients. Additionally, LA appendage emptying flow velocities were significantly greater during AF than after cardioversion to sinus rhythm. These findings demonstrated that LA appendage function worsened after

256

conversion to sinus rhythm. This in turn implied an alternative mechanism for embolic complications of electric cardioversion, such that a thrombogenic milieu may develop without pre-existing thrombus, providing a substrate for subsequent thromboembolic events.

Fatkin et al (1994) reported similar findings of increased SEC after electric cardioversion of 16 patients in whom TEE was also performed before and after the procedure. Although Doppler evaluation of LA or LA appendage mechanics was not performed in this study, the increase in SEC that was reported was an indirect indication of the phenomenon of atrial cavity "stunning" after cardioversion. In contrast to the report by Grimm et al (1993), Fatkin et al (1994) found an association between the number of electric shocks applied (and a higher mean energy shock level) and the development of new or increased SEC. Fatkin et al (1994) suggested that the electric energy applied during cardioversion may be the cause of impaired atrial function after cardioversion. In support of this theory, earlier investigators (Resnekov et al 1967, Dahl et al 1974) had reported myocardial damage as a result of direct current electric cardioversion. However, more recent studies (Georges et al 1996, Allan et al 1997) found minimal or no evidence of myocyte damage after cardioversion using the sensitive and specific cardiac troponin I assay. Manning et al (1995) reported more prolonged depression of LA cavity function in patients who had electrical versus chemical cardioversion. However, there were significant differences in that study between the two patient groups, including larger LA dimension in the electrical cardioversion group. Dodds et al (1996) found no effect of transthoracic cardioversion from ventricular tachycardia to sinus rhythm on left atrial mechanical function.

Recent evidence suggests that atrial "stunning" is one of many manifestations of a tachycardia-induced atrial cardiomyopathy occurring in AF (Zipes et al 1997). A similar process may occur in ventricular myocardium (Zipes et al 1997). This phenomenon contributes to the clinical and experimental observation that "Atrial

fibrillation begets atrial fibrillation"(Wijffels et al 1995). The immediate and long-term success rate of cardioversion is reduced as the duration of AF is prolonged (Van Gelder et al 1991, Crijns et al 1991). The landmark study of Wijffels et al (1995) showed that maintenance of AF leads to atrial electrical remodelling, with shortening of the atrial effective refractory period, a reversion of its physiologic rate adaptation, and an increase in the rate, inducibility and stability of AF. Chronic AF is also associated with structural changes in the atrium, including atrial dilatation (Van Gelder et al 1991, Morillo et al 1995) and ultrastructural changes including increased myocyte and mitochondrial size, disruption of the sarcoplasmic reticulum, loss of myofibrils, accumulation of glycogen, and dispersion of nuclear chromatin (Morillo et al 1995, Ausma et al 1997).

Several mechanisms have been postulated for tachycardia-induced atrial cardiomyopathy, including neurohormonal changes, mechanical atrial stretch, and atrial ischaemia (Wijffels et al 1995). However, an increasing body of evidence implicates alterations in intracellular calcium handling, including an impaired systolic calcium transient, associated with the rapid rate of atrial depolarisation during fibrillation (Sun et al 1988). Consistent with this hypothesis, atrial contractile dysfunction is reduced in experimental models with verapamil (Leistad et al 1996). Verapamil also reduces atrial electrical remodelling (Daoud et al 1997, Tieleman et al 1997). Calcium channel blockers including verapamil may also increase the likelihood of successful cardioversion of AF in the clinical setting (Tieleman et al 1997, Tieleman et al 1998).

Intracellular calcium overload may lead to down-regulation of atrial calcium receptors. Cessation of the calcium loaded state after the return to sinus rhythm may then result in relative calcium deficiency and associated decreased mechanical dysfunction, normalising over time (Leistad et al 1996, Falcone et al 1996). Atrial function may also be reduced due to the negative inotropic effects of antiarrhythmic drugs such as sotalol (Pollak and Falk 1995).

It is arguable that the widely used term atrial "stunning" is somewhat misleading, by implying that cardioversion causes atrial dysfunction, rather than simply revealing a pre-existing atrial cardiomyopathy. The term is retained in this thesis, albeit in quotation marks.

CONCLUSIONS

The clinical implications of these case studies are pertinent to the embolic risk associated with cardioversion of atrial arrhythmias and to the embolic risk attributed to AF. Electric cardioversion should not be abandoned for fear of causing LA appendage "stunning", which may in turn place the patient at increased risk for stroke after the procedure. A similar incidence of thromboembolic complications has been reported after chemical and electric cardioversion (Chapter 1) and antiarrhythmic therapy may itself impair LA function (Pollak and Falk 1995). Therefore, all patients undergoing cardioversion of atrial arrhythmias, whether by chemical or electric means, should be considered at risk for the development of post-cardioversion thromboembolism, and similar anticoagulation strategies should be used. The present study also provides insights into the mechanism of embolism in patients with paroxysmal AF, in whom there may be repeated episodes of atrial "stunning".

In summary, this report demonstrates the phenomenon of LA appendage "stunning" after spontaneous conversion to sinus rhythm without use of direct current countershock, therefore exonerating electric energy as the sole cause of post-cardioversion thrombogenesis.

CHAPTER 13

Cardioversion Guided by Transoesophageal

Echocardiography: the ACUTE Pilot Study.

A Randomised, Controlled Trial

ABSTRACT

Background and Objectives. Electrical cardioversion in patients with AF is associated with an increased risk for embolic stroke. Screening for LA thrombus with TEE before cardioversion has the potential to permit earlier and safer cardioversion than with prolonged conventional anticoagulation therapy. This study compared the feasibility and safety of TEE-guided cardioversion with conventional management of cardioversion in patients with AF.

Methods. 126 patients with AF > 2 days duration who were candidates for electrical cardioversion were enrolled from 10 hospitals in the United States, Europe, and Australia. Patients were randomised to conventional therapy or to early, TEE-guided cardioversion with short-term anticoagulation therapy.

Results. 62 patients were randomly assigned to receive TEE-guided cardioversion; TEE was performed in 56 (90%) of these patients. Atrial thrombi were detected in 7 patients (13%) and led to the postponement of cardioversion. Cardioversion was successful in 38 of 45 patients (84%) who had early cardioversion. No embolisation occurred with this strategy. Of the 64 patients receiving conventional therapy, 37 (58%) had cardioversion, which was successful in 28 patients (76%). One patient had a peripheral embolic event. The time to cardioversion was shorter in the TEE group (0.6 weeks compared with 4.8 weeks, $p < 0.01$). The incidence of clinical haemodynamic instability and bleeding complications tended to be greater in the conventional therapy group.

Conclusions. These results suggest that TEE-guided cardioversion with short-term anticoagulation therapy is feasible and safe. The use of TEE may allow cardioversion to be performed earlier, may decrease the risk for embolism associated with cardioversion, and may be associated with less clinical instability than conventional therapy. A large multicenter study to confirm these findings is currently under way.

INTRODUCTION

AF is characterised by the lack of organised electrical and mechanical atrial activity that results in an irregular heartbeat and an increased risk of congestive heart failure, thromboembolism and death (Stroke Prevention in Atrial Fibrillation Study 1991, Wolf et al 1987, Alpert et al 1988). Since 1962, direct current electrical cardioversion has been used to restore normal sinus rhythm in patients with AF (Lown et al 1963). However, successful cardioversion with the sudden resumption of sinus rhythm is itself associated with an increased risk of embolic stroke, which can result when thrombi in the LA appendage are dislodged (Balslov et al 1968, Aberg and Cullhed 1968, Lown 1967, Resnekov et al 1967, Selzer et al 1966, Bjerkelund et al 1969, Henry et al 1976, Stein et al 1990).

TEE has an excellent ability to detect LA thrombi (Aschenberg et al 1986, Bleifeld et al 1986, Matsumura et al 1989, Acar et al 1991, Hwang et al 1992, Lin et al 1992, Olson et al 1992, Manning et al 1995, Fatkin et al 1996) and therefore has been proposed as an approach to facilitate earlier and safer electrical cardioversion than conventional therapy of 7 weeks of warfarin therapy before and after cardioversion (Black et al 1991b, Black et al 1991c, Manning et al 1993, Manning et al 1995, Laupacis et al 1995). Recent studies indicate that TEE-guided cardioversion with short-term anticoagulation may offer several advantages over the conventional approach (Manning et al 1993, Grimm et al 1994, Manning et al 1995). These potential advantages include decreased embolic risk by avoiding cardioversion for those who have thrombi in the LA appendage (Grimm et al 1994), decreased risk of bleeding by allowing briefer anticoagulation therapy (Grimm et al 1994), greater initial conversion to and long-term maintenance of sinus rhythm resulting from earlier cardioversion (Manning et al 1995), and greater cost-effectiveness by decreasing the incidence of embolic stroke (Klein et al 1994).

The ACUTE (Assessment of Cardioversion Using Transoesophageal Echocardiography) Pilot Study was a prospective multicenter randomised clinical

trial designed to compare the feasibility and safety of a TEE-guided strategy to the conventional approach for patients with AF undergoing electrical cardioversion.

METHODS

Patient selection

Patients who were candidates for electrical cardioversion were eligible for inclusion if they had AF, or atrial flutter with a history of AF, of greater than 2 days duration. Patients were excluded if they had received anticoagulants for more than 7 days, required urgent cardioversion as a result of haemodynamic instability, had a cardioembolic event within the previous month, had contraindications to TEE or to warfarin, were women with child-bearing potential in whom pregnancy could not be excluded, were unable to give informed consent, or were unable to return for follow up. The protocol was approved by the institutional review boards at all clinical sites, and all patients provided written informed consent.

Study protocol

Patients who met the inclusion criteria were randomly assigned to either a conventional or TEE-guided approach (Figure 1) with the use of pre-sealed randomisation envelopes that were computer generated and distributed to each clinical site. Random assignments were stratified by site and were generated in blocks of six.

The conventional approach was that recommended by the American College of Chest Physicians (Laupacis et al 1992, 1995): 3 weeks of warfarin therapy before cardioversion, then electrical cardioversion, then 4 weeks of warfarin therapy, and then a follow-up examination at 4 weeks. International normalised ratios were monitored at least weekly with a target of 2.0 to 3.0.

In the TEE-guided approach, patients began receiving anticoagulant therapy at their initial visit. The goal was to have patients therapeutically anticoagulated,

263

defined as partial thromboplastin time of 1.5 to 2.5 times control or an INR of 2.0 to 3.0, at the time of electrical cardioversion and for 4 weeks thereafter. The initial choice of antithrombotic agent was determined by whether the patient was an inpatient or outpatient at the time of randomisation. Heparin was used for inpatients and warfarin for outpatients. TEE, with subsequent cardioversion immediately or within 24 hours to avoid thrombus formation between TEE and cardioversion, was then scheduled as soon as stable therapeutic anticoagulation was assured. For example, for inpatients receiving heparin, TEE was performed as soon as stable therapeutic partial thromboplastin time was documented for 24-36 hours, and subsequent cardioversion was performed if thrombus was excluded. A 4 to 5 day overlap of warfarin and IV heparin was typically necessary to maintain adequate anticoagulation after cardioversion. Anticoagulation for outpatients was initiated with warfarin on the day of study enrollment, and TEE and subsequent possible cardioversion scheduled for at least 5 to 7 days later. Again, TEE and cardioversion were performed when the patient was therapeutically anticoagulated, and patients received maintenance therapy for 4 weeks after cardioversion.

If atrial thrombus was documented by TEE, cardioversion was postponed and the patient received warfarin for 4 weeks. After 4 weeks, TEE was repeated and cardioversion was performed if no thrombus was detected. If the thrombus persisted, cardioversion was again deferred and warfarin was continued for at least 4 additional weeks.

Clinical outcomes

The feasibility outcomes were frequency of cardioversion, frequency of cardioversion occurring as scheduled, time to cardioversion and time to sinus rhythm. Safety outcomes were clinically apparent ischaemic stroke, transient ischaemic attack, systemic embolisation, deaths related to cardioversion, bleeding, and clinical instability that rendered the patient unable to complete the protocol. Other outcome variables were the prevalence of thrombi, the number of patients

without thrombi who had early cardioversion, and the immediate and follow-up rhythms after cardioversion.

These outcomes were assessed for as long as 4 weeks after cardioversion but for no longer than 8 weeks after randomisation. In patients who did not have cardioversion and who spontaneously reverted to sinus rhythm, follow-up was performed 4 weeks after spontaneous reversion.

Study Organisation

The administrative organisation of the study is described in the Appendix.

Echocardiography

Conventional TTE was performed in both arms of the study using commercially available equipment. Patients in the TEE arm underwent TEE according to standard techniques using biplane or multiplane transducers (Seward et al 1990, Seward et al 1993). A complete TEE exam was performed with special attention given to imaging the left and right atrial cavities and appendages to assess the presence or absence of thrombus and SEC.

Two-dimensional directed M-mode TTE was used to derive the left-ventricular septal and posterior wall thickness, end-diastolic, end-systolic, and LA dimensions. LV ejection fraction was calculated using standard techniques (Quinones et al 1981, Schiller et al 1989). The maximal LA and right atrial areas were planimetered on-line. The severity of mitral regurgitation was graded from 0 to 4+ using colour-flow mapping (Helmcke et al 1987).

A thrombus was considered to be present when a mass detected in the appendage or body of the atrium appeared to be distinct from underlying endocardium, was not caused by pectinate muscles and was detected in more than one imaging plane. LA SEC was diagnosed by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion

265

distinct from white noise artefact (Black et al 1991a). The degree of LA SEC if present was categorised as mild or severe (Beppu et al 1985, Daniel et al 1988).

Quality control

Standard definitions of echocardiographic measurements were provided to all clinical centres as part of an operations manual. Echocardiograms at each clinical centre were interpreted locally by a single physician highly experienced in echocardiography. Videotapes of the first five patients and all videotapes showing thrombi were forwarded to a central laboratory and overread by three experienced reviewers by consensus.

Electrical cardioversion

Electrical cardioversion was performed with the standard method of Lown et al (1963) and used an initial energy of at least 40 J for atrial flutter and 200 J for AF.

Statistical analysis

Data are expressed as mean or frequency (%) with 95% CIs. Data that were not normally distributed were log-transformed and presented as geometric means. Outcomes were compared for TEE-guided and conventional arms, patients with and without thrombus (TEE arm only), and cardioverted patients in the conventional and TEE-guided arms. These analyses used the t-test for independent groups for continuous variables and Fisher's exact test for categorical variables. Binary confidence intervals were computed by StatXact, and SAS was used for all other statistical calculations. Analyses were performed using the intention-to-treat principle; that is, patients were analysed in the group to which they were randomly assigned, regardless of the actual treatment they received. A two-tailed p value <0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

One hundred and twenty-six patients were enrolled and randomly assigned to the TEE-guided arm (n=62) or the conventional arm (n=64) at 10 clinical sites (Appendix). The patients in the two arms were well matched in terms of baseline clinical and echocardiographic variables (Table 1). Patients in the TEE-guided arm were more likely to be receiving heparin (mean duration of therapy 1.4 days) or heparin and warfarin at cardioversion, whereas patients in the conventional arm were more likely to be on warfarin (mean duration of therapy 36 days) (Table 2). The primary associations of atrial arrhythmia in the two arms were hypertension and coronary artery disease (Table 3).

TEE-guided approach

Of the 62 patients assigned to the TEE group, 56 (90%) had TEE and 6 (10%) did not (Figure 2). There were no complications of the TEE procedure. Of the 56 patients undergoing TEE, 45 (80%) had electrical cardioversion, with 44 patients cardioverted at the scheduled time and 1 patients cardioverted after a delay of more than 3 weeks resulting in a protocol violation. Thirty-eight (84%) of the 45 patients having cardioversion had successful early cardioversion. Two of the 6 patients who did not have TEE had successful cardioversion (Figure 2).

In contrast, of the 11 patients who had TEE but did not have cardioversion, 7 had thrombi, 3 spontaneously reverted to normal sinus rhythm (2 after receiving antiarrhythmic therapy and 1 without antiarrhythmic therapy), and 1 converted to sinus rhythm after receiving overdrive pacing.

Thus, 42 (75%) of the 56 patients who did not have thrombus on TEE had successful cardioversion using electrical cardioversion or other methods, without prolonged anticoagulation therapy.

Mild (n=30) or severe (n=14) SEC was present in the LA cavity, appendage or both in 44 (79%) of the 56 patients.

267

Of the 7 detected thrombi (13% of the 56 patients who underwent TEE), 6 were in the LA appendage and 1 was in the right atrial appendage (Table 4, Figure 3). No thrombi were detected by TTE. The thrombi varied from 7 mm to 22 mm in length. Six patients had protruding or mobile thrombi, while 1 had a sessile thrombus. Mild or severe LA SEC was detected in 5 (83%) of the 6 patients with LA thrombi. Severe SEC was detected in the right atrium in the patient with the right atrial appendage thrombus. The 6 patients with LA thrombi had a decreased LV ejection fraction and a trend in increased LA size compared with the 50 patients without LA thrombus (Table 5).

In 3 of the 6 patients with LA appendage thrombi, follow-up TEE examination showed no residual thrombus (after a mean of 1.5 months) and electrical cardioversion was subsequently performed successfully. In the 3 other patients, residual thrombi persisted for a mean of 3 months and electrical cardioversion was not attempted. The patient with the right appendage thrombus had no residual thrombus detected by TEE at 3 months. Electrical cardioversion in this patient was not successful but a subsequent pharmacological cardioversion with procainamide restored sinus rhythm.

Feasibility, safety and other clinical outcomes are summarised in Table 5. Forty-seven patients (76%) underwent electrical cardioversion. The time to cardioversion was much shorter in the TEE-guided arm, as was the time to return to sinus rhythm (Table 5). No patient (0%, 95% CI 0-5%) in the TEE-guided arm had a clinically apparent ischaemic stroke, transient ischaemic attack, systemic embolisation, or bleeding episode. Two deaths were unrelated to cardioversion. One patient with a LA appendage thrombus in whom cardioversion was postponed subsequently died of progressive heart failure. The second patient did not have a thrombus but died from respiratory failure after knee surgery. He had undergone a successful cardioversion 2 weeks earlier. TEE was not repeated in either patient.

The rhythm at follow-up was sinus rhythm in 34 (56%, 95% CI 42-68%) of the 62

patients in the TEE arm (Table 5).

Conventional Approach

Of the 64 patients assigned to the conventional arm, 37 (58%) underwent electrical cardioversion. Of these 37 patients, 26 patients (70%) had cardioversion as scheduled, 3 patients had early cardioversion due to acute haemodynamic instability (hypotension and congestive heart failure), and 8 patients had delayed cardioversion as a result of bleeding complications or sub-therapeutic INRs. Of the 37 patients who had cardioversion, 28 (76%) had an immediate successful cardioversion to sinus rhythm. There were 2 patients with bleeding complications. One 84 year old man had life threatening gastrointestinal bleeding 8 weeks after commencing warfarin, requiring endotracheal intubation and transfusion of 4 units of packed red blood cells. Endoscopy showed a bleeding duodenal ulcer. One 62 year old man fell at home 7 days after commencing warfarin, and was hospitalised with a chest wall haematoma and also small haemothorax. The admission was complicated by a right lower lobe pneumonia.

In 1 patient who had electrical cardioversion as scheduled, a peripheral embolism to an upper extremity occurred 3 days after electrical cardioversion (incidence 2%, 95% CI 0-8%), while the INR was 1.8. This patient required additional hospitalisation for 5 days and had a peripheral angiogram that documented the embolus, which was removed surgically. The cause of the AF was hypertension, and the patient had normal LV function and mild LA enlargement.

Of the 27 (42%) patients in the conventional arm who did not undergo electrical cardioversion, 20 (74%) patients reverted to sinus rhythm an average of 16 days after randomisation. These 20 patients included 9 receiving antiarrhythmic therapy and 11 who converted spontaneously. The other 7 patients had other reasons not to have electrical cardioversion (Figure 4), including bleeding.

The follow-up rhythm was sinus rhythm in 37 (59%, 95% CI 45-70%) of the 64

patients in the conventional arm. Table 5 summarised the feasibility, safety and other outcomes in these 64 patients.

Table 1. Characteristics of Patients Undergoing Cardioversion for AF, by Treatment Group.

	TEE-Guided Approach (n=62)	Conventional Approach (n=64)	p
Male	47 (76%)	50 (78%)	NS
Age (yrs)	67 ± 11	66 ± 10	NS
Inpatient	52 (84%)	49 (77%)	NS
AF	59 (95%)	62 (97%)	NS
Duration of AF (mths)	5 ± 15	6 ± 20	NS
Median Duration AF (mths)	0.3	0.3	NS
NYHA Class III- IV	7 (26%)	6 (23%)	NS
Prior DCC	2 (19%)	13 (20%)	NS
LVEDD	50 ± 10	51 ± 10	NS
LVESD	39 ± 13	37 ± 9	NS
LVEF (%)	48 ±18	48 ± 13	NS
LA size (mm)	48 ± 8	46 ± 7	NS
LA area (cm^2)	25.7 ± 7.7	25.4 ± 8.8	NS
Mitral regurgitation≥3+	3 (5%)	9 (15%)	0.083
Antiarrhythmics at DCC	24 (51%)*	17 (46%)*	NS
IV Heparin at DCC	25 (53%)*	2 (5%)	<0.001
Warfarin at DCC	9 (19%)	34 (92%)*	<0.001
IV Heparin and Warfarin at DCC n (%)	13 (28%)	1 (3%)	0.002
INR	2.9 ± 2.0	3.2 ± 1.5	NS

* n=47 for the TEE-guided approach, and n=37 for the conventional arm.

DCC = Direct current cardioversion, IV = Intravenous, ESD = End-systolic Dimension, EDD= End-diastolic dimension, LVEF = Left ventricular ejection fraction.

271

Table 2. Antiarrhythmic and Antithrombotic Therapy by Treatment Group.

	TEE-Guided Approach (n=62)	Conventional Approach (n=64)	p
Antiarrhythmic therapy, n (%)	24 (51%)	17 (46%)	NS
Heparin, n (%)	25 (53%)	2 (5%)	<0.01
Warfarin, n (%)	9 (19%)	34 (92%)	<0.01
Heparin + Warfarin, n (%)	13 (28%)	1 (3%)	<0.01
INR, mean	3.1	3.2	NS
APTT, mean seconds	69.1	68.5	NS
Heparin duration, mean days	1.4	0.8	NS
Warfarin duration, mean days	6.7	36.3	<0.01

Table 3. Conditions Associated with AF by Treatment Group.

Causes of AF	TEE-Guided Approach (n = 62)	Conventional Approach (n = 64)
Hypertension	23 (37%)	17 (26%)
CAD	13 (21%)	17 (26%)
Valvular heart disease	9 (14%)	7 (11%)
Cardiomyopathy	7 (11%)	5 (8%)
Chronic pulmonary disease	0 (0%)	6 (9%)
Lone AF	3 (5%)	5 (8%)
Postoperative	3 (5%)	5 (8%)
Pericardial disease	1 (2%)	0 (0%)
Sick sinus syndrome	0 (0%)	2 (3%)
Diabetes	0	1 (2%)
Miscellaneous	3 (5%)	1 (2%)

Table 4. Characteristics of Patients With and Without LA Thrombi Detected by TEE.

	LA Thrombus (n=6)	No LA Thrombus (n =50)	p
LVEF%	29 ± 19	55 ± 16	0.003
LVEF <30%	4 (67%)	6 (13%)	0.01
Mitral regurgitation >moderate	1 (17%)	0 (0%)	0.12
LA area (cm^2)	34.3 ± 13.6	24.9 ± 6.2	0.15
LA size (mm)	55 ± 12	47 ± 7	0.19
Male	5 (83%)	37 (74%)	NS
Age (years)	58 ± 21	68 ± 10	NS
Mean duration of AF (mth)	10 ± 15	5 ± 16	NS
Median duration of AF (mth)	0.2	0.3	NS
Previous cardioversion	0 (0%)	10 (20%)	NS
LA SEC	5 (83%)	37 (74%)	NS

DCC = direct current cardioversion, IV = Intravenous, LVEF = Left ventricular ejection fraction.

Table 5.   Endpoints of the ACUTE Pilot Study, by Treatment Group.

	TEE-Guided Approach (n = 62)	Conventional Approach (n = 64)	p
Feasibility outcomes			
Cardioversion, n/n (%)	47/62 (76%)	37/64 (58%)	0.03
Scheduled cardioversion	44/47 (94%)	26/37 (70%)	<0.01
Mean time to cardioversion (wks)	0.6	4.8	<0.01
Mean time to SR (wks)	1.0	4.3	<0.01
Safety outcomes			
Embolism	0	1 (1.6%)	NS
Cardioversion related death	0	0	NS
Haemodynamic instability			
& bleeding	1 (1.7%)	5 (7.9%)	0.21
Other outcomes			
RA or LA thrombi on TEE n/n (%)	7/56 (13%)	-	-
Conversion to SR in patients			
without thrombi on TEE	42/56 (75)	-	-
Sinus rhythm after cardioversion	40/47 (85%)	28/37 (76%)	NS
Sinus rhythm at follow-up	34/62 (55%)	37/64 (56%)	NS
Mean time from enrollment			
to follow-up (wks)	5.7	7.7	<0.01

SR=sinus rhythm, RA=right atrium

Atrial Fibrillation Lasting > 2 Days

Transesophageal
Echocardiography-Guided Group

Conventional
Therapy Group

Therapeutic Anticoagulation at Time
of Transesophageal Echocardiography
(Heparin or Warfarin)

LA or LAA Thrombus Detected

No Thrombus

3 Weeks
Warfarin

4 Weeks Warfarin

Cardioversion

Cardioversion

Repeated
Transesophageal
Echocardiography

Thrombus
Resolved

Thrombus
Persists

4 Weeks
Warfarin

4 Weeks
Warfarin

Cardioversion

No Cardioversion

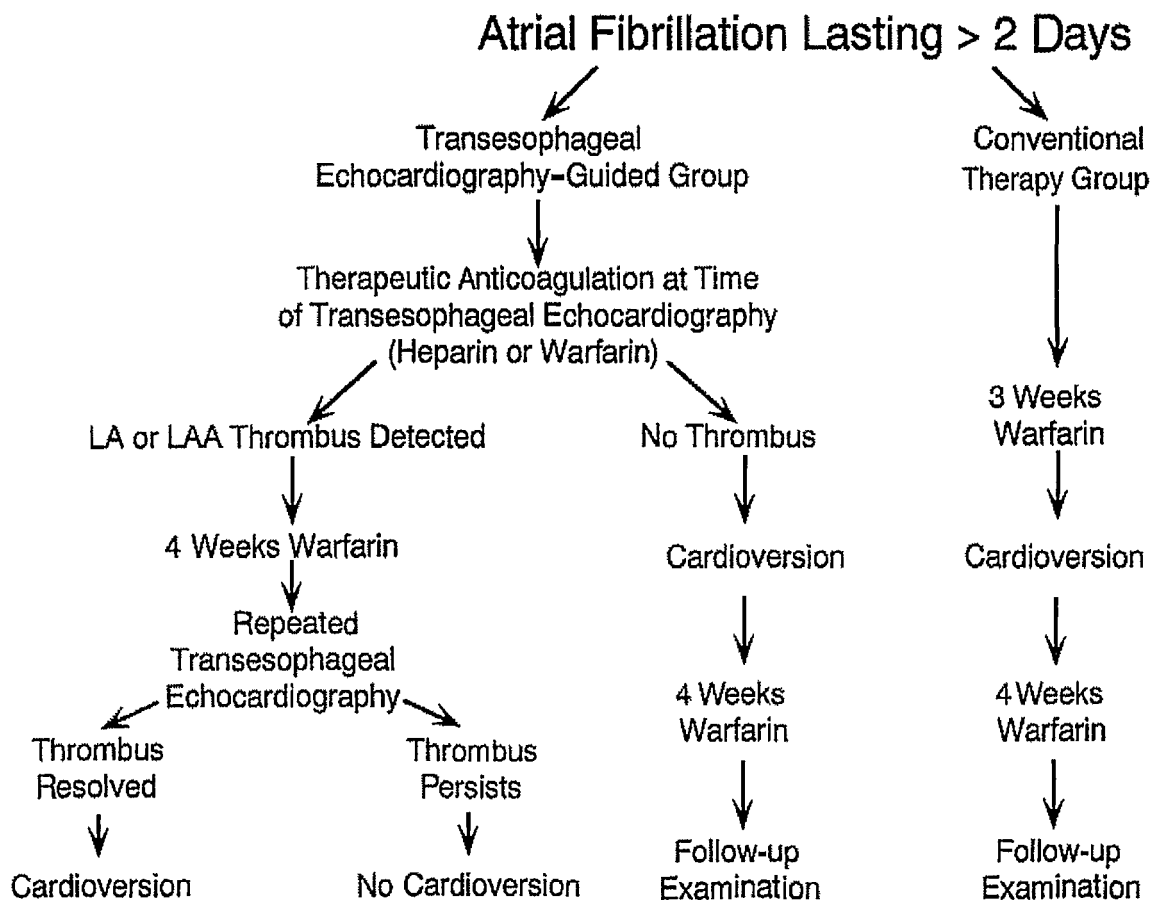Follow-up
Examination

Follow-up
Examination

Figure 1. The ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) Study Protocol.

Patients with atrial fibrillation were randomly assigned to receive either cardioversion with conventional therapy or cardioversion guided by transesophageal echocardiography (TEE) with brief anticoagulation therapy. The conventional therapy group received warfarin therapy for 3 weeks before and 4 weeks after cardioversion. In the TEE group, patients were stratified according to whether a thrombus was detected in either the left atrium or the left atrial appendage. Patients in the TEE group were fully anticoagulated at the time of cardioversion and for 4 weeks after cardioversion.
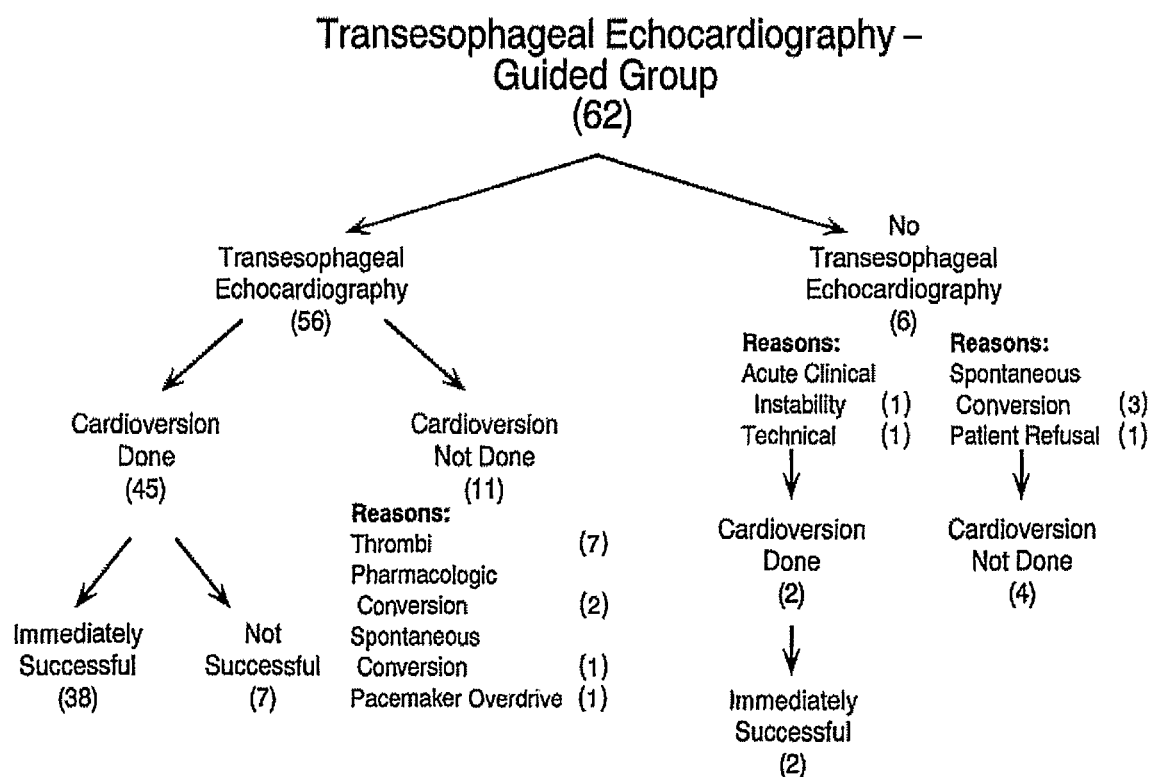
Figure 2. Outcome of the 62 Patients in the Group Assigned to Receive Transesophageal Echocardiography-Guided Cardioversion.

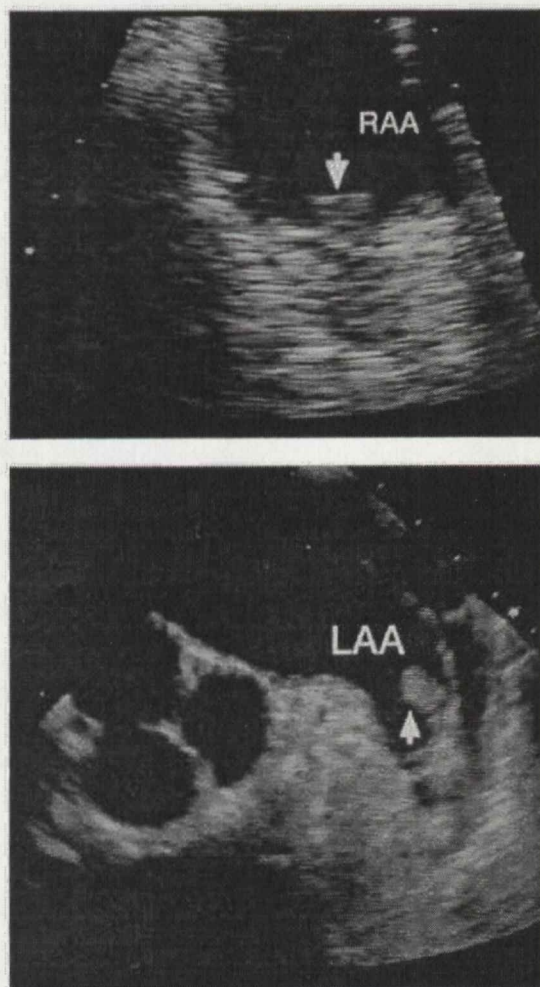Numbers in parentheses are numbers of patients.

Figure 3. Transesophageal Echocardiograms. Top. An 8.5 mm protruding thrombus (arrow) in the right atrial appendage (RAA) of a 53-year-old man. Bottom. A 9 mm LA appendage (LAA) thrombus (arrow) in a 70-year-old man.
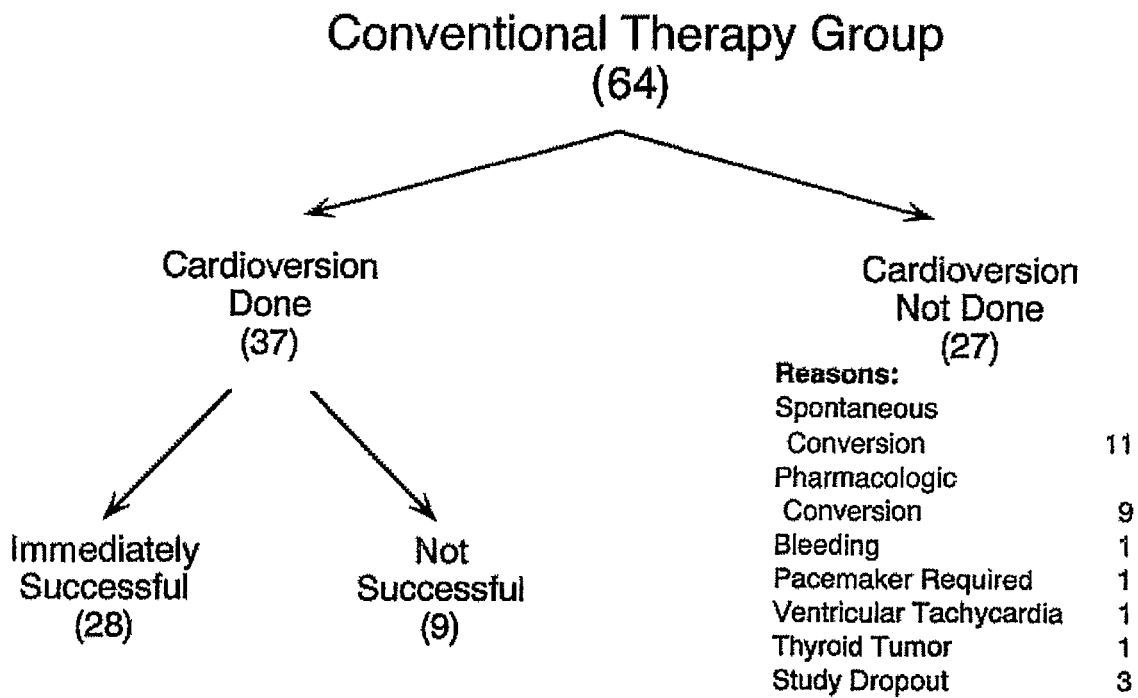
Conventional Therapy Group
(64)

Cardioversion Done (37)
    Immediately Successful (28)
    Not Successful (9)

Cardioversion Not Done (27)

Reasons:
Spontaneous Conversion	11
Pharmacologic Conversion	9
Bleeding	1
Pacemaker Required	1
Ventricular Tachycardia	1
Thyroid Tumor	1
Study Dropout	3

Figure 4. Outcome of the 64 Patients Assigned to Receive Conventional Therapy.

Numbers in parentheses are numbers of patients.

DISCUSSION

This study shows for the first time in a prospective, randomised controlled trial of patients with AF undergoing electrical cardioversion that a TEE-guided approach with short-term anticoagulation is both safe and feasible compared to conventional therapy. This approach allows for early and more convenient cardioversion and may potentially decrease the risk of embolism by detecting thrombi, reduce clinical instability and allow the resolution of thrombi to be followed. In addition, this is the first study to evaluate the conventional anticoagulation approach to electrical cardioversion as recommended by the American College of Chest Physicians (Laupacis et al 1995).

Rationale for the TEE-guided approach

Recently, there has been increasing interest in the use of TEE to screen for thrombi before electrical cardioversion and thus to decrease the risk of embolism (Laupacis et al 1995). Some studies initially advocated TEE to obviate the need for anticoagulation because of the excellent detection rate of thrombi, but this approach is flawed because it cannot exclude thrombi that may form after cardioversion (Black et al 1993b, Chan et al 1992, Orsinelli et al 1993, Stoddard et al 1993). Recent studies (Black et al 1994) have confirmed the need for anticoagulation in the pericardioversion period.

Based on these studies, the ACUTE study was designed to allow TEE to exclude thrombi and to have patients therapeutically anticoagulated at the time of cardioversion and for 4 weeks after cardioversion.

Rationale for the conventional approach

Embolic stroke has remained a significant complication of electrical cardioversion, occurring with a prevalence of 0.6% to 5.6% (Stein et al 1990). On the basis of previous studies that were neither randomised or controlled (Bjerkelund et al 1969, Arnold et al 1992), the American College of Chest Physicians (Laupacis et al 1992,

1995) recommended that 7 weeks of anticoagulation (3 weeks before and 4 weeks after cardioversion) be given to patients with AF of greater than 2 days duration. However, the major limitations to the conventional approach are the need to delay cardioversion for 3 weeks, the increased risk of bleeding, the inconvenience of re-admission for cardioversion, the lack of controlled studies showing its efficacy, and the low stroke rate among patients not taking anticoagulants.

The Effect of earlier electrical cardioversion

The delay and inconvenience of waiting 3 weeks before cardioversion are major limitations of the conventional strategy. By design of the study, cardioversion could be performed earlier with the TEE-guided approach than the conventional approach (0.6 weeks compared with 4.8 weeks). In addition, more patients in the TEE-guided arm underwent electrical cardioversion (76% compared with 58%) and more patients had electrical cardioversion as originally scheduled (71% vs. 41%).

However, one unexpected outcome of the 3 week delay associated with the conventional approach was that 20 (31%) of the 64 patients converted to sinus rhythm spontaneously or while receiving antiarrhythmic therapy. Thus, some delay before cardioversion may have benefits for patient comfort and for morbidity in patients with other serious disease. However, the risk of embolism during spontaneous or pharmacologic conversion may be similar to that during electrical cardioversion, and atrial "stunning" may still occur after conversion from AF to sinus rhythm (Grimm et al 1993, Fatkin et al 1994, Grimm et al 1995).

Potential advantages of the TEE-guided approach

This study indicates that the TEE-guided approach may have advantages over conventional approach. Thus, although the numbers of patients and events are small, clinically apparent embolism (stroke, TIA, and systemic embolisation) did not occur in the TEE arm, but was detected in 1 patient (1.6%) in the conventional arm (Table 5). The fact that no embolism occurred in the TEE arm is an important finding because the conventional approach has been the accepted standard for

281

cardioversion. The patient who had an embolic event 3 days after cardioversion required both an embolectomy, and 5 additional days in the hospital. This suggests that the TEE-guided approach may be more cost-effective than the conventional approach (Klein et al 1994).

This Pilot Study suggests that bleeding from prolonged anticoagulation with warfarin or heparin may represent potential morbidity for the conventional approach, which mandates 7 weeks of anticoagulation compared to 4 weeks with the TEE-guided approach. Bleeding complications occurred only in the conventional arm. Bleeding is an important complication of anticoagulant therapy, as shown in the recent randomised trials of anticoagulation in nonvalvular AF (Petersen et al 1989, Stroke Prevention in Atrial Fibrillation Investigators 1991, Connolly et al 1991, Ezekowitz et al 1992, The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990).

Effect of thrombus detection

Seven thrombi were detected in the TEE-guided arm, 6 in the left and 1 in the right atrial appendage. The finding of thrombi by TEE in 13% patients undergoing cardioversion is similar to the 10% to 15% reported in other series (Black et al 1991a, Manning et al 1995). Whether these thrombi would be present after 3 weeks of anticoagulation (as in the conventional arm), is uncertain, but at least 50% of the thrombi were still present after prolonged anticoagulation (6 weeks) in the TEE arm.

Follow-up rhythm

A major advantage of the TEE-guided approach is to enable earlier cardioversion to sinus rhythm, which may be important because the duration of AF may influence the success of cardioversion and the maintenance of sinus rhythm. However, patients in the TEE arm, despite having earlier cardioversion, showed immediate conversion rates similar to patients in the conventional arm (85% compared with 76%). Similarly, during the follow up period, the prevalence of sinus rhythm in the

TEE-guided arm and in the conventional arm was similar (55% compared to 56% respectively), reflecting the many variables that influence AF (Alpert et al 1988).

Previous studies of TEE-guided cardioversion

TEE-guided cardioversion was first reported by Black et al (1991b and 1991c). Manning et al (1993) reported the safety of TEE-guided cardioversion in 94 patients, followed by a report of a larger experience (Manning et al 1995) of 230 patients. Of the 196 patients without thrombi, 186 (95%) had successful electrical or pharmacologic cardioversion without an embolic event. Manning et al (1995) concluded that the TEE-guided approach to cardioversion was useful and may decrease the risk of embolism. However, Manning et al did not include a control group and evaluated a mixture of antiarrhythmic, anticoagulation, and cardioversion approaches. Stoddard et al (1995) also described TEE-guided cardioversion with brief anticoagulation in 206 patients, with no embolism. Although encouraging, these studies were not controlled and too small to establish clinical efficacy or cost-effectiveness. The present study is the first prospective, randomised study of TEE-guided electrical cardioversion with an adequate control group.

Limitations

The limited goal of the pilot study was to assess the feasibility and safety of a TEE-guided anticoagulation strategy for electrical cardioversion, which was demonstrated. Because of low event rates, a multicenter study of 3000 patients and adequate statistical power (alpha=0.05 and power=90%) is needed to definitively compare the TEE-guided approach with conventional therapy. The estimated stroke event rates for the conventional and TEE arm are 2.9% and 1.2% over 8 weeks, respectively (The Steering and Publications Committees of the ACUTE Study, for the ACUTE Investigators 1998). With the addition of major bleeding as a composite endpoint, the estimated rates of major complications are 3.5% and 1.5% respectively (The Steering and Publications Committees of the ACUTE Study, for the ACUTE Investigators 1998, Klein et al 1996).

One limitation of the pilot study is that the time periods of observations used in comparing the two approaches were unequal, with an endpoint at 4 weeks after cardioversion but no later than 8 weeks after randomisation. Differences in follow-up time from study enrollment resulted from differences between the two approaches in time to cardioversion and rates of spontaneous or pharmacologic conversion.

A limitation of the TEE-guided approach is that TEE may miss tiny thrombi in the LA appendage, which may have multiple lobes (Leung et al 1994). The possibility of missing thrombi was reduced because all patients in the TEE-guided arm underwent biplane or multiplane imaging by experienced echocardiographers. In addition, all patients in the TEE arm were fully anticoagulated at the time of cardioversion and for 4 weeks after, which would minimise the embolic risk from small undetected thrombi. Finally, patients with recent embolism, in whom the prevalence of LA thrombus is increased (Black et al 1991a), were excluded from the present study.

CONCLUSIONS

The ACUTE Pilot Study shows that the TEE-guided approach to cardioversion with short-term anticoagulation is feasible and safe compared to conventional therapy. The TEE-guided approach allows for early and more convenient cardioversion, may decrease the risk of embolism by detecting thrombi, may reduce clinical instability and allows the resolution of thrombi to be followed. This study is also the first to formally evaluate the conventional anticoagulation approach. However, the findings of the present study should be considered preliminary due to the small number of patients and events. More definitive guidance on the management of electrical cardioversion for AF must await the results of the main ACUTE trial, which is currently underway with >1000 patients randomised.

APPENDIX

Co-ordinating Centre

The Cleveland Clinic Foundation Department of Cardiology

Principal Investigator and Project Director: Allan L. Klein, MD

Co-principal Investigators: Richard A. Grimm, DO; Ian W. Black MBBS, and Dominic Y. Leung MBBS

Core Echocardiography Laboratory

The Cleveland Clinic Foundation Department of Cardiology Cardiovascular Imaging Center

Allan L. Klein, MD; Richard A Grimm, DO; Ian W. Black, MBBS; R. Daniel Murray, PhD; Dominic Y. Leung, MBBS; Susan E Vaughn, RN.

Executive Committee

Warren J. Manning, MD; David A. Orsinelli, MD; Marcus F. Stoddard, MD.

Operating Committee

Ravin Davidoff, MB BCH; Roberto M Lang, MD; Tuimothy P. Obarski, DO; Alan S. Pearlman, MD; Thomas R. Porter, MD; Miguel A. Quinones, MD; Rita I. Redberg, MD; Miguel Zabalgoitia, MD.

Statistical Coordinating Centre

The Cleveland Clinic Foundation

Dave P. Miller, MS, and Kristopher L. Arheart EdD

Clinical Centres and Collaborating Investigators

The Cleveland Clinic Foundation, University of Nebraska (Thomas R. Porter, MD) Riverside Methodist Hospital Columbus OH (Timothy P. Obarski, DO), Ohio State University (Anthony C. Pearson, MD, David A. Orsinelli, MD), University of California San Francisco Medical Center (Rita F. Redberg, MD), University of

Louisville (Marcus F. Stoddard, MD), Texas Heart Institute (Susan Wilansky, MD), Prince Henry Hospital Australia (Warren F. Walsh, MD), Bronx Veteran Affairs Medical Center (Larry Baruch, MD), University Gesamthochschule-Essen (Raimund Erbel, MD).

References

Abascal VM, Wilkins GT, O'Shea JP, Choong CY, Palacios IF, Thomas JD, Rosas E, Newell JB, Block PC, Weyman AE. Prediction of successful outcome in 130 patients undergoing percutaneous balloon mitral valvotomy. Circulation 1990;82:448-456.

Aberg H, Cullhed I. Direct current countershock complications. Acta Med Scand 1968;183:415-421.

Aberg H. Atrial fibrillation: a study of atrial thrombosis and systemic embolism in a necropsy material. Acta Med Scand 1969;185:373-379.

Acar J, Cormier B, Grimberg D, Kawthekar G, Iung B, Scheuer B, Farah E. Diagnosis of left atrial thrombi in mitral stenosis - usefulness of ultrasound techniques compared with other methods. Eur Heart J 1991;12(Suppl B):70-76.

Acar J, Michel PL, Cormier B, Vahanian A, Iung B. Features of patients with severe mitral stenosis with respect to atrial rhythm. Acta Cardiologica 1992;67:115-124.

Adams GF, Merrett JD, Hutchinson WM, Pollock AM. Cerebral embolism and mitral stenosis: survival with and without anticoagulants. J Neurol Neursurg Psychiatry 1974;37:378-83.

AFFIRM. Atrial fibrillation: A study of optimal therapy. Preliminary Protocol. June 23, 1995.

Alam M, Thorstrand C. Left ventricular function in patients with atrial fibrillation before and after cardioversion. Am J Cardiol 1992;69:694-696.

Albers GW, Comess KA, DeRook FA, Bracci P, Atwood JE, Bolger A. Transesophageal echocardiographic findings in stroke subtypes. Stroke

1994;25:23-28.

Albers GW. Atrial fibrillation and stroke. Three new studies, three remaining questions. Arch Intern Med 1994;154:1443-8.

Allan JJ, Feld RD, Russell AA, Ladenson JH, Rogers MA, Kerber RE, Jaffe AS. Cardiac troponin I levels are normal or minimally elevated after transthoracic cardioversion. J Am Coll Cardiol 1997;30:1052-1056.

Alpert JS, Petersen P, Godtfredsen J. Atrial fibrillation: natural history, complications, and management. Ann Rev Med 1988;39:41-52.

Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy: I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelt therapy in various categories of patients. BMJ 1994;308:81-106.

Arani DT, Carleton RA. The deleterious role of tachycardia in mitral stenosis. Circulation 1967;36:511-516.

Arnold AZ, Mick MJ, Mazurek RP, Loop FD, Trohman RG. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. J Am Coll Cardiol 1992;19:851-5.

Aronow WS, Gutstein H, Hsieh FY. Risk factors for thromboembolic stroke in elderly patients with chronic atrial fibrillation. Am J Cardiol 1989;63:366-367.

Aschenberg W, Schluter M, Kremer P, Schroder E, Siglow V, Bleifeld W. Transoesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. J Am Coll Cardiol 1986;7:163-6.

Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449-57.

Atrial Fibrillation Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation. A prospective study of 1066 patients from 3 clinical trials. Arch Intern Med 1998;158:1316-1320.

Atwood JE, Myers J, Sullivan M, et al . The effect of cardioversion on maximal exercise capacity in patients with chronic atrial fibrillation. Am Heart J 1989;118:913-8.

Ausma J, Wijffels M, Thone F, Wouters L, Allessie M, Borgers M. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. Circulation 1997;96:3157-3163.

Badimon L, Badimon JJ, Fuster V. Pathogenesis of thrombosis. In: Fuster V, Verstraete M (Eds). Thrombosis in cardiovascular disorders. WB Saunders: Philadelphia, 1992:25.

Balslov JT, Holm I, Jorgensen HE, Winkler K. Treatment of cardiac arrest in 200 patients with special reference to results and complications. Nord Med 1968;79:243-9.

Bansal R, Heywood TJ, Applegate PM, Jutzy K. Detection of left atrial thrombi by two-dimensional echocardiography and surgical correlation in 148 patients with mitral valve disease. Am J Cardiol 1989;64:243-246.

Barzilai B, Vered Z, Mohr GA, et al. Myocardial ultrasonic backscatter for characterisation of ischaemia and reperfusion: relationship to wall motion. Ultrasound Med Biol 1990;16:391-8.

Barzilai B, Thomas LJ, Glueck RM, et al. Detection of remote myocardial infarction with quantitative real-time ultrasonic characterization. J Am Soc Echocardiogr 1988;1;179-86.

Beppu S, Nimura Y, Sakakibara H, Nagata S, Park YD, Izumi S. Smoke-like echo in the left atrial cavity in mitral valve disease: its features and significance. J Am Coll of Cardiol 1985;6:744-9.

Beppu S, Park YD, Sakakibara H, Nagata S, Nimura Y. Clinical features of intracardiac thrombosis based on echocardiographic observation. Jpn Circ J 1984;48:75-82.

Beppu S, Nimura Y, Sakakibara H, Nagata S, Park YD, Izumi S. Smoke-like echo in the left atrial cavity in mitral valve disease: its features and significance. J Am Coll Cardiol 1985;6:744-749.

Bessos H, Murphy WG. A new competitive binding enzyme-linked immunosorbent assay for glycocalicin in plasma and platelet concentrate supernatants. Thromb Res 1990;59:497-507.

Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to DC electrical conversion of atrial fibrillation. Am J Cardiol. 1969;23:208-216.

Black IW, Fatkin D, Sagar KB, Khandheria BK, Leung DY, Galloway JM, Feneley MP, Walsh WF, Grimm RA, Stollberger C, Verhorst PMJ, Klein AL. Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation: A multicenter study. Circulation 1994;89:2509-2513.

Black IW, Chesterman CN, Hopkins AP, Lee LCL, Chong BH, Walsh WF.

Haematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation. J Am Coll Cardiol 1993a;21:451-7.

Black IW, Hopkins AP, Lee LCL, Walsh WF. Evaluation of transesophageal echocardiography prior to cardioversion of atrial fibrillation and flutter in non-anticoagulated patients. Am Heart J 1993b;126:375-381.

Black IW, Stewart WJ. The role of echocardiography in the evaluation of cardiac source of embolism: Left atrial spontaneous echo contrast. Echocardiography 1993;10:429-439

Black IW. Role of transesophageal echocardiography in cardioversion. ACCEL (American College of Cardiology Extended Learning) September 1993.

Black IW, Cranney GB, Walsh WF, Brender D. Embolization of a left atrial ball thrombus during transesophageal echocardiography. J Am Soc Echocardiogr 1992;5:271-3.

Black IW, Hopkins AP, Lee LCL, Walsh WF. Left atrial spontaneous echo contrast: A clinical and echocardiographic analysis. J Am Coll Cardiol 1991a;18:398-404.

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Role of transoesophageal echocardiography in evaluation of cardiogenic embolism. Br Heart J 1991b;66:302-7.

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. The clinical role of transoesophageal echocardiography. Aust NZ J Med 1990;20:759-64.

Black IW, Fatkin D, Sagar KB, Khandheria BK, Leung DY, Galloway JM, Feneley MP, Walsh WF, Grimm RA, Stollberger C, Verhorst PMJ, Klein AL. Unexpected

embolism (despite screening) after cardioversion of atrial fibrillation. Cardiology Board Review 1995;12:17-20.

Black IW, Stewart WJ, Walsh WF, Grimm RA, Leung DYC, Ward MR, Cranney GB, Klein AL, Hopkins AP, Thomas JD. Different aetiology of left atrial appendage vs cavity thrombus assessed by transoesophageal echocardiography. Aust NZ J Med 1995;25:610. (Abstract)

Black IW, Stewart WJ, Grimm RA, Klein AL, Thomas JD, Cosgrove DM. Role of direct epivascular echocardiography in intraoperative assessment of aortic atheroma. Aust NZ J Med 1994;24:645. (Abstract)

Black IW, Grimm RA, Walsh WF, Leung DY, Cranney GB, Stewart WJ, Thomas JD, Klein AL. Transoesophageal echocardiographic findings and clinical outcome in 223 patients undergoing cardioversion. Aust NZ J Med 1994;24:639. (Abstract)

Black IW, Klein AL, Grimm RA, Murray RD, Stewart WJ, Thomas JD. Quantification of left atrial spontaneous echo contrast using integrated backscatter. Aust NZ J Med 1994;24:625. (Abstract)

Black IW, Fatkin D, Sagar KB, Leung DY, Galloway JM, Feneley MP, Walsh WF, Grimm RA, Klein AL. Does exclusion of atrial thrombus by transesophageal echocardiography preclude embolism after cardioversion? A multicenter study. Circulation 1993;88(Suppl):314. (Abstract)

Black IW, Stewart WJ, Grimm RA, Savage RM, Klein AL, Thomas JD, Cosgrove DM. Direct epivascular echocardiography is essential for complete intraoperative assessment of aortic atheroma. Circulation 1993;88(Suppl):387. (Abstract)

Black IW, Grimm RA, Walsh WF, Stewart WJ, Hopkins AP, Lee LCL, Thomas JD, Klein AL. Low incidence of stroke after cardioversion in patients screened by

transesophageal echocardiography. Eur Heart J 1993;14(Suppl):356. (Abstract)

Black IW, Stewart WJ, Klein AL, Thomas JD, Cosgrove DM. Intraoperative assessment of aortic atheroma: comparison of epivascular and transesophageal echocardiography. Eur Heart J 1993;14(Suppl):358. (Abstract)

Black IW, Grimm RA, Walsh WF, Klein AL, Stewart WJ, Hopkins AP, Lee LCL. Risk factors for atrial thrombus and stroke in 156 patients undergoing electrical cardioversion: a multicenter transesophageal echocardiographic study. J Am Coll Cardiol 1993;21(Suppl A):28. (Abstract)

Black IW, Stewart WJ, Walsh WF, Klein AL, Hopkins AP, Duffy CI, Lee LCL, Cohen GI, Lever HM, Salcedo EE. Location of left atrial thrombi (appendage vs cavity) is dependent on underlying cardiac disease. J Am Coll Cardiol 1993;21(Suppl A):200. (Abstract)

Black IW, Hopkins AP, Lee LCL, Walsh WF. Haematological factors in left atrial spontaneous echo contrast and thromboembolism. Aust NZ J Med 1993;23:106. (Abstract)

Black IW, Hopkins AP, Lee LCL, Walsh WF. Thromboembolic risk of atrial flutter. J Am Coll Cardiol 1992;19(Suppl A):314. (Abstract)

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Role of transesophageal echocardiography in the cardioversion of atrial arrhythmias. Circulation 1991c;84(Suppl II):694. (Abstract)

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Improved detection of source of peripheral arterial embolism with transesophageal echocardiography. Circulation 1991;84(Suppl II):22. (Abstract)

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Left atrial spontaneous echo contrast and thromboembolic risk in nonvalvular atrial fibrillation. Aust NZ J Med 1991;21(Suppl II):521. (Abstract)

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Detection of left atrial thrombi by transoesophageal echocardiography prior to elective cardioversion of atrial arrhythmias. Aust NZ J Med 1991;21(Suppl II):521. (Abstract)

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Should all patients with embolic events have transesophageal echocardiography?. Circulation 1990;82(Suppl III):246. (Abstract)

Black IW, Hopkins AP, Lee LCL, Jacobson BM, Walsh WF. Cardiac rhythm, mitral valve disease and left atrial spontaneous echo contrast. Circulation 1990;82(Suppl III):31. (Abstract)

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. Diagnosis of aortic disease with transoesophageal echocardiography. Aust NZ J Med 1990;20(Suppl I):318. (Abstract)

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. Transoesophageal colour flow mapping of clinically normal prosthetic valves. Aust NZ J Med 1990;20(Suppl I):318. (Abstract)

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. The role of transoesophageal echocardiography in the diagnosis of left atrial thrombi. Aust NZ J Med 1990;20(Suppl I):317. (Abstract)

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. The clinical value of transoesophageal echocardiography. Proceedings, Australian Society for Ultrasound in Medicine 19th Annual Scientific Meeting, Melbourne, 1989:68.

(Abstract)

Black IW, Hopkins A, Lee CL, Jacobson B, Walsh WF. Cardiogenic brain embolism: role of anticoagulants. Aust NZ J Med 1990;20:630-1. (Letter)

Bleifeld W. Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. J Am Coll Cardiol 1986; 7:163-166.

Bogousslavsky J, van Melle G, Regli F, Kappenberger L. Pathogenesis of anterior circulation stroke in patients with nonvalvular atrial fibrillation: the Lausanne Stroke Registry. Neurology 1990;40:1046-50.

Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, van Melle G. Stroke recurrence in patients with patent foramen ovale: the Lausanne Study. Lausanne Stroke with Paradoxical Embolism Study Group. Neurology 1996;46:1301-5.

Bracewell RN. The Fourier Transform and Its Applications. New York: McGraw-Hill, 1978.

Brand FN, Abbott RD, Kannell WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. JAMA 1985;254:3449-3453.

Brignole M, Menozzi C, Gianfranchi L, Musso G, Mureddu R, Bottoni N, Lolli G. Assessment of atrioventricular junction ablation and VVIR pacemaker versus pharmacological treatment in patients with heart failure and chronic atrial fibrillation: a randomized, controlled study. Circulation 1998;98:953-960.

Britton M, Gustafsson C. Non-rheumatic atrial fibrillation as a risk factor for stroke. Stroke 1985;16:182-188.

Brown J, Sadler DB. Left atrial thrombi in nono-rheumatic atrial fibrillation:

assessment of prevalence by transesophageal echocardiography. Int J Card Imaging 1993;9:66-72.

Brugada R, Tapscott T, Czernuszewicz GZ, Marian AJ, Iglesias A, Mont L, Brugada J, Girona J, Domingo A, Bachinski LL, Roberts R. Identification of a genetic locus for familial atrial fibrillation. N Engl J Med 1997;27:905-11.

Byrne-Quinn E, Wing AJ. Maintenance of sinus rhythm after DC reversion of atrial fibrilllation. A double-blind controlled trial of long-acting quinidine bisulphate. Br Heart J 1970;32:370-6.

Cabin HS, Clubb KS, Hall C, Perlmutter RA, Feinstein AR. Risk for systemic embolization of atrial fibrillation without mitral stenosis. Am J Cardiol 1990;65:1112-1116.

Cairns JA, Connolly SJ. Nonrheumatic atrial fibrillation. Risk of stroke and role of antithrombotic therapy. Circulation 1991;84:469-481.

Cameron A, Schwartz MJ, Kronmal RA, Kosinski AS. Prevalence and significance of atrial fibrillation in coronary heart disease (CASS Registry). Am J Cardiol 1988;61:714-717.

Campbell A, Caird FI, Jackson TFM. Prevalence of abnormalities of electrocardiogram in old people. Br Heart J 1974;36:1005-11.

Caplan LR, D'Cruz I, Hier DB, Reddy H, Shah S. Atrial size, atrial fibrillation and stroke. Ann Neurol 1986;19:158-161.

Cassella K, Abelmann WH, Ellis LB. Patients with mitral stenosis and systemic emboli. Arch Intern Med 1964;114;773.

Castello R, Pearson AC, Labovitz AJ. Prevalence and clinical implications of atrial spontaneous contrast in patients undergoing transesophageal echocardiography. Am J Cardiol 1990;65:1149-1153.

Castello R, Lenzen P, Aguirre F, Labovitz A. Variability in the quantitation of mitral regurgitation by doppler color flow mapping: comparison of transthoracic and transesophageal studies. J Am Coll Cardiol 1992;20:433-438.

Cerebral Embolism Task Force. Cardiogenic Brain Embolism. Arch Neurol 1989; 46:727-43.

Chan M, Marcus R, Bednarz J, Childers R, Lang R. Contribution of transesophageal echocardiography to cardioversion protocols for atrial fibrillation. J Am Soc Echocardiog (Abstract) 1992;5:4B:308.

Chandrasekaran K, Aylward PE, Fleagle SR, et al. Feasibility of identifying amyloid and hypertrophic cardiomyopathy with the use of computerised quantitative texture analysis of clinical echocardiographic data. J Am Coll Cardiol 1989;13:832-40.

Chantarangkul V, Tripodi A, Mannucci PM. Evaluation of a fully automated centrifugal analyser for performance of hemostasis tests. Clin Chem 1987;33:1888-90.

Chen YT, Kan MN, Chen JS et al. Contributing factors to formation of left atrial spontaneous echo contrast in mitral valvular disease. J Ultrasound Med 1990;9:151-5.

Chia BL, Choo MH, Yan PC, Ee BK, Lee CN, Shears JH. Intra-atrial smoke-like echoes and thrombi formation. Chest 1989;95:912-14.

Chiang CW, Pang SC, Len FC, Fang BR, Kuo CT, Lee YS, Chang CH. Diagnostic

accuracy of two-dimensional echocardiography for detection of left atrial thrombus in patients with mitral stenosis. J Ultrasound Med 1987;6:525-529.

Chien S, Usami S, Taylor HM, Lundberg JL, Gregersen MI. Effects of hematocrit and plasma proteins on human blood rheology at low shear rates. J Appl Physiol 1966;21:81-7.

Coelho E, Pinto LS, Luiz AS, Coelho EM, Pereira AL, Barreiros R. Long-term results of conversion of atrial fibrillation by direct current countershock. Cardiology 1967;50:147-55.

Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. J Am Coll Cardiol 1991;18:349-355.

Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: a meta analysis of randomized control trials. Circulation 1990;82:1106-1116.

Corbalan R, Arriagada D, Braun S, et al. Risk factors for systemic embolism in patients with paroxysmal atrial fibrillation. Am Heart J 1992;124:149-153.

Cormier B, Vahanian A, Iung B, Porte JM, Dadez E, Lazarus A, Starkman C, Acar J. Influence of percutaneous mitral commissurotomy on left atrial spontaneous contrast of mitral stenosis. Am J Cardiol 1993;71:842-847.

Coulshed N, Epstein EJ, McKendrick RW, Galloway RW, Walker E. Systemic embolism in mitral valve disease. Br Heart J 1970;32:26-34.

Cox JL, Schuessler RB, D'Agostino HJ Jr, Stone CM, Chang BC, Cain ME, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. III. Development of a

definitive surgical procedure. J Thorac Cardiovasc Surg 1991;101:569-83.

Crijns HJ, Van Gelder IC, Van Gilst W, Hillege H, Gosselink AM, Lie KI. Serial antiarrhythmic drug treatment to maintain sinus rhythm after electrical cardioversion for chronic atrial fibrillation or atrial flutter. Am J Cardiol 1991;68:335-341.

Cujec B, Polasek P, Voll C, Shuaib A. Transesophageal echocardiography in the detection of potential cardiac source of embolism in stroke patients. Stroke 1991;22:727-733.

Dahl CF, Ewy GA, Warner ED, Thomas ED. Myocardial necrosis from direct current countershock. Effect of paddle electrode size and time interval between discharges. Circulation 1974;50:956-61.

Daigle RE, Miller CW, Histand MB, McLeod FD, Hokanson DE.Nontraumatic aortic blood flow sensing by use of an ultrasonic esophageal probe. J Appl Physiol 1975;38:1153-60.

Daley R, Mattingly TW, Holt CL, Bland F, White PD. Systemic arterial embolism in rheumatic heart disease. Am Heart J 1951;566-581.

Daniel WG. Should transesophageal echocardiography be used to guide cardioversion? N Engl J Med 1993;328:803-4.

Daniel WG, Erbel R, Kasper W, et al. Safety of transesophageal echocardiography. A multicenter survey of 10,419 examinations. Circulation 1991;83:817-821.

Daniel WG, Angermann C, Engberding R et al. Transoesophageal echocardiography in patients with cerebral ischaemic events and arterial embolism

- A European Multicenter Study (Abstract). Circulation 1989; 80 (Suppl II): II-473.

Daniel WG, Nellessen U, Schroder E, Nonnast-Daniel B, Bednarski P, Nikutta P, Lichtlen PR. Left atrial spontaneous echo contrast in mitral valve disease: an indicator for an increased thromboembolic risk. J Am Coll Cardiol 1988;11:1204-1211.

Daoud EG, Knight BP, Weiss R, Bahu M, Paladino W, Goyal R, Man KC, Strickberger SA,Morady F. Effect of verapamil and procainamide on atrial fibrillation-induced electrical remodeling in humans. Circulation 1997;96:1542-1550.

Darling RC, Austen G, Linton RR. Arterial embolism. Surg Gynecol Obstet 1967;106-14.

Davison G, Greenland P. Predictors of left atrial thrombus in mitral valve disease. J Gen Intern Med 1991;6:108-12.

De Silva RA, Graboys TB, Podrid PJ, Lown B. Cardioversion and defibrillation. Am Heart J 1980;100: 881-895.

DeKroon MG, Slager CJ, Gussenhoven WJ. Serruys PW, Roelandt JRC, Bom N. Cyclic changes of blood echogenicity in high frequency ultrasound. Ultrasound Med Biol 1991;17:723-8.

DeMaria A, Lies J, King J, et al. Echocardiographic assessment of atrial transport, mitral movement and ventricular performance following electroversion of supraventricular arrythmias. Circulation 1975; 51: 273-82.

DeRook FA, Comess KA, Albers GW, Popp RL. Transesophageal echocardiography in the evaluation of stroke. Ann Intern Med 1992;117:922-932.

Deverall PB, Olley PM, Smith DR, Watson DA, Whitaker W. Incidence of systemic embolism before and after mitral valvotomy. Thorax 1968;23:530-536.

DiMinno G, Cerbone AM, Margaglione M et al. Searching for the thrombogenic mechanism(s) of fibrinogen. Thromb Res 1990; Suppl 11:61-7.

Disch DL, Greenberg ML, Holzberger PT, Malenka DJ, Birkmeyer JD. Managing chronic atrial fibrillation: A Markov decision analysis comparing warfarin, quinidine and low-dose amiodarone. Ann Intern Med 1994;120:449-457.

Dittrich HC, Erickson JS, Schneiderman T, Blacky AR, Savides T, Nicod PH. Echocardiographic and clinical predictors for outcome of elective cardioversion of atrial fibrillation. Am J Cardiol 1989; 63: 193-197.

Dodds GA 3rd, Wilkinson WE, Greenfield RA, Natale A, Kisslo J, Pritchett EL. Evaluation of the effect of transthoracic cardioversion from ventricular tachycardia to sinus rhythm on left atrial mechanical function. Am J Cardiol 1996;78:1436-1439.

Douglas P, D'Sa A, Katz S, Howell S. Ultrasonic integrated backscatter: a new method for imaging and analysis [Abstract]. Circulation 1994;90 Suppl 1:1-326.

Dregelid EB, Stangeland LB, Eide GE, Trippestad A. Characteristics of patients operated on because of suspected arterial embolism: A multivariate analysis. Surgery 1988; 104:530-6.

EAFT (European Atrial Fibrillation Trial) Study Group: Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993;342:1255-1262.

Easton JD, Sherman DG. Management of cerebral embolism of cardiac origin.

Stroke 1980;11:433-442.

Einthoven W. Le télécardiogramme. Archives Internationales de Physiologie 1906;4:132-64.

Ellis LB, Harken DE. Arterial embolization in relation to mitral valvuloplasty. Am Heart J 1961;62:611-620.

Enriquez-Sarano M, Tajik AJ, Bailey KR, Seward JB. Color flow imaging compared with quantitative Doppler assessment of severity of mitral regurgitation: Influence of eccentricity of jet and mechanism of regurgitation. J Am Coll Cardiol 1993;21:1211-1219.

Erbel R, Stern H, Ehrenthal W, Schreiner G, Treese N, Krämer G, Thelen M, Schweizer P, Meyer J. Detection of spontaneous echocardiographic contrast within the left atrium by transesophageal echocardiography: spontaneous echocardiographic contrast. Clin Cardiol 1986;9:245-252.

Ernst G, Stollberger C, Abzieher F, Bonner E, Bibus B, Slany J. Transesophageal echocardiography in assessment of left atrial appendage morphology - pathology correlation. (abstract) Eur Heart J. 1993;14(Suppl):391.

Evans W, Swann P. Lone auricular fibrillation. Br Heart J 1954;189-94.

Ezekowitz MD, Bridgers SL, James KE, Carliner NH , Colling CL, Gornick CC, Krause-Steinrauf H, Kurtzke JF, Nazarian SM, Radford MJ. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. N Engl J Med 1992;327:1406-1412.

Ezekowitz MD, James KE, Sarkis MN, Davenport J, Broderick JP, Gupta SR,

Thadani V, Meyer ML, Bridgers SL. Silent cerebral infarction in patients with nonrheumatic atrial fibrillation. circulation 1995;21:2178-2182.

Fabry TL. Mechanism of erythrocyte aggregation and sedimentation. Blood 1987;70:1572-6.

Fahr G. The treatment of cardiac irregularities. JAMA 1938;111:2268-75.

Falcone RA, Morady F, Armstrong WF. Transesophageal echocardiographic evaluation of left atrial appendage function and spontaneous contrast formation after chemical or electrical cardioversion of atrial fibrillation. Am J Cardiol 1996;78:435-9.

Fatkin, D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. J Am Coll Cardiol 1994;23:961-9.

Fatkin D, Kuchar DL, Thorburn CW, Feneley MP, Transesophageal echocardiograpjy before and during direct current cardioversion of atrial fibrillation: evidence for "atrial stunning" as a mechanism of thromboembolic complications. J Am Coll Cardio. 1994;23:307-16.

Fatkin D, Herbert E, Feneley MP. Haematologic correlates of spontaneous echo contrast in patients with atrial fibrillation and implications for thromboembolic risk. Am J Cardiol 1994;73:672-6.

Fatkin D, Scalia G, Jacobs N, Burstow D, Leung D, Walsh W, Feneley M. Accuracy of biplane transesophageal echocardiography in detecting left atrial thrombus. Am J Cardiol 1996;77:321-3.

Feigenbaum H. Echocardiography (4th Ed). Philadelphia: Lea and Febiger,

1986:144-148.

Feinberg WM, Seeger JF, Carmody RF, Anderson DC, Hart RG, Pearce LA. Epidemiologic features of asymptomatic cerebral infarction in patients with nonvalvular atrial fibrillation. Arch Intern Med 1990;150:2340-4.

Fisher M, Meiselman HJ. Hemorheological factors in cerebral ischemia. Stroke 1991;22:1164-9.

Fisher CM. Reducing risks of cerebral embolism. Geriatrics 1979;34:59-66.

Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG. Anti-arrhythmic drug therapy and cardiac mortality in atrial fibrillation. J Am Coll Cardiol 1992;20:527-532.

Flegel KM, Hanley J. Risk factors for stroke and other embolic events in patients with nonrheumatic atrial fibrillation. Stroke 1989;20:1000-1004.

Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. Lancet 1987;1:526-9.

Flegel KM. From delirium cordis to atrial fibrillation: Historical development of a disease concept. Ann Intern Med 1995;122:867-73.

Fleming HA, Bailey SM. Mitral valve disease, systemic embolism and anticoagulants. Postgrad Med J 1971;47:599-604.

Forfar JC. A 7 year analysis of haemorrhage in patients on longe term anticoagulant treatment. Br Heart J 1979;42:128-32.

Frazin L, Talano JV, Stephanides L, Loeb HS, Kopel L, Gunnar RM. Esophageal

echocardiography. Circulation 1976;54:102-108.

Freeman I, Wexler J. Anticoagulants for treatment of atrial fibrillation. JAMA 1963;184:1007-10.

Frey W. Uber Vorhofflimmern beim Menschen and Seine Beseitigung durch Chinidin. Berl Klin Wehnschr 1918;55:417-50.

Fulton RM, Duckett K. Plasma fibrinogen and thromboemboli after myocardial infarction. Lancet 1976,ii:1161-4.

Galvin IF, Black IW, Lee CL, Horton DA. Transoesophageal echocardiography in acute aortic transection. Ann Thorac Surg 1991;51:310-1.

Gavaghan TP, Hickie JB, Krilis SA, et al. Increased plasma beta-thromboglobulin in patients with coronary artery vein graft occlusion: Response to low dose aspirin. J Am Coll Cardiol 1990;15:1250-8.

Georges JL, Spentchian M, Caubel C, Collignon I, Schwob J, Livarek B, Normand JP. Time course of troponin I, myoglobulin, and cardiac enzyme release after electrical cardioversion. Am J Cardiol 1996;78:825-826.

Glueck RM, Mottley JG, Miller JG, Sobel BE, Perez JE. Effects of coronary artery occlusion and reperfusion on cardiac cycle-dependent variation of myocardial ultrasonic backscatter. Circ Res 1985;56:683-9.

Gohlke-Bärwolf C, Acar J, Oakley C, et al. Guidelines for prevention of thromboembolic events in valvular heart disease. Study Group of the Working Group on Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 1995;16;1320-30.

306

Goldman MJ. The management of chronic atrial fibrillation: Indications for and method of conversion to sinus rhythm. Prog Cardiovasc Dis 1960;2:465-479.

Goldman ME, Bovill EG. Association of plasma fibrinogen, density of spontaneous echo-contrast and atrial appendage function in atrial fibrillation [Abstract]. Circulation 1995;92 Suppl 1:1-181.

Goldsmith HL, Turitto VT. Rheological aspects of thrombosis and haemostasis: basic principles and applications. Thromb Haemostas 1986;55:415-35.

Gosselink AT, Crijns HJ, Hamer HP, Hillege H, Lie KI. Changes in left and right atrial size after cardioversion of atrial fibrillation: role of mitral valve disease. J Am Coll Cardiol 1993;22:1666-72.

Gosselink AT, Crijns HJ, van den Berg MP, van den Broek SA, Hillege H, Landsman ML, Lie KI. Functional capacity before and after cardioversion of atrial fibrillation: a controlled study. Br Heart J 1994;72:161-6.

Gosselink AT, Bijlsma EB, Landsman ML, Crijns HJ, Lie KI; Long-term effect of cardioversion on peak oxygen consumption in chronic atrial fibrillation. A 2-year follow-up. Eur Heart J 1994;15:368-72.

Greenwood WF, Aldridge HE, Mckelvey AD. Effects of mitral commissurotomy on duration of left, functional capacity, hemoptysis and systemic embolism. Am J Cardiol 1963;11:348-356.

Grimm RA, Chandra S, Klein AL, Stewart WJ, Black IW, Kidwell GA, Thomas JD. Characterization of left atrial appendage Doppler flow in atrial fibrillation and flutter by Fourier analysis. Am Heart J 1996;132:286-96.

Grimm RA, Leung DY, Black IW, Thomas JD. Left atrial appendage "stunning"

after spontaneous conversion of atrial fibrillation demonstrated by transesophageal Doppler echocardiography. Am Heart J 1995;130:174-6.

Grimm RA, Stewart WJ, Black IW, Thomas JD, Klein AL. Should all patients undergo transesophageal echocardiography before electrical cardioversion of atrial fibrillation?. J Am Coll Cardiol 1994;23:533-41.

Grimm RA, Stewart WJ, Maloney JD, Cohen GI, Pearce GL, Salcedo EE, Klein AL. Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterisation by simultaneous transesophageal echocadiography. J Am Coll Cardiol 1993;22:1359-66.

Grimm RA, Klein AL, Stewart WJ, Maloney JD, Black IW, Thomas JD. Characterization of left atrial appendage flow by Fourier analysis: application to patients with atrial fibrillation and flutter. J Am Coll Cardiol 1993;21(Suppl A):29. (Abstract)

Grimm RA, Klein AL, Black IW, Stewart WJ, Pacheco TR, Kidwell GA. Can patients with atrial arrhythmias susceptible to postcardioversion thromboembolism be identified precardioversion by clinical or echocardiographic parameters? Circulation 1993;88(Suppl):313. (Abstract)

Grimm RA, Klein AL, Stewart WJ, Kidwell GA, Castle LW, Black IW, Underwood DA, Thomas JD. Left atrial appendage function in atrial fibrillation and flutter as a predictor of outcome following cardioversion: A transesophageal echo Doppler study with one year follow-up. J Am Coll Cardiol 1994;23(Suppl):281. (Abstract)

Grimm RA, Klein AL, Cohen GI , Maloney JD, Stewart WJ, Salcedo EE. Return of left atrial appendage function post electrical cardioversion of atrial fibrillation by transesophageal echo (abstract). J Am Coll Cardiol 1992;19:156A.

Grimm RA, Klein AL, Stewart WJ, Greenberg N, Kidwell GA, Chung MK, Black IW, Thomas JD. Left atrial appendage function does not predict immediate success of cardioversion for atrial fibrillation and flutter. J Am Soc Echocardiogr 1994;7(Suppl):57. (Abstract)

Grimm RA, Klein AL, Cohen GI, et al. Concurrent transesophageal echo and electrical cardioversion in patients with atrial fibrillation: Effect of cardioversion on left atrial smoke (abstract). J Am Coll Cardiol 1992;19:155A..

Grimm RA, Klein AL, Stewart WJ, Pacheco TR, Black IW, Lever HM, Castle LW. Why are patients with atrial flutter less susceptible to systemic embolization following cardioversion than those with atrial fibrillation?. Circulation 1992;86(Suppl 1):663. (Abstract)

Grimm RA, Black IW, Klein AL. Transesophageal echocardiography before cardioversion (Letter) New Eng J Med 1993;329:577-8.

Grogan M, Smith HC, Gersh BJ, Wood DL. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. Am J Cardiol 1992;69:1570-3.

Guidotti M, Tadeo G, Zanasi S, Pellegrini G. Silent cerebral ischemia in patients with chronic atrial fibrillation: a case-control study. Irish J Med Sci 1990;159:96-97.

Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, Boysen G. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. Arch Intern Med 1998; 27:1513-21.

Gustafsson C, Blomback M, Britton M, Hamsten A, Svensson J. Coagulation

factors and the increased risk of stroke in nonvalvular atrial fibrillation. Stroke 1990;21:47-51.

Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc. 1984;59:17-20.

Hall JI, Wood DR. Factors affecting cardioversion of atrial arrhythmias with special reference to quinidine. Br Heart J 1968;30:84-90.

Halmos PB. Direct current conversion of atrial fibrillation. Br Heart J 1966;28:302-308.

Halperin JL, Petersen P. Thrombosis in the cardiac chambers: Ventricular dysfunction and atrial fibrillation. In: Fuster V, Verstraete M (Eds). Thrombosis in cardiovascular disorders. WB Saunders: Philadelphia, 1992:215-236.

Halperin JL, Fuster V. Left ventricular thrombus and stroke after myocardial infarction: Toward prevention or perplexity?. J Am Coll Cardiol 1989;14:912-4.

Hanley PC, Tajik AJ, Hynes JK, Edwards WD, Reeder GS, Hagler DJ, Seward JB. Diagnosis and classification of atrail septal aneurysm by two-dimensional echocardiography: report of 80 consecutive cases. J Am Coll Cardiol. 1985;6:1370-1382.

Hansen WB, McClendon RO, Kinsman JM. Auricular fibrillation: hemodynamic studies before and after conversion with quinidine. Am Heart J 1952;44:499-516.

Harker LA, Mann KG. Thrombosis and fibrinolysis. In: Fuster V, Verstraete M (Eds). Thrombosis in cardiovascular disorders. WB Saunders: Philadelphia, 1992:1-16.

Hart RG, Halperin JL. Atrial fibrillation and stroke: revisiting the dilemmas. Stroke 1994;25:1337-1341.

Hatle L, Angelsen B, Tromsdal A. Non-invasive assessment of atrioventricular pressure half-time by Doppler ultrasound. Circulation 1979;60:1096-1104.

Hausmann D, Mugge A, Becht I, Daniel WG. Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral embolic events. Am J Cardiol 1992;70:668-672.

Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, Gatewood RP,Jr. Color Doppler assessment of mitral regurgitation with orthogonal planes. Circulation 1987;75:175-183.

Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz SB, Epstein SE. Relation between echocardiographically determined left atrial size and atrial fibrillation. Circulation 1976;53:273-279.

Hill JD, Mottram EM, Killeen PD. Study of the prevalence of atrial fibrillation in general practice patients over 65 years of age. J Roy Coll Gen Pract 1987;37:172-3.

Hinton RC, Kistler JP, Fallon JT, Friedlich AL, Fisher CM. Influence of etiology of atrial fibrillation on incidence of systemic embolism. Am J Cardiol 1977;40:509-513.

Hirschfeld DS, Emilson BB. Echocardiogram in calcified mitral annulus. Am J Cardiol 1975;36:354.

Hiss RG, Lamb LE. Electrocardiographic findings in 122,043 individuals. Circulation 1962;25:947-61.

Hoffman R, Lambertz H, Kreis A, et al. Failure of trifluoperazine to resolve spontaneous echo contrast evaluated by transesophageal echocardiography. Am J Cardiol 1990;66:648.

Hoit BD, Shao Y, Gabel M. Influence of acutely altered loading conditions on left atrial appendage flow velocities. J Am Coll Cardiol 1994, 24:1117-23.

Hopkins AP, Black IW, Lee LCL, Jacobson BM, Walsh WF. Clinical and echocardiographic relationships of left atrial spontaneous contrast detected by transesophageal echocardiography. Proceedings, Australian Society for Ultrasound in Medicine 20th Annual Scientific Meeting, Adelaide, 1990:50. (Abstract)

HP Acoustic Densitometry. Andover (MA): Hewlett-Packard, 1994.

Humphrey PRD, Harrison MJG. How often can an embolic stroke be diagnosed clinically? a clinicopathological correlation. Postgrad Med J 1985;61:1039-42.

Hurst JW, Paulk EA, Proctor HD, Schlant RC. Management of patients with atrial fibrillation. Am J Med 1964;37:728-741.

Hwang JJ, Kuan P, Lin SC, Chen WJ, Lei MH, Ko YL, Cheng JJ, Lin JL, Chen JJ, Lien WP. Reappraisal by transesophageal echocardiography of the significance of left atrial thrombi in the prediction of systemic arterial embolization in rheumatic mitral valve disease. Am J Cardiol 1992;70:769-773.

Hwang JJ, Lin SC, Lei MH, Cheng JJ, Kuan P, Lien WP. Diagnostic accuracy of transesophageal echocardiography in the detection of left atrial thrombus in rheumatic mitral valve disease. (abstract) J Am Coll Cardiol. 1992;19(Suppl A):236.

Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med 1996;335:540-6.

Ikram H, Nixon P, Arcan T. Left atrial function after electrical cardioversion to sinus rhythm. Brit Heart J 1968; 30: 80-3.

Iliceto S, Antonelli G, Sorino M, Biasco G, Rizzon P. Dynamic intracavitary left atrial echoes in mitral stenosis. Am J Cardiol 1985;55:603-6

Inoue K, Owaki T, Nakamura T, Kitamura F, Miyamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. J Thorac Cardiovasc Surg 1984;87:394-402.

Izumida Y, Sciyama A, Maeda N. Erythrocyte aggregation: bridging by macromolecules and electrostatic repulsion by sialic acid. Biochim Biophys Acta 1991;1067:221-6.

Jaffe WM, Roche AH. Doppler echocardiographic assessment of atrial filling fraction in severe mitral stenosis. Am J Cardiol 1988;61:1254-5.

Jafri SM, Caceres L, Rosman HS, Ozawa T, Mammen E, Lesch M, Goldstein S. Activation of the coagulation system in women with mitral stenosis and sinus rhythm. Am J Cardiol 1992;70:1217-1220.

Jones EF, Calafiore P, Donnan GA, Tonkin AM. Evidence that patent foramen ovale is not a risk factor for cerebral ischemia in the elderly. Am J Cardiol 1994;74:596-599.

Jordaens L, Germonpre E, Vandenbogaerde J. Atrial stunning lasts more than one week after conversion of atrial flutter (abstract). J Am Coll Cardiol 1991;17:325A.

Jordan RA, Scheifley CH, Edwards JE. Mural thrombosis and systemic embolism in mitral stenosis: a clinicopathologic study of 51 cases. Circulation 1951;3:363-7.

Jugdutt BI, Sivaram CA. Prospective two-dimensional echocardiographic evaluation of left ventricular thrombus and embolism after acute myocardial infarction. J Am Coll Cardiol 1989;13:554-566.

Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease: The Framingham study. JAMA 1987;258:1183-6.

Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: The Framingham Study. N Engl J Med 1982;306:1018-1022.

Kannel WB, Abbott RD, Savage DD, McNamara PM. Coronary heart disease and atrial fibrillation: The Framingham Study. Am Heart J 1983;106;389-96.

Kannel WB, Gordon T, Wolf PA, McNamara P. Hemoglobin and the risk of cerebral infarction: The Framingham study. Stroke 1972;3:409-20.

Karalis DG, Chandrasekaran K, Victor MF, Ross JJ,Jr., Mintz GS. Recognition and embolic potential of intraaortic atherosclerotic debris. J Am Coll Cardiol 1991;17:73-78.

Karatasakis GT, Gotsis AC, Cokkinos DV. Influence of mitral regurgitation on left atrial thrombus and spontaneous echocardiographic contrast in patients with rheumatic mitral valve disease. Am J Cardiol 1995;76:279-81.

Karnegis JN, Matoole JJ, Bjorling VG. Immediate improvement in left ventricular function after cardiversion of atrial flutter. Am Journal Cardiol 1989;64:1043-1047

Kataoka H, Yano S, Tamura A. Hemostatic changes induced by percutaneous mitral valvuloplasty. Am Heart J 1993;125:777-82.

Katz ES, Tunick PA, Rusinek H, Ribakove G, Spencer FC, Kronzon I. Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: experience with intraoperative transesophageal echocardiography. J Am Coll Cardiol 1991;20:70-77.

Kelley RE, Berger JR, Alter M, Kovacs AG. Cerebral ischemia and atrial fibrillation: prospective study. Neurology 1984;34:1285-1291.

Kempster PA, Gerraty RP, Gates PC. Asymptomatic cerebral infarction in patients with chronic atrial fibrillation. Stroke 1988;19:955-957.

Keren G, Etzion T, Sherez J, Zelcer AA, Megidish R, Miller HI, Laniado S. Atrial fibrillation and atrial enlargement in patients with mitral stenosis. Am Heart J 1987;114:1146-1155.

Keren G, Etzion T, Sherez J et al. Atrial fibrillation and atrial enlargement in patients with mitral stenosis. Am Heart J 1987;114:1146-1155.

Killip T. Synchronized DC precordial shock for arrhythmias: Safe new technique to establish normal rhythm may be utilized on an elective or emergency basis. JAMA 1963;186:1-7.

Kitchin AH, Milne JS. Longitudinal survey of ischaemic heart disease in randomly selected sample of older population. Br Heart J 1977;39:889-893.

Klein AL, Grimm RA, Black IW, Leung DY, Chung MK, Vaughn SE, Murray RD, Miller DP, Arheart KL. Cardioversion guided by transesophageal echocardiography: The ACUTE Pilot Study. A randomized, controlled trial. Ann

Intern Med 1997;126:200-209.

Klein AL, Murray RD, Black IW, Chandra S, Grimm RA, D'Sa AP, Leung DYC, Miller D, Morehead AJ, Vaughn SE, Thomas JD. Integrated backscatter for quantification of left atrial spontaneous echo contrast. J Am Coll Cardiol 1996;28:222-31.

Klein AL, Murray RD, Grimm RA, Bailey AS, Piedmonte M, Black IW. The effect of technical factors on the quality of pulmonary venous flow from the transverse and longitudinal imaging planes with transesophageal echocardiography. J Am Soc Echocardiogr 1995;8:879-87.

Klein AL, Tajik AJ. Doppler assessment of pulmonary venous flow in healthy subjects and in patients with heart disease. J Am Soc Echocardiogr 1991;4:379-92.

Klein AL, Grimm RA, Black IW. Transesophageal echo screen for left atrial thrombus prior to cardioversion for atrial fibrillation. MVP Video Journal of Cardiology 1993;VIII;14:00.

Klein AL, Grimm RA, Bailey AS, Black IW, Murray RD, Cohen GI, Lever HM, Griffin BP. The longitudinal imaging plane by biplane TEE is required for complete assessment of pulmonary venous flow in patients with heart disease. Circulation 1993;88(Suppl):305. (Abstract)

Klein AL, Grimm RA, Murray RD, Morehead AJ, Black IW, D'Sa A, Meyer A, Stewart WJ, Thomas JD. Quantification of left atrial spontaneous echo contrast using a new approach of integrated backscatter. J Am Coll Cardiol 1994;23(Suppl):77. (Abstract)

Klein AL, Grimm RA, Black IW, Orsinelli DA, Manning WJ, Stoddard MF,

316

Piedmonte M. Cost effectiveness of TEE-guided cardioversion with anticoagulation compared to conventional therapy in patients with atrial fibrillation. J Am Coll Cardiol 1994;23(Suppl):128. (Abstract)

Klein AL, Miller DP, Grimm RA, Murray RD, Leung DY, Arheart K. Model of clinical endpoints for the ACUTE clinical trial (abstract). J Am Soc Echocardiog 1996;9:387.

Klein AL, Grimm RA, Black IW, Bailey AS, McQueen YM, Cohen GI, Pearce GL, Maloney JD, Castle LW. Return of atrial function postcardioversion: comparison between left atrial appendage and left atrial cavity function by Doppler transesophageal echocardiography. J Am Coll Cardiol 1993;21(Suppl A):28. (Abstract)

Klein AL, Murray RD, Grimm RA, Morehead AJ, Black IW, Miller D, D'Sa A, Meyer A, Stewart WJ, Thomas JD. The utility of integrated backscatter to quantify left atrial spontaneous echo contrast. Can J Cardiol 1994;10(Suppl C):97. (Abstract)

Klein AL, Grimm RA, Black IW, Stoddard MF, Orsinelli DA, Manning WJ, Leung DY, Miller DP for the ACUTE Investigators. Assessment of cardioversion using transesophageal echocardiography compared to conventional therapy: The ACUTE Randomized Pilot Study. Circulation 1994;90:21. (Abstract)

Klein AL, Grimm RA, Murray RD, et al. Quantification of left atrial spontaneous echo contrast using integrated backscatter [Abstract]. J Am Coll Cardiol 1993;21::76A.

Knopman DS, Anderson DC, Asinger RW, Greenland P, Mikell F, Good DC. Indications for echocardiography in patients with ischemic stroke. Neurology 1982; 32:1005-11.

Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR Jr, Ilstrup DM, Frye RL. The natural history of lone atrial fibrillation. A population-based study over three decades. N Engl J Med 1987;317:669-74.

Korsgren M, Leskinen E, Peterhoff V. Conversion of atrial arrhythmias with DC shock. Primary results and a follow-up investigation. Acta Med Scand 1965;178(Suppl):431.

Kronik G, Stollberger C, Schuh M, Abzieher F, Slany J, Schneider B. Interobserver variability in the detection of spontaneous echo contrast, left atrial thrombi, and left atrial appendage thrombi by transesophageal echo-cardiography. Br Heart J 1995;74:80-3.

Kronzon I, Tunick PA, Glassman E, Slater J, Schwinger M, Freedberg RS. Transesophageal echocardiography to detect atrial clots in candidates for percutaneous transseptal mitral balloon valvuloplasty. J Am Coll Cardiol 1990;16:1320-1322.

Kumagai K, Fukunami M, Ohmori M, Kitabatake A, Kamada T, Hoki N. Increased intracardiovascular clotting in patients with chronic atrial fibrillation. J Am Coll Cardiol 1990;16:377-80.

Kuschner M, Ferrer MI, Harvey RM, Wylie RH. Rheumatic carditis in surgically removed auricular appendages. Am Heart J 1991;43:286-292.

Kutner M, Nixon G, Silverstone F. Physicians' attitudes toward oral anticoagulants and antiplatelet agents for stroke prevention in elderly patients with atrial fibrillation. Arch Intern Med 1991;151:1950-3.

Lake FR, McCall MG, Cullen KJ, Rosman DL, de Klerk NH. Atrial fibrillation and mortality in an elderly population. Aust NZ J Med 1989;19:321-6.

Laupacis A, Albers G, Dalen J, Dunn M, Feinberg W, Jacobson A. Antithrombotic therapy in atrial fibrillation. Fourth ACCP Consensus Conference on Antithrombotic Therapy. Chest 1995;108(Suppl):352-9.

Laupacis A, Albers G, Dunn M, Feinberg W. Antithrombotic therapy in atrial fibrillation. Third ACCP Consensus Conference on Antithrombotic Therapy. Chest 1992;102(Suppl):426-433.

Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, Drobinski G, Thomas D, Grosgogeat Y. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med. 1988;318:1148-1152.

Lee RJ, Bartzokia T, Yeoh TK, Grogin HR, Choi D, Schnittger I. Enhanced detection of intracardiac sources of cerebral emboli by transesophageal echocardiography. Stroke 1991;22:734-739.

Lee LCL, Black IW, Hopkins A, Walsh WF. Transoesophageal echocardiography in heart disease - old technologies, new tricks. Aust NZ J Med 1992;22:527-531.

Leistad E, Aksnes G, Verburg E, Christensen G. Atrial contractile dysfunction after short-term atrial fibrillation is reduced by verapamil but increased by BAY K8644. Circulation 1996;93:1747-54.

Lesser MF. Safety and efficacy of in-office cardioversion for treatment of supraventricular arrhythmias. Am J Cardiol 1990;66:1267-1268.

Leung DYC, Black IW, Cranney GB, Walsh WF, Grimm RA, Stewart WJ, Thomas JD. Selection of patients for transesophageal echocardiography after stroke and systemic embolic events. Role of transthoracic echocardiography. Stroke 1995;26:1820-4.

Leung DYC, Black IW, Cranney GB, McCredie RM, Hopkins AP, Walsh WF.

Resolution of left atrial spontaneous echocardiographic contrast after percutaneous mitral valvuloplasty: Implications for thromboembolic risk. Am Heart J 1995;129:65-70.

Leung DYC, Black I, Cranney GB, Hopkins AP, Walsh WF. Prognostic Implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. J Am Coll Cardiol 1994; 24:755-62.

Leung DY, Davidson PM, Cranney GB, Walsh WF. Thromboembolic risks of left atrial thrombus detected by transesophageal echocardiogram. Am J Cardiol 1997;79:626-629.

Leung DYC, Cranney GB, Black IW, Stewart WJ, Thomas JD, Walsh WF. Patients with suspected embolism can be selected for transesophageal echocardiography based on clinical and transthoracic echo variables: Analysis of 824 cases. Aust NZ J Med 1995;25:610. (Abstract)

Leung DY, Black IW, Grimm RA, Klein AL. Multi-lobed appendage: Visualization by multiplane transesophageal echocardiography. (Abstract) Circulation 1994;90:1-224.

Leung DY, Cranney GB, Black IW, McCredie RM, Walsh WF. Left atrial spontaneous echo contrast resolves after successful percutaneous mitral valvuloplasty. Aust NZ J Med 1994;24:628. (Abstract)

Leung DY, Black IW, Cranney GB, Hopkins AP, Walsh WF. Left atrial spontaneous echo contrast is a risk factor for future thromboembolic events in non valvular atrial fibrillation: Results of a prospective study. Aust NZ J Med 1994;24:640. (Abstract)

Leung DY, Black IW, Grimm RA, Klein AL. Multi-lobed left atrial appendage: Visualization by multiplane transesophageal echocardiography. Circulation

1994;90:224. (Abstract)

Leung DY, Black IW, Cranney GB, Walsh WF. Left atrial spontaneous echo contrast is a risk factor for future thromboembolic events in non valvular atrial fibrillation: Results of a prospective study. J Am Coll Cardiol 1994;23(Suppl):441. (Abstract)

Leung DY, Black IW, Grimm RA, Cranney GB, Walsh WF. Transesophageal echo findings in patients with suspected embolism can be predicted from clinical and transthoracic variables: Analysis of 800 cases. Circulation 1994;90:237. (Abstract)

Leung DY, Black IW, Cranney GB, McCredie RM, Walsh WF. Determinants of spontaneous echo contrast after percutaneous mitral valvuloplasty: implications for thromboembolic risk. J Am Soc Echocardiogr 1994;7(Suppl):54. (Abstract)

Levine HJ, Pauker SG, Eckman MH. Fourth ACCP Consensus Conference on Antithrombotic Therapy. Chest 1995;108(Suppl): 360-370.

Levy S, Lauribe P, Dolla E, Kou W, Kadish A, Calkins H, Pagannelli F, Moyal C, Bremondy M, Schork A. A randomized comparison of external and internal cardioversion of chronic atrial fibrillation. Circulation 1992;86:1415-20.

Lie JT. Atrial fibrillation and left atrial thrombus: an insufferable odd couple. Am Heart J 1988;116:1374-1377.

Lin SL, Hsu TL, Liou JY, Chen CH, Chang MS, Chiang HT, Chen CY. Usefulness of transesophageal echocardiography for the detection of left atrial thrombi in patients with rheumatic heart disease. Echocardiography 1992;9:161-168.

Lip GY, Lowe GD, Rumley A, Dunn FG. Fibrinogen and fibrin D-dimer levels in paroxysmal atrial fibrillation: evidence for intermediate elevated levels of

intravascular thrombogenesis. Am Heart J 1996;131:724-30.

Lip GY, Lip PL, Zarifis J, Watson RD, Bareford D, Lowe GD, Beevers DG. Fibrin D-dimer and beta-thromboglobulin as markers of thrombogenesis and platelet activation in atrial fibrillation. Effects of introducing ultra-low-dose warfarin and aspirin.Circulation 1996;94:425-431.

Lip GY, Rumley A, Dunn FG, Lowe GD. Plasma fibrinogen and fibrin D-dimer in patients with atrial fibrillation: effects of cardioversion to sinus rhythm. Int J Cardiol 1995;51:245-51.

Lip GYH, Beevers DG. History, epidemiology, and importance of atrial fibrillation. BMJ 1995,311:1361-3.

Lip GY, Lowe GD, Rumley A, Dunn FG. Increased markers of thrombogenesis in chronic atrial fibrillation: effects of warfarin treatment. Br Heart J 1995;73: 527-33.

Lipkin DR, Frenneaux M, Stewart R, Joshi J, Lowe T, McKenna WJ. Delayed improvement in exercise capacity after cardioversion of atrial fibrillation to sinus rhythm. Br Heart J 1988;59:572-7.

Lovett JL, Sandok BA, Giulani ER, Nasser FN. Two-dimensional echocardiography in patients with focal cerebral ischemia. Ann Intern Med 1981; 95:1-4.

Lowe GDO. Blood rheology and hyperviscosity syndromes. London: Bailliere Tindall, 1987;614-7. (Clinical Haematology International Practice and Research; vol 1, no 3).

Lown B, Amarasingham R, Neuman J. New method for terminating cardiac arrhythmias: use of synchronized capacitor discharge. JAMA 1962;182:548-555.

Lown B, Perlroth MG, Kaidbey S, Abe T, Harren DE. "Cardioversion" of atrial fibrillation: a report on the treatment of 65 episodes in 50 patients. N Engl J Med 1963;269:325-331.

Lown B. Electrical reversion of cardiac arrythmias. Br Heart J 1967;29:469-489.

Mahony C, Sublett KL, Harrison MR. Resolution of spontaneous contrast with platelet disaggregatory therapy (trifluoperazine). Am J Cardiol 1989;63:1009-1010.

Mancini GBJ, Goldberger AL. Cardioversion of atrial fibrillation: Consideration of embolization, anticoagulation, prophylactic pacemaker, and long term success. Am Heart J 1982;104:617-621.

Manning WJ, Silverman DI, Keighley CS, Oettgen P, Douglas PS. Transesophageal echocardiography facilitated early cardioversion from atrial dfibrillation using short term anticoagulation: Final results of a prospecrtive 4.5 year study. J Am Coll Cardiol 1995;25:1354-61.

Manning WJ, Weintraub RM, Waksmonski CA, Haering JM, Rooney PS, Maslow AD, Johnson RG, Douglas PS. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. Ann Intern Med 1995; 123:817-22.

Manning WJ, Leeman DE, Gotch PJ, Come PC. Pulsed Doppler evaluation of atrial mechanical function after electrical cardioversion of atrial fibrillation. J Am Coll Cardiol 1989;13:617-623.

Manning WJ, Silverman DI, Katz SE, Riley MF, Come PC, Doherty RM, Munson JT, Douglas PS. Impaired left atrial mechanical fucntion after cardiversion: relation to the duration of atrial fibrillation. J Am Coll Cardiol 1994;23:1535-1540.

Manning WJ, Silverman DI, Katz SE, Riley MF, Doherty RM, Munson JT, Douglas PS. Temporal dependence of the return of atrial mechanical function on the mode of cardioversion of atrial fibrillation to sinus rhythm. Am J Cardiol 1995;75:624-6.

Manning WJ, Silverman DI, Gordon SPF, Krumholz HM, Douglas PS. Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. N Engl J Med 1993;328:750-5.

Manning WJ, Douglas PS. Transesophageal echcocardiography and atrial fibrillation: Added value or expensive toy?. Ann Intern Med 1998;128:685-7.

Masawa N, Yoshida Y, Yamada T, Joshita T, Ooneda G. Diagnosis of cardiac thrombosis in patients with atrial fibrillation in the absence of maroscopically visible thrombi. Archiv A Path 1993;422:67-71.

Masuyama T, Valantine H, Gibbons R, Schnittger I, Popp R. Serial measurement of integrated ultrasonic backscatter in human cardiac allografts for the rejection of acute rejection. Circulation 1990;81:829-39.

Matsumura M, Shah P, Kyo S, Omoto R. Advantages of transesophageal echo for correct diagnosis on small left atrial thrombi in mitral stenosis. (abstract) Circulation 1989;80(Suppl II):II-678.

Mattioli AV, Castellani E, Casali E, Mattioli G. Relationship between duration of atrial fibrillation and thrombi. Eur Heart J 1994;15(Suppl):311.

Maze SS, Kottler MN, Parry WR. Flow characteristics in the dilated left ventricle with thrombus: Qualitative and quantitative Doppler analysis. J Am Coll Cardiol 1989;13:873-81.

McCarthy PJ, Varghese PJ, Barritt DW. Prognosis of atrial arrhythmias treated by electrical counter shock therapy. Br Heart J 1969;31:496-500.

McCredie RM, Allan RM, Smith R. Non-surgical mitral valvotomy. Med J Aust 1990;152:250-251.

McCredie RM, Allan RM, Black IW, Hill AT. Percutaneous transseptal mitral valvotomy. Aust NZ J Med 1998 (in press).

McCullaugh P. Regression models for ordinal data. J R Statist Soc 1980;B42:109-42.

McPherson DD, Knosp BM, Kieso RA, et al. Ultrasound characterisation of accoustic properties of acute intracardiac thrombi: studies in a new experimental model. J Am Soc Echocardiogr 1988;1:264-70.

Mehta D, Baruch L. Thromboembolism following cardioversion of "common" atrial flutter. Risk factors and limitations of transesophageal echocardiography. Chest 1996;110:1001-1003.

Meltzer LE, Aytan N, Yun DD, et al. Atrial fibrillation treated with direct current countershock. Arch Intern Med 1965;115:537-41.

Merino A, Hauptman P, Badimon L, et al. Echocadiographic "smoke" is prodsuced by an interaction of erythrocytes and plasma proteins modulated by shear forces. J Am Coll Cardiol 1992;20:1661-8.

Mikell FL, Asinger RW, Elsperger KJ, Anderson WR, Hodges M. Regional stasis of blood in the dysfunctional left ventricle: Echocardiographic detection and differentiation from early thrombosis. Circulation 1982;66:755-63.

Miller VT, Rothrock JF, Pearce LA, Feinberg WM, Hart RG, Anderson DC, on behalf of the Stroke Prevention in Atrial Fibrillation Investigators. Ischemic stroke in patients with atrial fibrillation: Effect of aspirin according to stroke mechanism. Neurology 1993;43:32-36.

Missault L, Jordaens L, Gheeraert P, Adang L, Clement D. Embolic stroke after unanticoagulated cardioversion despite prior exclusion of atrial thrombi by transoesophageal echocardiography. Eur Heart J 1994;15:1279-1280.

Mitusch R, Siemens HJ, Garbe M, Wagner T, Sheikhzadeh A, Diederich KW. Detection of a hypercoagulable state in nonvalvular atrial fibrillation and the effect of anticoagulant therapy. Thromb Haemost 1996,75:219-23.

Mohr JP, Caplan LR, Melski JW, Goldstein RJ, Duncan GW, Kistler JP, Pessin MS, Bleich HL. The Harvard cooperative stroke registry: a prospective registry. Neurology 1978;28:754-762.

Mohr JP, Albers GW, Amarenco P, Babikian VL, Biller J, Brey RL, Coull B, Easton JD, Gomez CR, Helgason CM, Kase CS, Pullicino PM, Turpie AG. American Heart Association Prevention Conference. IV. Prevention and Rehabilitation of Stroke. Etiology of stroke. Stroke 1997;28:1501-1506.

Monsuez JJ, Miclea JM, Brice P, Chauveinc L, Boiron M. Platelet infusion related echocardiographic contrast. Am J Cardiol 1990;66:244.

Moreya E, Finkelhor RS, Cebul RD. Limitations of transesophageal echocardiography in the risk assessment of patients before nonanticoagulated cardioversion from atrial fibrillation and flutter: An analysis of pooled trials. Am Heart J 1995;129:71-5.

Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing.

Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995;91:1588-1595.

Morris JJ, Kong YK, North WC, McIntosh HD. Experience with "cardioversion" of atrial fibrillation and flutter. Am J Cardiol 1964;94-100.

Morris JJ, Peter RH, McIntosh HD. Electrical conversion of atrial fibrillation: immediate and long-term results and selection of patients. Am J Cardiol 1966;65:216-231.

Movsowitz C, Movsowitz HD, Jacobs LE, Meyerowitz CB, Podolsky LA, Kotler MN. Significant mitral regurgitation is protective against left atrial spontaneous echo contrast and thrombus as assessed by transesophageal echocardiography. J Am Soc Echocardiogr 1993;6:107-114.

Movsowitz C, Podolsky LA, Meyerowitz CB, Jacobs LE, Kitler MN. Patent foramen ovale: a nonfunctional embryological remnant or a potential cause of significant pathology? J Am Soc Echocardiogr 1991;5:259-270.

Mugge A, Daniel WG, Hausmann D, Godke J, Wagenbreth I, Lichtlen PR. Diagnosis of left atrial appendage thrombi by transesophageal echocardiography: clinical implications and follow up. Am J Card Imag 1990;4:173-179.

Murray RD, Klein AL, Chandra S, Grimm RA, Black IW, Morehead A, Stewart WJ, Thomas JD. The "swirling" pattern of atrial spontaneous echo contrast can be characterized by integrated backscatter using Fourier analysis. J Am Coll Cardiol 1995;25(Suppl):202. (Abstract)

Murray RD, Gupta R, Scalia G, Grimm RA, Leung DY, Black IW, Vaughn SE, Thomas JD, Klein AL. The quantitative measure of spontaneous echo contrast as a predictor of left atrial mechanical function. *Journal of the American College of*

Cardiology 1997;29(Suppl):440.

Nagelhout DA, Pearson AC, Labovitz AJ. Diagnosis of paradoxic embolism by transesophageal echocardiography. Am Heart J 1991;121:1552-1554.

Nattel S. Newer developments in the management of atrial fibrillation. Am Heart J 1995;130:1094-1106.

Neilson GH, Galea EG, Hossack KF. Thromboembolic complications of mitral valve disease. Aust N Z J Med 1978;8:372-376.

Nellessen U, Danuiel WG, Matheis G, Oelert H, Depping K, Lichtlen R. Impending paradxical embolism from atrial trhombus: correct diagnosis by transesophageal echocardiography and prevention by surgery. J Am Coll Cardiol 1985;5:1002-1004.

Nicols HT, Blaco G, Morse DP, Adam A, Baltazar N. Open mitral commissurotomy: experience with 200 consecutive cases. JAMA 1962;182:268-270.

Nishimura RA, Holmes DR Jr, Reeder GS. Percutaneous balloon valuloplasty. Mayo Clin Proc 1990; 65:198-220.

Obeid AI, Marvasti M, Parker F, Rosenberg J. Comparison of transthoracic and transesophageal echocardiography in diagnosis of left atrial myxoma. Am J Cardiol 1989;63:1006-1008.

Olson JD, Goldenberg IF, Pedersen W, Brandt D, Kane M, Daniel JA, Nelson RR, Mooney MR, Lange HW. Exclusion of atrial thrombus by transesophageal echocardiography. J Am Coll Cardiol 1992;5:52-55.

O'Neil P, Puleo P, Bolli R, Rokey R. Return of mechanical function following

electrical conversion of atrial dysrhythmias. Am Heart J 1990;120:353-9.

Onundarson PT, Thorgeirsson G, Jonmundsson E, Sigfusson N, Hardson T. Chronic atrial fibrillation-Epidemiologic features and 14 year follow-up. Eur Heart J 1987;3:521-7.

Oram S, Davies JPH. Further experience of electrical conversion of atrial fibrillation to sinus rhythm: Analysis of 100 patients. Lancet 1964;1:1294-1298.

Orsinelli DA, Pearson AC. Usefulness of transesophageal echocardiography to screen for left atrial thrombus before elective cardioversion for atrial fibrillation. Am J Cardiol 1993;72:1337-9.

Ostrander LD Jr, Brandt RL, Kjelsberg MO, Epstein FH. Electrocardiographic findings among the adult population of a total natural community. Circulation 1965;31:888-98.

Partridge JF, Halmos PB. Conversion of atrial fibrillation by direct-current countershock. Br Heart J 1965;27:128-131.

Pearson AC, Labovitz AJ, Tatineni S, Gomez CR. Superiority of transesophageal echocardiography in detecting cardiac source of embolism in patients with cerebral ischemia of uncertain etiology. J Am Coll Cardiol 1991;17:66-72.

Pearson AC, Nagelhout D, Castello R, Gomez CR, Labovitz AJ. Atrial septal aneurysm and stroke: a transesophageal echocardiographic study. J Am Coll Cardiol. 1991;18:1223-1229.

Pearson AC. Transesophageal echocardiographic screening for atrial thrombus before cardioversion of atrial fibrillation: when should we look before we leap? J Am Coll Cardiol 1995;25:1362-4.

Perez JE, Miller JG, Holland MR, et al. Ultrasonic tissue characterisation: integrated backscater imaging for detecting myocardial structural properties and on-line quantitation of cardiac function. Am J Card Imag 1994;8:106-12.

Perez JE, Waggoner AD, Barzilai B, Melbon HJ, Miller JG, Sobel BE. On-line assessment of ventricular function by automatic boundary detection and ultrasonic backscatter imaging. J Am Coll Cardiol 1992;19:313-20.

Perry GJ, Helmcke F, Nanda NC, Byard C, Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping. J Am Coll Cardiol 1987;9:952-959.

Peters KG, Kienzle MG. Severe cardiomyopathy due to chronic rapidly conducted atrial fibrillation: complete recovery after restoration of sinus rhythm. Am J Med 1988;85:242-4.

Petersen P, Kastrup J, Helweg-Larsen S, Boysen G, Godtfredsen J. Risks factors for thromboembolic complications in chronic atrial fibrillation. Arch Intern Med 1990;150:819-821.

Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. Stroke 1986;17:622-6.

Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK Study. Lancet 1989;1:175-9.

Petersen P, Madsen EB, Brun B, Pedersen F, Gyldensted C, Boysen G. Silent cerebral infarction in chronic atrial fibrillation. Stroke 1987;18:1098-1100.

Peverill RE, Gelman J, Harper RW, Smolich JJ. Stability of left atrial spontaneous

echo contrast at repeat transesophageal echocardiography in patients with mitral stenosis. Am J Cardiol 1997;79:516-518.

Pollak A, Falk RH. Aggravation of postcardioversion atrial dysfunction by sotalol. J Am Coll Cardiol 1995,25:665-71.

Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. Circulation 1991;84:223-231.

Pop G, Sutherland GR, Koudstaal PJ, Sit TW, de Jong G, Roelandt JRTC. Transoesophageal echocardiography in the detection of intracardiac embolic sources in patients with transient ischemic attacks. Stroke 1990; 21:560-5.

Pozzoli M, Febo O, Torbicki A, et al. Left atrial appendage dysfunction: a cause of thrombosis?. Evidence by transesophageal echocardiography-Doppler studies. J Am Soc Echo 1991;4:435-41.

Price TR, Manolio TA, Kronmal RA, Kittner SJ, Yue NC, Robbins J, Anton-Culver H, O'Leary DH. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. Stroke 1997;28:1158-1164.

Prystowsky EN, Benson DW Jr, Fuster V, Hart RG, Kay GN, Myerburg RJ, Naccarelli GV, Wyse DG. Management of patients with atrial fibrillation. A Statement for Healthcare Professionals. From the Subcommittee on Electrocardiography and Electrophysiology, American Heart Association. Circulation 1996;93:1262-1277.

Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Winters WL, Riberior LG, Miller RR. A new simplified and accurate method for determining

ejection fraction with two-dimensional echocardiography. Circulation 1981;64:744-53.

Rabbino MD, Likoff W, Drisfus LS. Complications and limitations of direct current countershock. JAMA 1964;190:417-20.

Radford MD, Evans DW. Long-term results of DC reversion of atrial fibrillation. Br Heart J 1968;30:91-96.

Ramirez-Lassepas M, Cipolle RJ, Bjork RJ et al. Can embolic stroke be diagnosed in the basis of neurologic clinical criteria?. Arch Neurol 1987;44:87-9.

Ranoux D, Cohen A, Cabanes L, Amarenco P, Bousser MG, Mas JL. Patent foramen ovale: is stroke due to paradoxical embolism? Stroke. 1993;24:31-34.

Reinikainen M, Koskinen P, Pontinen P, Siltonen L. Experiences in the use of direct current countershock in the treatment of cardiac arrhythmias. Acta Med Scand 1965;178(Suppl):437.

Resnekov L, McDonald L. Complications in 220 patients with cardiac dysrhythmias treated by phased direct current shock, and indications for electroconversion. Br Heart J 1967;29:926-936.

Roberts WC, Siegel RJ, McManus BM. Idiopathic dilated cardiomyopathy: analysis of 152 necropsy patients. Am J Cardiol 1987;60:1340-1355.

Roberts WC, Virmani R. Aschoff bodies at necropsy in valvular heart disease: evidence from an analysis of 543 patients over 14 years of age that rheumatic heart disease, at least anatomically, is a disease of the mitral valve. Circulation 1978;57:803-807.

Rokseth R, Storstein D. Quinidine therapy of chronic auricular fibrillation: The occurence and mechanism of syncope. Arch Intern Med 1963:111:184-189.

Rossi E, Mondonico P, Lombardi A, Freda L. Method for the determination of functional (clottable) fibrinogen by the new family of ACL coagulometers. Thromb Res 1988;52:453-68.

Roy D, Marchand E, Gagne P, Chabot M, Cartier R. Usefulness of anticoagulant therapy in the prevention of embolic complications of atrial fibrillation. Am Heart J 1986;112:1039-1043.

Sadler TW. Langman's Medical Embryology. Baltimore: Williams and Wilkins,1985:178-9.

Sagar KB, Ryne TL, Warltier DC, Pelc L. Wann LS. Intramyocardial variability in integrated backscatter: effects of coronary occlusion and reperfusion. Circulation 1987;75:436-42.

Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantification in M-mode echocardiography: Results of a survey of echocardiographic measurements. Circulation 1978;58:1072-1082.

Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantification in M-mode echocardiography: Results of a survey of echocardiographic measurements. Circulation 1978;58:1072-1082.

Salka S, Saeian K, Sagar KB. Cerebral thromboembolization after cardioversion of atrial fibrillation in patients without transesophageal echocardiographic findings of left atrial thrombus. Am Heart J 1993;126:722-4.

Sanfilippo AJ, Abascal VM, Sheehan M, Oertel LB, Harrigan P, Hughes RA,

Weyman AE. Atrial enlargement as a consequence of atrial fibrillation: a prospective echocardiographic study. Circulation 1990;82:792-797.

Sansoy V, Abbott RD, Jayaweera AR, Kaul S. Low yield of transthoracic echocardiography for cadiac source of embolism. Am J Cardiol 1995;75:166-169.

Savage RM, Duffy CI, Thomas JD, Stewart WJ, Black IW, Licina M, James KB, O'Conner M, McCarthy PM, and the LVAD Study Group. Transesophageal echocardiography is indicated in the placement of the implantable left ventricular assist device. J Am Coll Cardiol 1993;21(Suppl A):321. (Abstract)

Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Getgesell H, Reiuchek N, Sahn D, Schnittger I, Silverman N, Tajik AJ. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiog 1989;2:358-67.

Schmid-Schonbein H, Gaehtgens P, Hirsch H. On the shear rate dependence of red cell aggregation in vitro. J Clin Invest 1968;47:1447-54.

Schweizer P, Bardos P, Erbel R, Meyer J, Merx W, Messmer BJ, Effert S. Detection of left atrial thrombi by echocardiography. Br Heart J 1981;45:148-156.

Selzer A, Kelly JJ, Johnson RB, Kerth WJ. Immediate and long term results of electrical cardioversion of arrhythmias. Prog Cardiovasc Dis 1966;9:90-104.

Seward JB, Khandheria BK, Oh JK, Abel MD, Hughes RW Jr, Edwards WD, Nichols BA, Freeman WK, Tajik AJ. Transesophageal echocardiography: Technique, anatomic correlations, implementation, and clinical applications. Mayo Clin Proc. 1988;63:649-680.

Seward JB, Khandheria BK, Edwards WD, Oh JK, Freeman WK, Tajik AJ. Biplane

transesophageal echocardiography: anatomic correlations, implementation, and clinical applications. Mayo Clin Proc 1990;65:1193-213.

Seward JB, Khanderia BK, Freeman WK, Oh JK, Enriques-Sarano M, Miller FA, Edwards ED, Tajik AJ. Multiplane transesophageal echocardiography: Image orientation, examination technique, anatomic correlations and clinical applications. Mayo Clin Proc 1993;68:523-551.

Sgarbossa EB, Black IW, Maloney JD. Pacemakers, defibrillators, and direct current cardioversion. Current Opinion in Cardiology 1993;8:27-38.

Shapiro EP, Effron MB, Lima S, Ouyang P, Siu CO, Bush D. Transient atrial dysfunction after conversion of chronic atrial fibrillation to sinus rhythm. Am J Cardiol 1988;62:1202-1207.

Sheldon WS, Vandervoort PM, Black IW, Grimm RA. Aortic intramural hematoma in patients evaluated for aortic dissection: Clinical, echocardiographic, radiographic and pathologic findings. Circulation 1994;90:385. (Abstract)

Sherman W, Nozad SE, Stoian A, Madias JE. Free-floating left atrial thrombus and systemic embolization. Chest 1985;87:694-695.

Sherman DG. Cardiac embolism: the neurologist's perspective. Am J Cardiol 1990;65:32C-37C.

Sherman DG, Dyken ML, Gent M, Harrison MJG, Hart RG, Mohr JP. Antithrombotic therapy for cerebrovascular disorders. An update. Fourth ACCP Consensus Conference on Antithrombotic Therapy. Chest 1995;108(Suppl):444-456.

Shiba A, Yamada I, Murakami K, Shuimura T. A measurement method for

absolute value of integrated backscatter. In: Proceedings, IEEE Ultrasonics Symposium. New York: IEEE, 1991;2:1089-92.

Shimomura K, Ohe T, Ueharas S, Matsuhisa M, Kamakura S, Sato I. Significance of atrial fibrillation as a precursor of embolism. Am J Cardiol 1989;63:1405-7.

Shiran A, Goldstein SA, Zafar S, Ellahham S, Sears-Rogan P, Pinnow E, Lindsay J Jr. Determination of pretest probability for detection of a cardiovascular source of emboli by transesophageal echocardiography using clinical and transthoracicechocardiographic data. Am J Cardiol 1998;81:1506-1508.

Shrestha NK, Moreno FL, Narciso FV, Torres L, Calleia HB. Two dimensional echocardiographic diagnosis of left atrial thrombus in rheumatic heart disease: a clinicopathologic study. Circulation 1983;2:341-347.

Shung KK, Fei DY, Ballard J. Further studies on ultrasonic properties of blood clots. J Clin Ultrasound 1986;14:269-75.

Side CD, Gosling RG. Non-surgical assessment of cardiac function. Nature 1971;232:335-6.

Sigel B, Feleppa EJ, Swami V, et al. Ultrasonic tissue characterisation of blood clots. Drug Clin North Am 1990;70:13-29.

Sigel B, Coelho JCU, Schade SG, Justin J, Spigos DG. Effect of plasma proteins and temperature on echogenicity of blood. Invest Radiol 1982;17:29-33.

Sigel B, Coelho JO, Spigos DG et al. Ultrasonography of blood during stasis and coagulation. Invest Radiol 1981;16:71-6.

Sigel B, Machi J, Beitler JC, Justin JR. Red cell aggregation as a cause of blood-

flow echogenicity. Radiology 1983;148:799-802.

Sigel B, Machi J, Beitler JC, Ramos JR, Justin JR, Reinberg H. Ultrasonic detection of red cell aggregation immediately preceding blood clotting. Invest Radiol 1984;19:458-61.

Silver MD, Dorsey JS. Aneurysms of the septum primum in adults. Arch Pathol Lab Med 1978;102:62-65.

Silvey SV, Stoughton TL, Pearl W, Collazo WA, Belbel RJ. Rupture of the outer partition of aortic dissection during transesophageal echocardiography. Am J Cardiol 1991;68:286-287.

Sjoberg SG. The diagnostic use of ultrasound in heart disease. Acta Med Scand Suppl 1954;308:32-36.

Skorton D, Miller J, Wickline S, Barzilai B, Collins S. Perez J. Ultrasonic characterisation of cardiovascular tissue. In:Marcus M, Schelbert H, Skorton D, Wolf G, eds. Cardiac Imaging. Philadelphia: WB Saunders, 1991:53856.

Sokolow M, Ball RE. Factors influencing conversion of chronic atrial fibrillation with special reference to serum quinidine concentration. Circulation 1956;14:568-585.

SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. JAMA 1998;22:1273-1277.

Speechly-Dick ME, Middleton SJ, Foale RA. Impending paradoxical embolism: a rare but important diagnosis. Br Heart J 1991;65:163-165.

337

Stafford RS, Singer DE. National patterns of warfarin use in atrial fibrillation. Arch Intern Med 1996;156:2537-2541.

Stein B, Halperin JL, Fuster V. Should patients with atrial fibrillation be anticoagulated prior to and chronically following cardioversion? Cardiovasc Clin 1990;21:231-249.

Steinberg MH, Kelton JG, Coller BS. Plasma glycocalicin: An aid in the classification of the thrombocytopenic disorders. N Engl J Med 1987;317:1037-42.

Stewart WJ, Ares M, Klas B, Black I, Duffy C, Vandervoort P, Barzilai B, Lytle B. Epicardial 3-dimensional echo using a standard transthoracic transducer: promises and limitations. Circulation 1993;88(Suppl):350. (Abstract)

Stoddard ME, Longaker RA. Role of transesophageal echocardiography prior to cardioversion in patients with atrial fibrillation. (Abstract) J am Coll Cardiol 1993;21:28A.

Stoddard ME, Dawkins PR, Prince CR, Longaker RA. Transesophageal echocardiographic guidance of cardioversion in patients with atrial fibrillation. Am Heart J 1995,129:1204-1215.

Stroke Prevention in Atrial Fibrillation Investigators. Preliminary report of the Stroke Prevention in Atrial Fibrillation Study. N Engl J Med 1990; 322:863-8.

Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991;84:527-539.

Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk. Ann Intern Med 1992;116:1-5.

Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. Ann Intern Med 1992;116:6-12.

Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. Lancet 1994;343:687-91.

Stroke Prevention in Atrial Fibrillation Investigators. Bleeding during antithrombotic therapy in patients with atrial fibrillation. Arch Intern Med 1996;156:409-16.

Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. Lancet 1996;348:633-38.

Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. Ann Intern Med 1998;128;639-47.

Sun H, Gaspo R, Leblanc N, Nattel S. Cellular mechanisms of atrial contractile dysfunction caused by sustained atrial tachycardia. Circulation 1998;98:719-727.

Szekely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. Br Med J 1964;1:1209-1212.

Takano K, Yamaguchi T, Kato H, Omae T. Activation of coagulation in acute cardioembolic stroke. Stroke 1991;22:12-6

Tanahashi N, Gotoh F, Tomita M et al. Enhanced erythrocyte aggregability in

occlusive cerebrovascular disease. Stroke 1989;20 1202-7.

The Cardiac Arrhythmia Suppression Trial (CAST) Investigators: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406-12.

The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990;323:1505-1511.

The Steering and Publications Committees of the ACUTE Study, for the ACUTE Investigators. Design of a clinical trial for the Assessment of Cardioversion Using Transesophageal Echocardiography (The ACUTE Multicenter Study). Am J Cardiol 1998;81:877-83.

Thiedemann KU, Ferrans VJ. Left atrial ultrastructure in mitral valvular disease. Am J Path 1977;89:575-593.

Thompson M, Metzger C, Shaver J, et al. Assessment of left atrial transport function immediately after cardioversion. Am J Card 1972; 29: 481-9.

Thomson GW. Quinidine as a cause of sudden death. Circulation 1956;14:757-65.

Tieleman RG, Gosselink AT, Crijns HJ, van Gelder IC, van den Berg MP, de Kam PJ, van Gilst WH, Lie KI. Efficacy, safety, and determinants of conversion of atrial fibrillation and flutter with oral amiodarone. Am J Cardiol 1997;79:53-57.

Tieleman RG, De Langen C, Van Gelder IC, de Kam PJ, Grandjean J, Bel KJ, Wijffels
MC, Allessie MA, Crijns HJ. Verapamil reduces tachycardia-induced electrical remodeling of the atria. Circulation 1997;95:1945-1953.

Tieleman RG, Van Gelder IC, Crijns HJ, De Kam PJ, Van Den Berg MP, Haaksma J, Van Der Woude HJ, Allessie MA. Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodeling of the atria? J Am Coll Cardiol 1998;31:167-173.

Tomlin PJ, Duck FA. Transesophageal aortic velography in man. Canadian Anaesthetists' Society Journal 1975;22:561-571.

Triposkiadis F, Wooley CF, Boudoulas H. Mitral stenosis: left atrial dynamics reflect altered passive and active emptying. Am Heart J 1990;120:124-132.

Tunick PA, Rosenzweig BP, Katz ES, Freedberg RS, Perez JL, Kronzon I, High risk for vascular events in patients with protruding aortic atheromas: a prospective study. J Am Coll Cardiol 1994;23:1085-1090.

Tsai LM, Chen JH, Fang CJ, Lin LJ, Kwan CM. Clinical implications of left atrial spontaneous echo contrast in nonrheumatic atrial fibrillation. Am J Cardiol 1992;70:327-331.

Tsai LM, Hung JS, Chen JH, Lin LJ, Fu M. Resolution of left atrial appendage thrombus in mitral stenosis after warfarin therapy. Am Heart J 1991;121:1232-1234.

Tsai LM, Chen JH, Yang YJ. Role of transesophageal echocardiography in detecting atrial thrombus and spontaneous echo contrast in patients with mitral valve disease or non-rheumatic atrial fibrillation. J Formosan Med Ass 1990;89:270-274.

Tunick PA, Perez JL, Kronzon I. Protruding atheromas in the thoracic aorta and systemic embolization. Ann Intern Med 1991;115:423-427.

Turner JRB, Towers JRH. Complications of cardioversion. Lancet 1965;2:612-4.

Unverferth DV, Fertel RH, Unverferth BJ, Leier CV. Atrial fibrillation in mitral stenosis: histologic, hemodynamic and metabolic factors. Int J Cardiol 1984;5:143-152.

Vahanian A, Michel PL, Cormier B, Ghanem G, Vitoux B, Maroni JP, Cazaux P, Acar J. Immediate and mid-term results of percutaneous mitral commissurotomy. Eur Heart J 1991;12:Suppl B:84-89.

Van Gelder IC, Crijns HJ, VanGilst WH, Verwer R, Lie KI. Prediction of uneventful cardioversion and maintenance of sinus rhythm from direct current electrical cardioversion of chronic atrial fibrillation and flutter. Am J Cardiol 1991;68:41-46.

Van Gelder IC, Crijns HJ, VanGilst WH, Hamer HP, Lie KI. Decrease of right and left atrial sizes after direct current electrical cardioversion in chronic atrial fibrillation. Am J Cardiol 1991;67:93-95.

Vandenbogaerde J, De Bleecker J, Decoo D, Francois K, Cambier B, Vandermersch C, De Reuck J, Clement DL. Transoesophageal echo-Doppler in patients suspected of a cardiac source of peripheral emboli. Eur Heart J 1992;13:88-94.

Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation 1994;89:724-30.

Veinot JP, Harrity PJ, Gentile F, Khandheria BK, Bailey KR, Eickholt JT, Seward JB, Tajik AJ, Edwards WD. Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination. Circulation 1997;96:3112-15.

Vered Z, Barzilai B, Mohn GA, et al. Quantitative ultrasonic tissue characterisation with real-time integrated backscatter imaging in normal human subjects and in patients with dilated cardiomyopathy. Circulation 1987;76:1067-73.

Vered Z, Mohr G, Barzilai B, et al. Ultrasonic integrated backscatter tissue characterisation of remote myocardial infarction in human subjects. J Am Coll Cardiol 1989;13:84-91.

Vigna C, Rito V, Criconia GM, Russo A, Testa M, Fanelli R, Francesco L. Left atrial thrombus and spontaneous echo-contrast in nonanticoagulated mitral stenosis: a transesophageal echocardiographic study. Chest 1993;103:348-352.

Vigna C, Russo A, DeRito V, Perna GP, Villella A, Testa M, Sollazzo V, Fanelli R, Loperfido F. Frequency of left atrial thrombi by transesophageal echocardiography in idiopathic and in ischemic dilated cardiomyopathy. Am J Cardiol 1992;70:1500-1501.

Viko LE, Marvin HM, White PD. A clinical report on the use of quinidine sulphate. Arch Intern Med 1923;31:345-363.

Virmani R, Roberts WC. Aschoff bodies in operatively excised atrial appendages and in papillary muscles: frequency and clinical significance. Circulation 1977;55:559-563.

Voci P, Scibilia G, Bilotta F, Maugeri B, Caretta Q, Mercanti C, Marino B, Reale A. Spontaneous left atrial echocardiographic contrast in mitral stenosis: early disappearance after valve replacement. J Am Soc Echocardiogr 1991;4:648-650.

Wallach JB, Lukash L, Angrist AA. An interpretation of the incidence of mural thrombi in the left auricle and appendage with particular reference to mitral commissurotomy. Am Heart J 1953;45:252-254.

Walsh WF, Black IW (Anonymous). Transoesophageal echocardiography (Editorial). Lancet 1992;339:709-11.

Webster MW, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM, Glasgow GL. Patent foramen ovale in young stroke patients. Lancet 1988;2:11-12.

Weinberg DM, Mancini GBJ. Anticoagulation for cardioversion of atrial fibrillation. Am J Cardiol 1989;63:745-746.

Weinberger J, Rothlauf E, Materese E, Halperin J. Noninvasive evaluation of the extracranial carotid arteries in patients with cerebrovascular events and atrial fibrillation. Arch Internal Medicine 1988;148:1785-1788.

Wells P, Biomedical Ultrasonics. New York: Academic Press, 1977:120-3.

Whitaker AN, Elms MJ, Masci PP, et al. Measurement of cross-linked fibrin derivatives in plasma: an immunoassay using monoclonal antibodies. J Clin Pathol 1984;37:882-7.

Wiener I. Clinical and echocardiographic correlates of systemic embolization in nonrheumatic atrial fibrillation. Am J Cardiol 1987;59:177.

Wijffels M, Kirchhof C, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: A study in awake chronically instrumented goats. Circulation 1995;92:1954-1968.

Wikland B, Edhag O, Eliasch H. Atrial fibrillation and flutter treated with synchronized DC shock. A study on immediate and long-term results. Acta Med Scand 1967;182:665-71 .

Wilhelmsen L, Svardsudd K, Korsan-Bengtsen K, Larsson B, Welin L, Tibblin G.

Fibrinogen as a risk factor for stroke and myocardial infarction. N Engl J Med 1984;311:501-5

Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Br Heart J 1988;60:299-308.

Williamson BD, Man KC, Daoud E, Niebauer M, Strickberger SA, Morady F. Radiofrequency catheter modification of atrioventricular conduction to control the ventricular rate during atrial fibrillation. N Engl J Med 1994;331:910-7.

Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-988.

Wolf PA, Abbott Rd, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly: the Framingham study. Arch Intern Med 1987;147:1561-4.

Wolf PA, Dawber TR, Thomas HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. Neurology 1978;28:973-7.

Wolf PA, Kannel WB, McGee DL, Meeks SL, Bharucha NE, McNamara PM. Duration of atrial fibrillation and imminence of stroke: the Framingham study. Stroke 1983;14:664-667.

Wrisley D, Giambartolomei A, Lee I, Brownlee W. Left atrial ball thrombus: Review of clinical and echocardiographic manifestations with suggestions for management. Am Heart J 1991;121:1784-1790.

Yamamoto K, Ikeda U, Shimada K. A hypercoagulable state in the left atrum of patients with mitral stenosis. N Engl J Med 1993;328:1043-1044.

Yamamoto K, Ikeda U, Minezaki KK, Fukazawa H, Mizuno O, Kim S, Fujikawa H, Sekiguchi H, Shimada K. Effect of mitral valvuloplasty in mitral stenosis on coagulation activity. Am J Cardiol 1997;79:1131-35.

Yasaka M, Miyatake K, Mitani M, Beppu S, Nagata S, Yamaguchi T, Omae T. Intracardiac mobile thrombus and D-dimer fragment of fibrin in patients with mitral stenosis. Br Heart J 1991;66:22-25.

Yasaka M, Yamaguchi T, Miyashita T, Park YD, Sawada T, Omae T. Predisposing factors of recurrent embolization in cardiogenic cerebral embolism. Stroke 1990;21:1000-7

Yoshida K, Yoshikawa J, Yamaura Y, Hozumi T, Akasaka T, Fukaya T. Assessment of mitral regurgitation by biplane transesophageal color Doppler flow mapping. Circulation 1990;82:1121-1126.

Yuan Y, Shung K. Ultrasonic backscatter from flowing whole blood, I: Dependence on shear rate and hematocrit. J Acoust Soc Am 1988;84:52-8.

Yuan YW, Shung KK. Ultrasonic backscatter from flowing whole blood. II:Dependence on frequency and fibrinogen concentration. J Acoustic Soc Am 1988b;84:1195-1200.

Zabalgoitia M on behalf of the SPAF Investigators. Stroke prevention in atrial fibrillation III and transesophageal echo study. Design and progress report. Eur Heart J 1994;15(Suppl):28.

Zabalgoitia M. Transesophageal echocardiography in atrial fibrillation: report of the Stroke Prevention in Atrial Fibrillation III Study. Circulation. 1994;90:(suppl 1):1-237. (Abstract)

Zenker G, Erbel R, Kramer G, Mohr-Kahaly S, Drexler M, Harnoncourt K, Meyer J. Transoesophageal two-dimensional echocardiography in young patients with cerebral ischemic events. Stroke 1988; 19:345-8.

Zipes DP. Atrial fibrillation. A tachycardia-induced atrial cardiomyopathy. Circulation 1997;95:562-564.

Zipes DP. Electrophysiological remodeling of the heart owing to rate. Circulation 1997;95:1745-1748.