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Arterial Stiffness Indices in Healthy Volunteers Using Non-Invasive Digital Photoplethysmography

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Abstract.

Background. Increased arterial stiffness is a marker of cardiovascular damage, even in the absence of clinically apparent disease. It is likely to become an important clinical tool in cardiovascular risk assessment. *Aims & Methods.* We studied a group of healthy subjects and measured their arterial stiffness by digital photoplethysmography. We aimed to obtain a range of arterial stiffness values, and investigated the influence of age, gender, race, BMI, fasting lipids and haemodynamic factors. *Results.* 152 healthy subjects, aged between 18-67 years, on no medications and with no significant medical illnesses were recruited. The population was predominantly Caucasian (n=112). Two measures of arterial stiffness were obtained: stiffness index (SI), a measure of large arterial stiffness, and reflection index (RI), a measure of small to medium-sized arterial stiffness. SI and RI were significantly correlated with age, total cholesterol, LDL-c, heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP). Race was a significant independent predictor of SI. *Conclusion.* Digital photoplethysmography is a portable, operator-independent, reproducible and simple method of measuring arterial stiffness. Ranges of normality of arterial stiffness will depend on the individual's age, race, lipid levels, HR and BP.

Key words: digital photoplethysmography, arterial stiffness, stiffness index, reflection index, blood pressure, dyslipidaemia

Introduction.

Cardiovascular disease remains one of the biggest causes of mortality in the world, accounting for 29.3% of deaths[1] recorded in the WHO's World Health report in 2004. The recent years have therefore seen a focus in developing techniques to facilitate early identification of individuals at increased cardiovascular risk. In particular, there has been much interest in arterial stiffness measurement as a method of detecting cardiovascular changes before the onset of established cardiovascular disease. Indeed, arterial stiffness is now recognized as an independent and significant predictor of cardiovascular morbidity and mortality[2-5] and its application to everyday clinical practice appears inevitable.

Vascular stiffening, however, is a complex phenomenon involving structural and cellular elements of the vessel wall. Although it is independently associated with cardiovascular morbidity and mortality, this effect is not mutually exclusive of intrinsic factors such as an individual's age, gender and race[6-10]. In addition, normal reference values for arterial stiffness will also depend on the technique used to obtain the measurement. These are significant issues to consider if this technology is to be implemented in everyday clinical practice.

We studied a group of healthy individuals and measured their arterial stiffness by digital photoplethysmography. We aimed to obtain a range of arterial stiffness values, and investigated the influence of age, gender, race, BMI, fasting lipids and haemodynamic factors on arterial stiffness measurements using digital photoplethysmography.

Methods

The study was performed at the University of New South Wales St George Clinical School, St George Hospital, Australia. Approval to perform the study was obtained from the South Eastern Sydney and Illawarra Area Health Service Research and Ethics Committee (06/92 O'Sullivan).

Subjects:

Subjects were recruited through public advertisements posted within the hospital for healthy non-smoking volunteers. Inclusion criteria include: age greater than 18 years, non-pregnant women, non-smoker, no known cardiovascular disease, no diabetes mellitus, dyslipidaemia or hypertension, and no medications including bronchodilators or hormone replacement therapy. Patients with significant medical illnesses such as malignancy and any active infection were excluded. Written informed consent was obtained after the nature of the study was explained to each participant.

A brief history was taken to assess cardiovascular risk, and establish the subject's race. Height and weight measurements were performed.

Blood Pressure Measurement:

Blood pressure was measured over the brachial artery of the right arm in the sitting position using a cuff-appropriate automated oscillometric device (Omron T-5, Omron

Healthcare, Milton, Keynes, UK). Three measurements were taken after 15 minutes' rest. The mean of the three consecutive measurements was calculated and used for analysis.

Mean arterial pressure (MAP) was calculated using: DBP + 1/3 (pulse pressure).

Measurement of arterial stiffness:

Arterial stiffness was measured in a sitting position after 15 minutes' rest, using the Pulse Trace system (Micro Medical, Gillingham, Kent, UK). A digital photoplethysmograph transmitting infra-red light was applied to the left index finger. The amount of light transmitted through the finger varies proportionally to changes in its blood volume. The signal from the photoplethysmograph obtained over a 30 second period is averaged by the system, to produce a single digital volume pulse (DVP) waveform (Figure 1). Chowienczyk et al [11] demonstrated that the peripheral pressure pulse is related to the DVP by a single generalized transfer function, which is in-built in the Pulse Trace system.

The DVP wave (Figure 1) consists of an early systolic peak (a), which results from an increase in digital blood volume from a pressure wave transmitted from the left ventricle to the finger along a direct path. The second peak (b), occurs in diastole, and is formed by pressure waves reflected back up to the aorta and thence to the finger, from sites of impedance mismatch in the lower body. The time between the systolic and diastolic peaks (peak to peak time, *PPT*) can be used to infer the time taken for the pressure wave

to travel from the aorta to the lower body, and thence as a reflected wave back up to the aorta to the finger. This path length is unknown, but is proportional to the subject's height (h). An index of large arterial stiffness (stiffness index, SI) can therefore be derived, similar to the calculation of pulse wave velocity (PWV) by the formula: h/PPT. Indeed, SI has been shown to be strongly correlated to central (aortic and carotid-femoral) PWV [11, 12].

An index of small to medium-sized arterial stiffness can be derived from the magnitude of the reflected waves from the lower limbs to the aorta. The reflection index (RI) is thus measured using: b/a x 100%. The Pulse Trace system analyzes the average DVP waveform, and gives absolute values of SI and RI, based on the entered subject's height.

Using this method in 115 subjects, we were able to obtain good same day intra-individual reproducibility, with a co-efficient of variation (CV) for SI of 8%, and for RI, 5%.

Blood Samples:

A subset of normal subjects who have participated in other studies in our department had fasting blood samples taken for total cholesterol (TC), triglycerides (TG), calculated LDL-cholesterol (c-LDL) and HDL-cholesterol. The blood samples were analyzed by accredited private and hospital-based laboratories.

Statistical Analysis:

All statistical tests were performed using STATISTICA 7.0 software (Statsoft, Inc, Tulsa, OK, USA).

Results are summarized as means ± SD. Normality of distribution of all parameters (age, body mass index (BMI), heart rate (HR), SBP, DBP, MAP, PP, SI and RI) were tested using the Shapiro-Wilk test.

SI was not normally distributed. Results were therefore presented as mean ± SD along with the 25^{th} and 75^{th} percentile values. Spearman's correlation analysis was used to investigate the relationship between cardiovascular risk factors (age, BMI, fasting TC, TG. c-LDL, HDL, MAP, SBP and DBP) and SI. Simple correlation analysis was used to investigate the relationship between cardiovascular risk factors and RI, which was normally distributed. Multivariate regression analysis was performed to investigate the relationship of cardiovascular risk factors on arterial stiffness indices. For SI, the variables were inverse log transformed prior to regression analysis to correct the skewed distribution. None of the other variables were transformed.

The effect of gender and race was investigated using the student's unpaired *t*-test to compare continuous variables between male and female subjects and Caucasian and non-Caucasian subjects. Analysis of covariance (ANCOVA) was performed to compare the groups. SI values were inverse log transformed prior to this analysis. Significant cardiovascular risk factors were used as covariates and arterial stiffness indices (SI, RI

and PP) as dependent variables.

Results:

Baseline Characteristics

A total of 152 subjects met inclusion criteria. Only 119 of the 152 subjects had their blood pressure measurements recorded. Forty-four subjects had fasting blood lipids measured.

Table 1a outlines the demographic features of the volunteers. The lipid profiles of the 44 subjects who had fasting blood samples taken are outlined in Table 1b. None were regular drinkers of alcohol. Nine subjects had blood pressure measurements consistent with hypertension (BP ≥140/90 mmHg). The maximum SBP was 153 mmHg, and maximum DBP was 94 mmHg. All nine subjects had no prior history of hypertension and no other known cardiovascular risk factors, and were referred to their local medical officer for further assessment.

One subject had known sinus tachycardia (HR of 101 bpm), which had previously been investigated, with no cause found.

Association of Arterial Stiffness Indices with Cardiovascular Risk Factors:

SI was strongly associated with age, total cholesterol, LDL-c, HR and all measures of blood pressure (Table 2) using Spearman's correlation analysis. In the multiple regression analysis without haemodynamic factors (age, total cholesterol and LDL-c, whole model

R^2=0.37) only age (p=0.001) and total cholesterol (p=0.01) were independently associated with SI. When haemodynamic factors were included (whole model R^2=0.52), only age was independently associated with SI (p=0.02). 45% of the variance in SI was due to age, SBP and DBP (p=0.01).

RI was significantly associated with age, total cholesterol, and all measures of blood pressure (Table 2). It was negatively correlated with heart rate. In the multiple regression analysis with haemodynamic parameters (age, total cholesterol, LDL-c, SBP, DBP and HR, whole model R^2=0.33), total cholesterol (p=0.01), LDL-c (p=0.05), HR (p=0.02), SBP (p=0.03) and DBP (p=0.01) were all independently associated with RI. Age, SBP and DBP accounted for 9% of the variance in RI (p=0.01). No factors were independently associated with RI when haemodynamic parameters were excluded.

Due to the significant correlation between fasting lipids and arterial stiffness, we further investigated the relationship between lipids and blood pressure. We found a strong correlation between SBP and total cholesterol (r=0.43, p=0.004) and LDL-c (r=0.42, p=0.005), but no significant correlations with HDL-c and TG (not illustrated). Similarly, DBP was strongly correlated with total cholesterol (r=0.43, p=0.004) and LDL-c (r=0.44, p=0.003), but not with HDL-c and TG.

Effect of Gender

42% of the group were males (Table 1). For the same age, men had significantly higher blood pressure (SBP, DBP and MAP) readings (Table 3), and a strong tendency to higher

LDL cholesterol levels (p=0.06).

After correction for SBP, DBP and LDL, there were no significant differences in any of the arterial stiffness indices between males and females. These findings remained robust when correction was made for age, SBP and DBP only.

Effect of Race

The majority of subjects were Caucasian (Table 1). The non-Caucasian group include people of Asian (n=34), Black African (n=4), and "other" (n=2) origin. For a similar age group, the Caucasians had significantly higher blood pressures (SBP, DBP and MAP) and heart rate (p=0.001), and significantly lower HDL levels (p=0.0003) (Table 4).

Age, HDL, HR, SBP and DBP account for 56% of the variance in SI. After correction for these factors, SI was statistically significantly higher in the non-Caucasian group compared with the Caucasian group (SI mean for non-Caucasians: 7.21±0.03 m/s, for Caucasians: 6.36±0.04 m/s, p=0.01). No significant differences in RI was found.

Correcting for HR, SBP and DBP only, no significant difference in arterial stiffness indices between races was found.

In the multiple regression analysis which included race and gender, race was an independent predictor of SI (p=0.04), but not for RI (p=0.21). Gender was not a predictor for either arterial stiffness indices.

Discussion.

Arterial stiffness measurement is currently mainly employed in a research setting than in clinical practice. In the near future, however, it is likely that this technology will become an important tool in cardiovascular risk assessment, and clinicians will need to become familiar with the various techniques available and also have an understanding of the factors which influence arterial stiffness readings.

Digital photoplethysmography with the Pulse Trace system is a portable, operator-independent, reproducible and simple method of measuring arterial stiffness. It provides two indices of arterial stiffness: SI, which is a measure of large arterial stiffness, and RI, a measure of small to medium-sized arterial stiffness.

Increased arterial stiffness is a marker of cardiovascular damage, even in the absence of clinically apparent disease[13, 14]. It is an established predictor of cardiovascular morbidity and mortality[2-5], and is, itself, implicated in the development of cardiovascular disease[13, 14].

Age is a well-described predictor of arterial stiffness. Vascular stiffening occurs from age twenty [10, 15], with an apparent reduction in, as well as fragmentation and degeneration of, elastic tissue. This occurs mainly in large conduit arteries such as the aorta, thus the strong correlation of age to SI ($r = 0.57$, $p < 0.001$), and to a lesser extent, RI ($r = 0.26$, $p = 0.005$).

SBP and DBP are also known to increase with age. The increase in SBP can in part, be attributed to the age-related vascular stiffening described above. In addition, with increased vascular stiffness, pulse wave reflections from peripheral arteries arrive at the aortic root earlier in the cardiac cycle. This results in summation of the antegrade wave, with a consequent increase in peak systolic pressure, that is, systolic hypertension. Isolated systolic hypertension is a major cause of cardiovascular morbidity, particularly in those aged > 55 years[14]. This age group is also characterized by a reduction in DBP [13, 14], causing a widening in pulse pressure (PP). Both are clinical manifestations of increased arterial stiffness, and is associated with increased risk for strokes, myocardial infarction, heart failure, and overall mortality in the elderly [15]. In contrast, in younger hypertensive subjects, SBP, DBP and MAP are better predictors of cardiovascular disease, implying a different pathophysiological mechanism [15] . Our cohort consisted predominantly of people aged < 65 years, thus MAP was measured, and not peripheral PP. We found SBP, DBP and MAP to be independent predictors of SI and RI. This is consistent with other studies employing other methods of measuring arterial stiffness, particularly large artery stiffness [5, 16-19] . Together, age and blood pressure accounted for 45% of the variance in SI, as opposed to 9% of the variance in RI.

It is interesting that we have also found a strong correlation between BP and total cholesterol and LDL-c. This was previously described by McMahon et al [20] in their population study of 5603 Australians in 1986 , where they found an increased prevalence of dyslipidaemia (including high TG, but not low HDL) in subjects with untreated hypertension compared with normotensive individuals. There is no clear link between

lipid deposition in vessel walls, nor of atherosclerosis formation and processes which lead to the remodeling associated with arterial stiffness. Despite this, several studies [16, 17, 21-23] including ours have found a strong positive relationship between arterial stiffness (central and peripheral) and total cholesterol or LDL-c.

The relationship of HR with arterial stiffness is complex. Resting HR is an independent risk factor for death due to cardiac causes [24, 25]. In our study, HR was positively correlated with SI, but was not an independent predictor of SI. Other studies have found HR to be an independent predictor of large arterial stiffness, and have suggested that it may contribute to the association between large arterial stiffness and increased cardiovascular risk [18, 26]. In contrast to SI, RI is negatively correlated with HR, as wave reflection is reduced with tachycardia.

There is evidence that gender is an independent predictor of arterial stiffness[5, 10]. Gender did not appear to have an effect on arterial stiffness indices in this cohort (Table 3), despite a significantly increased mean SBP and DBP in males compared with females. There was no significant difference in age between the genders, and only 1% of our female population was over the age of 60, therefore menopausal status could not account for this lack of difference. Consistent with this finding, there was little difference in the mean SI and RI across the different age groups in males and females (Table 5), with the exception of the 18-34 year old age group, which, as expected, showed reduced mean large arterial stiffness in the females, compared to males.

There was a strong trend towards an increased SI (p=0.06) in our Caucasian group compared with the non-Caucasian group. This is partly because of significant differences in mean HR, SBP and DBP, and the non-Caucasian population tending to be younger. It is interesting that after correction for these factors, SI was significantly increased in non-Caucasians compared with Caucasians, confirming that race is a significant independent predictor of SI. The ethnic differences in arterial stiffness is complex. There is some evidence that healthy South Asian men may have increased arterial stiffness compared with healthy white Caucasians [27], although another study using the same population, and measuring peripheral, as well as central PWV, found no difference [28]. In patients with type 2 diabetes, race appears to have a significant influence, with Afro-Caribbeans having the highest mean PWV, followed by Caucasians, then Asians [29-31]. We had mixed results in our study (Figure 5), with small to medium-sized arterial stiffness being higher in our (predominantly Asian) non-caucasian group who were aged less than 50 years, and the converse pattern for large arterial stiffness. Interestingly, non-caucasians over 50 years in our cohort had higher mean SI and RI than their Caucasian counterparts. It is well-described that Asians have increased cardiovascular risk [27], and it may be that factors which increase arterial stiffness in this population may contribute to this risk.

Interpretation of our study results should take into account that there is an under-representation of healthy individuals aged > 65 years. This is a result of recruitment bias, as most of our volunteers are healthy hospital personnel, most of which are aged less than 65 years. Despite this, we were able to demonstrate an age-dependent increase in arterial stiffness. Another limitation of the study is the small proportion who had fasting lipids

(n=44) taken, although we were still able to demonstrate convincingly significant correlations between fasting lipids and arterial stiffness indices and BP.

In conclusion, arterial stiffness measurement is likely to become an important clinical tool in the near future to assist in the assessment of cardiovascular risk before the onset of established cardiovascular disease. Arterial stiffness is implicated in the development of cardiovascular disease such as isolated systolic hypertension. Digital photoplethysmography with the Pulse Trace system is a portable, operator-independent, reproducible and simple method of measuring arterial stiffness. Ranges of normality using this method will depend on the individual's age, race, lipid levels, HR and BP.

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Table 1a. Demographic features of population cross-section. *Note n=119 for SBP, DBP and MAP.		
	Mean ± SD	**25th and 75th Centile**
TOTAL	152	
Gender Female	89	
Race Caucasian	112	
age (yrs)	36 ± 12	27 and 42
BMI(kg/m2)	25.2 ± 4.7	22.2 and 27.6
SI (m/s)	8.17 ± 2.17	6.80 and 9.16
RI (%)	73 ± 12	68 and 82
HR (bpm)	72 ± 10	65 and 78
SBP (mmHg)*	118 ± 14	108 and 127
DBP (mmHg)*	72 ± 10	66 and 80
MAP (mmHg)*	87 ± 11	80 and 95

Table 1b. Lipid profiles of 44 subjects who had fasting blood samples taken.		
Triglyceride (mmol/L)	1.2 ± 0.7	0.7 and 1.4
Total Chol (mmol/L)	4.8 ± 1.1	3.9 and 5.3
HDL-C (mmol/L)	1.4 ± 0.4	1.1 and 1.7
LDL-C (mmol/L)	2.8 ± 0.9	2.2 and 3.5

Table 2. Correlation co-efficients (*r*) relating cardiovascular risk factors and arterial stiffness measurements.

	SI		RI	
	Spearman ***r***	*p*	***r***	*p*
Age	0.57	0.0000000	0.26	0.005
BMI	0.09	0.28	-0.15	0.87
HR	0.28	0.0006	-0.31	0.001
SBP	0.42	0.000002	0.18	0.05
DBP	0.52	0.000000	0.25	0.007
MAP	0.51	0.000000	0.24	0.01
Triglyceride	0.20	0.19	0.16	0.30
Total Chol	0.47	0.001	0.33	0.03
LDL-Chol	0.44	0.003	0.25	0.11
Calc HDL	0.21	0.17	0.21	0.18

Table 3. Comparison of demographic features in male and female subjects, using the student's unpaired *t*-test.

	Females (n=89)	25th and 75th centile	Males (n=63)	25th and 75th centile	p
age (yrs)	36 ± 12	26 and 44	35 ± 11	27 and 40	0.52
BMI(kg/m2)	25.0 ± 5.2	21.8 and 27.6	25.5 ± 3.9	22.8 and 27.3	0.52
TG	1.2 ± 0.7	0.7 and 1.3	1.3 ± 0.7	0.8 and 1.6	0.46
TC	4.6 ± 1.1	3.7 and 5.2	5.1 ± 1.1	4.3 and 6.1	0.14
HDL	1.5 ± 0.4	1.2 and 1.7	1.3 ± 0.4	1.0 and 1.6	0.20
LDL	2.5 ± 0.8	1.7 and 3.2	3.1 ± 0.9	2.4 and 3.5	0.02
SI (m/s)	8.11 ± 2.21	6.77 and 9.22	8.26 ± 2.13	6.91 and 9.11	0.47
RI (%)	74 ± 11	69 and 81	73 ± 14	66 and 83	0.51
HR (bpm)	73 ± 9	67 and 77	72 ± 12	63 and 81	0.62
SBP	113 ± 12	103 and 120	124 ± 13	116 and 133	0.00001
DBP	70 ± 11	62 and 78	74 ± 9	68 and 81	0.03
MAP	85 ± 11	77 and 93	91 ± 9	84and 97	0.001

Table 4. Comparison of demographic features in subjects of Caucasian and non-Caucasian origin, using the student's unpaired *t*-test.

	Caucasians (n=112)	25th and 75th centiles	Non-Caucasians (n =40)	25th and 75th centiles	p
age (yrs)	37 ± 12	27 and 46	33 ± 10	25 and 36	0.08
BMI(kg/m2)	25.5 ± 4.7	22.3 and 27.8	24.5 ± 4.5	22.1and 27.1	0.24
TG	1.2 ± 0.7	0.7 and 1.3	1.3 ± 0.8	0.7 and 1.6	0.57
TC	4.5 ± 1.0	3.7 and 5.2	5.0 ± 1.2	4.3 and 6.1	0.11
HDL	1.2 ± 0.3	1.0 and 1.3	1.7 ± 0.4	1.4 and 1.9	0.0002
LDL	2.8 ± 0.7	2.2 and 3.2	2.8 ± 1.0	1.7 and 3.5	0.94
SI (m/s)	8.35 ± 2.18	6.93 and 9.37	7.66 ± 2.10	6.49 and 7.84	0.06
RI (%)	73 ± 12	67 and 81	75 ± 13	70 and 84	0.36
HR (bpm)	74 ± 11	68 and 80	68 ± 8	63 and 73	0.002
SBP	120 ± 14	110 and 130	113 ± 11	103 and 120	0.007
DBP	74 ± 10	67 and 81	68 ± 10	61 and 77	0.002
MAP	89 ± 10	83 and 97	83 ± 10	75 and 89	0.002

Table 5. Ranges for SI and RI according to age in the overall population, in Caucasian and non-Caucasian subjects and female and male subjects.

Age (yrs)	Stiffness Index (m/s)					Reflection Index (%)				
	Overall	Caucasian	Non-caucasian	Female	Male	Overall	Caucasian	Non-caucasian	Female	Male
18-34	7.19 ± 1.26	7.31 ± 1.31	6.91 ± 1.10	6.89 ± 1.10	7.55 ± 1.34	71 ± 14	69 ± 14	73 ± 15	72 ± 12	69 ± 16
35-49	8.66 ± 1.63	9.01 ± 1.70	7.93 ± 1.14	8.74 ± 1.48	8.76 ± 1.90	75 ± 8	76 ± 9	76 ± 9	76 ± 8	76 ± 9
50-67	10.50 ± 3.07	10.46 ± 3.01	11.89 ± 3.78	10.58 ± 2.93	10.57 ± 3.65	79 ± 7	79 ± 6	83 ± 10	79 ± 7	82 ± 7

Figure 1. The digital volume pulse waveform.

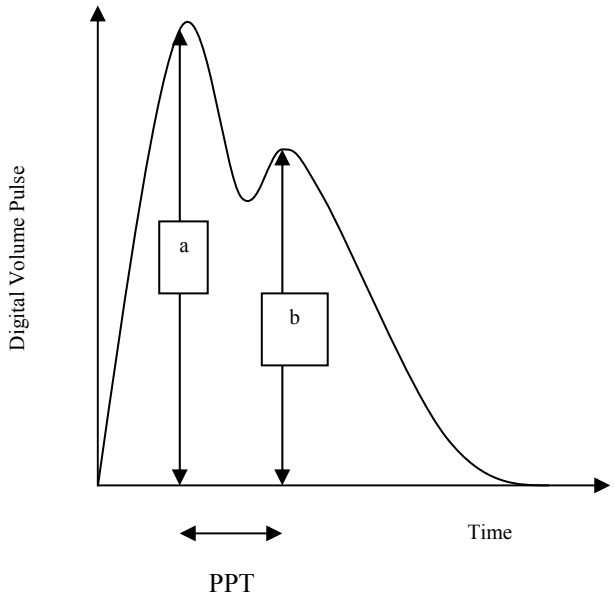
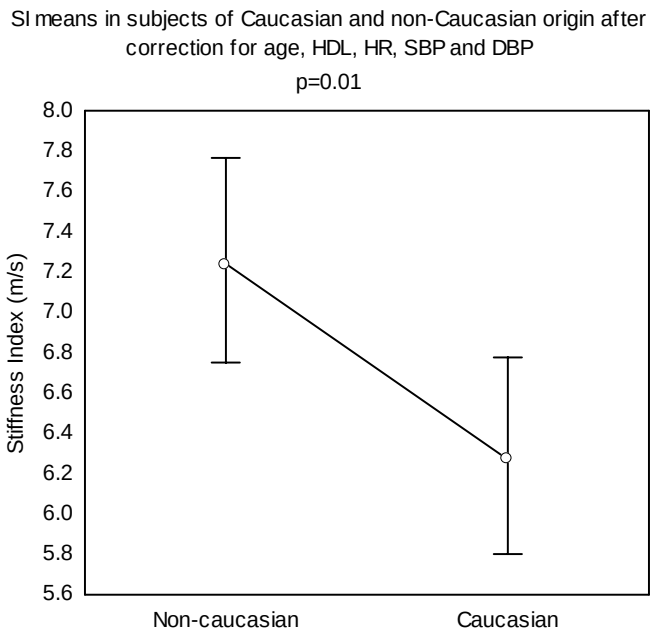
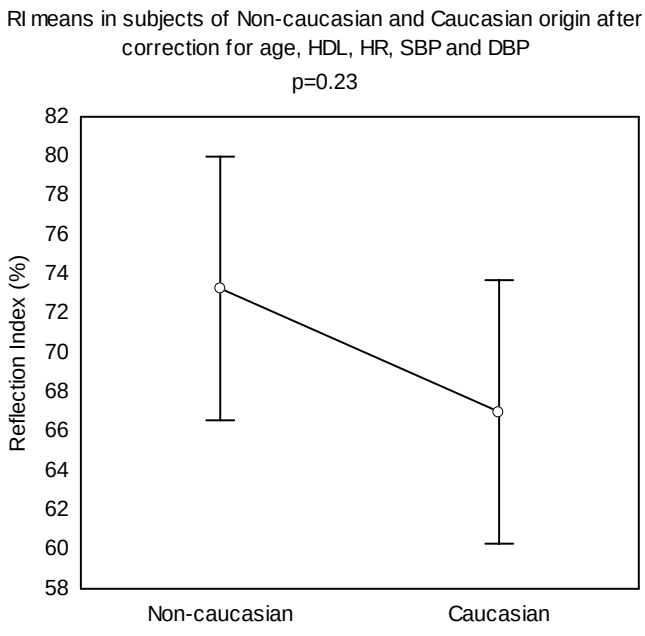


Figure 2. Arterial stiffness means in subjects (n=44) of Caucasian and non-Caucasian origin after correction for differences in age, HDL, HR, SBP and DBP. (A) Stiffness index (SI) means, (B) Reflection index (RI) means, Vertical bars denote 95% confidence interval, ○ corrected average mean for variable.



(A)



(B)