Lippincott Williams & Wilkins
a Wolters Kluwer business

EUROPEAN SOCIETY OF CARDIOLOGY

Original Scientific Paper

Arterial wave reflection is associated with severity of extracoronary atherosclerosis in patients with coronary artery disease

John P. Lekakis, Ignatios Ikonomidis, Athanasios D. Protogerou, Theodoros G. Papaioannou, Kimon Stamatelopoulos, Christos M. Papamichael and Myron E. Mavrikakis

Department of Clinical Therapeutics, Alexandra Hospital, University of Athens, Greece.

Received 22 May 2005 **Accepted** 25 October 2005

Background **Arterial wave reflection is a major determinant of left ventricular function, coronary perfusion and cardiovascular risk. We investigated whether arterial wave reflection may detect atherosclerosis of peripheral arteries in patients with documented coronary artery disease (CAD).**

Methods **Radial artery applanation tonometry and pulse wave analysis was performed in 184 patients with documented CAD at coronary angiography; central blood pressures and augmentation index (AI) were measured. Ankle–brachial (ABI) index and intima–media thickness (IMT) were used as indices of atherosclerosis of the lower limbs and the carotid arteries respectively.**

Results **Patients with abnormal IMT (>0.7 mm, first tertile) or ABI (<0.94, first tertile) had higher AI than patients with lower IMT or higher ABI (24 ± 17 versus 17 ± 16% and 23 ± 18 versus 18 ± 13%, respectively, $P<0.05$). In multivariate analysis, increasing AI was associated with age, female gender, heart rate, mean blood pressure, hyperlipidaemia, and use of statins (regression coefficient (β) = 0.50, β = 0.15, β = −0.60, β = 0.23, β = 0.16 and β = −0.14, respectively, $P<0.05$). Increasing AI was associated with an adjusted-odds ratio of 1.035 [95% confidence interval (CI), 1.005–1.066], $P=0.02$ for an abnormal IMT and of 1.08 (95% CI, 1.024–1.146), $P=0.005$ for ABI after adjustment for age, gender, heart rate, height, blood pressure, atherosclerotic risk factors, obesity and medication. No relation was found between AI and Gensini score or for the number of diseased coronary vessels.**

Conclusion **Augmentation index is a marker of extensive extracoronary atherosclerosis in patients with CAD. *Eur J Cardiovasc Prev Rehabil* 13:236–242 © 2006 The European Society of Cardiology**

European Journal of Cardiovascular Prevention and Rehabilitation 2006, **13**:236–242

Keywords: augmentation index, arterial wave reflection, coronary artery disease, peripheral artery disease, statins

Introduction

Increased arterial wave reflection leads to augmentation of the central arterial pressure and rise of the pulse pressure, affecting the function and structure of the left ventricle, as well as coronary perfusion; many studies have shown the importance of increased pulse pressure and arterial wave reflection as markers of cardiovascular risk in normotensive and hypertensive patients, end-stage renal failure and patients with coronary artery disease [1–5].

Correspondence and requests for reprints to John Lekakis, MD, 12 Iridanou str., 115 28 Athens, Greece.
Tel: +30 210 729 9200; fax: +30 210 729 9201;
e-mail: lekakis@tellas.gr

The association of arterial wave reflection to atherosclerosis has not been fully defined; local arterial stiffness assessed in the aorta has been shown to be abnormal in patients with coronary artery disease [6,7], especially those with multi-vessel disease. On the contrary Megnien *et al.* [8] showed that arterial stiffening assessed by carotid to femoral artery pulse wave velocity could not predict the presence of coronary or extracoronary atherosclerosis in asymptomatic men. Recently, Weber *et al.* [9] have shown that increased values of pulse wave analysis parameters values are associated with increased risk for coronary artery disease (CAD) only in young men with suspected CAD. Additionally lower extremity arterial compliance assessed by air plethysmography has been associated with presence of significant coronary stenoses in a cardiac catheterization laboratory referral population [10]. Pulse wave analysis is a useful, non-invasive method for assessing central blood pressure and augmentation index, a measure of arterial wave reflection [11,12]; pulse wave analysis has been previously used in subjects with cardiovascular risk factors for atherosclerosis [13,14]. Furthermore, pulse wave velocity has been associated with peripheral artery atherosclerosis in elderly subjects [15] or high prevalence of carotid plaques in subjects with atherosclerotic risk factors [16]. However, data about the relation between arterial wave reflection and presence of extracoronary atherosclerosis assessed by ankle–brachial index [17] and carotid intima–media thickness [18] in patients with documented CAD are lacking.

In the present study we examined whether enhanced arterial wave reflection assessed by pulse wave analysis may detect the presence of severe atherosclerosis in peripheral arteries in patients with documented CAD.

Methods

Study population

Two hundred and thirty-five consecutive patients referred for elective coronary angiography for suspected coronary artery disease comprised the study group. Of those 51 were excluded because no significant coronary vessel disease (> 50% stenosis, $n = 51$) was confirmed. Thus, 184 patients with documented CAD were examined. Age was 61.3 ± 10.9 years and 158 participants were men; 113 patients had a history of myocardial infarction with an ejection fraction > 50% at angiography, 11 had a history of transient ischaemic attack, nine a history of stroke and 34 intermittent claudication. Characteristics of the study population are shown in Table 1. All patients gave informed consent before entering the study and the protocol was approved by the Local Ethics Committee.

Coronary angiography

Coronary angiography was performed in all patients using standard Judkins technique via the right femoral artery. The percentage diameter stenosis was evaluated by one observer unaware of the results of vascular studies; disposition between zero, one, two, or three vessel disease group was based on the presence of a 50% or greater diameter narrowing for each of the three main coronary arteries. Gensini score was used for estimation of the extent and severity of coronary atherosclerosis. The ejection fraction was calculated during left ventriculography.

Biochemical studies

In the morning before cardiac catheterization, blood was drawn after 12 hours of fasting for determination of the following parameters using standard biochemical techniques: Cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol (Friedewald formula).

Table 1 Characteristics of the study population

Number of patients (*n*)	184
Age (years)	61.3 ± 10.9
Males (*n*)	158
Cholesterol (mg/dl)	208 ± 54
Triglycerides (mg/dl)	125 ± 69
HDL-cholesterol (mg/dl)	45 ± 16
LDL-cholesterol (mg/dl)	129 ± 41
BMI (kg/m^2)	27.5 ± 3.3
Smoking (*n*)	81
Hypertension (*n*)	74
Diabetes mellitus (*n*)	50
Ejection fraction (%)	65 ± 5
Previous myocardial infarction (*n*)	113
Angina (*n*)	92
Gensini score	38.3 ± 37.4
Common carotid artery IMT (mm)	0.81 ± 0.22
Carotid bifurcation IMT (mm)	1.16 ± 0.41
Ankle–brachial index	1.06 ± 0.17

HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; IMI, intima–media thickness.

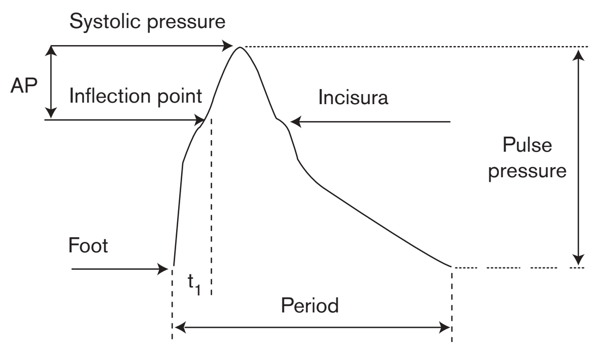
Pulse wave analysis

All participants were examined the day after coronary arteriography, in the morning hours and after a 10-min rest period. Patients did not receive their medications on the day of the examination. Blood pressure (systolic and diastolic) was measured at the brachial artery using an Omron 70SCP device. Arterial pressure waveforms were recorded by applanating the radial artery with a hand-held tonometer; pressure waveforms obtained by this method have been validated before by comparing them with waveforms obtained by high fidelity transducer within the artery [3,11]. The systolic and diastolic blood pressures of the brachial artery were used for the calibration of the radial pulse wave. Central waveforms were then derived from the radial artery waveforms by using a transfer function as previously described [3,12]. The following parameters were measured using the PWV Medical blood pressure analysis system (Sphygmocor; ATCOR Medical, Sydney, Australia): central systolic, diastolic and mean pressure, central pulse pressure, augmentation pressure and augmentation index (Fig. 1).

Measurement of carotid atherosclerosis

B-mode ultrasonographic examination was performed the day after coronary angiography in all patients using the same echo-Doppler ultrasound. Scanning included left and right carotid arteries for the measurement of the intima–media thickness (IMT). The carotid artery image was focused in the far wall and two segments were identified on each side: the distal 1.0 cm of the common carotid proximal to the bifurcation and the carotid bulb, as previously described [18]. The average IMT of all four segments (right common carotid and bulb and left common carotid and bulb) was used in the statistical

Fig. 1



Analysis of aortic pressure waveform. AP is the augmentation of systolic aortic pressure due to early return of reflected waves. Augmentation index (AI) is defined as the ratio of AP to aortic pressure and it characterizes systemic arterial compliance and the pulsatile component of left ventricular afterload.

analysis. All scans were recorded on S-VHS videotape for off-line analysis. An intima–media thickness greater than 2 mm was defined as plaque.

Ankle–brachial index

This index was used as an estimate of the atherosclerotic changes of the lower limbs and it was measured both at left and right as previously described [17]. The average value of the two sides was used in statistical analysis.

Statistical analysis

All data are presented as means ± SD. SPSS (10.0 version; SPSS Inc., Chicago, Illinois, USA) software was used for statistical analysis. Pearson chi-squared and unpaired *t*-test were used to analyse categorical and continuous data respectively. Spearman's correlation coefficient was used to describe the correlation of augmentation index with other parameters. Analysis of variance was used to describe the differences between patients with one, two or three vessel disease.

We prospectively chose to divide IMT, ABI and Gensini score into tertiles (IMT: <0.7 mm [$n=61$], 0.71–0.86 mm [$n=61$] and >0.87 mm [$n=62$]; ABI: <0.93 [$n=62$], 0.94–1.049 [$n=61$], >1.05 [$n=61$]; Gensini score: <17 [$n=62$], 18–33 [$n=61$], >34 [$n=61$]) [10]. Patients were categorized into groups based on the tertiles of the measured IMT, ABI or Gensini score and differences among groups in indices of systemic arterial stiffness were examined by ANOVA. Because the values of augmentation index for the second and third tertile of IMT and of ABI were not statistically different, they were combined for the final comparisons between subgroups and for multivariate logistic regression analysis. The cut off values for IMT (>0.7 mm) and ABI (<0.94) used in our analysis have been reported as the upper normal limits for these markers, by other investigators [17–21].

The relation of AI (dependent variable) with the patients' clinical characteristics (age, gender, heart rate, blood pressure, height, obesity [body mass index (BMI) $>27\,\mathrm{kg/m^2}$], atherosclerotic risk factors and medication) was examined by multiple linear regression analysis using the backward method.

Multivariable logistic regression analysis was performed to examine the association of AI and the odds (95% confidence intervals) of having an abnormal IMT (>0.7 mm), ABI (<0.94) or Gensini score (>17) (dependent variables) in three different models. Each multivariate model was constructed using the following covariates: augmentation index, age, gender, heart rate, mean blood pressure, smoking status, presence of hyperlipidaemia, of diabetes mellitus, history of parental CAD, obesity (BMI $>27\,\mathrm{kg/m^2}$), use of beta-blockers, of calcium blockers, of nitrates, of angiotensin converting enzyme inhibitors, of diuretics, and of statins. A P value <0.05 was considered statistically significant.

Results

Patients' characteristics

Of the 184 patients with suspected CAD, 51 patients had single vessel disease, 53 patients had two-vessel disease, and 80 patients, three-vessel disease. Data from the peripheral and central haemodynamics of the patient population are shown in Table 2.

Relation of augmentation index with patients' characteristics

By linear regression analysis augmentation index (AI) was related significantly to peripheral systolic (regression coefficient [β] = 0.21, $P=0.04$) and mean blood pressure ($\beta=0.23$, $P=0.02$), heart rate ($\beta=-0.60$, $P<0.001$), age ($\beta=0.50$, $P<0.001$), female gender ($\beta=0.15$, $P=0.005$), hyperlipidaemia ($\beta=0.16$, $P=0.003$), use of statins ($\beta=-0.14$, $P=0.008$) and use of nitrates ($\beta=-0.15$, $P=0.007$). Patients older than 57 years had higher AI compared to younger patients (23.1 ± 16.6 versus 17.9 ± 18%, $P=0.035$). Females had higher AI than men (28.9 ± 20.5 versus 20.5 ± 16.5%, $P=0.028$).

Table 2 **Peripheral and central haemodynamics in the study population**

Heart rate (beats per minute)	71.5 ± 13.8
Systolic blood pressure (mmHg)	122.5 ± 17.7
Diastolic blood pressure (mmHg)	73.2 ± 11.7
Central systolic pressure (mmHg)	109 ± 16.6
Central diastolic pressure (mmHg)	73.3 ± 12
Central pulse pressure (mmHg)	35.7 ± 13
Augmentation index (%)	21.3 ± 17.1
Augmentation pressure (mmHg)	7.5 ± 7

Table 3 Three different multivariable logistic regression models assessing the association of augmentation index with either abnormal IMT, ABI, or high Gensini score

	IMT > 0.7 mm		ABI < 0.94		Gensini > 17	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Augmentation index	1.035 (1.005–1.066)	0.02	1.08 (1.024–1.146)	0.005	1.01 (0.97–1.04)	0.52
Mean blood pressure	1.019 (0.984–1.054)	0.28	0.99 (0.95–1.037)	0.73	0.97 (0.97–1.01)	0.15
Age	1.081 (1.039–1.124)	<0.001	1.05 (1.001–1.103)	0.04	1.02 (0.98–1.06)	0.30
Heart rate	1.033 (0.099–1.071)	0.07	1.06 (1.02–1.11)	<0.001	0.98 (0.95–1.02)	0.39
Female gender	0.56 (0.14–2.24)	0.41	1.02 (0.11–9.09)	0.98	0.20 (0.05–0.81)	0.02
Height	1.054 (0.99–1.118)	0.08	1.006 (0.92–1.10)	0.89	1.001 (0.99–1.003)	0.71
Hyperlipidaemia	1.33 (0.55–3.22)	0.52	0.50 (0.15–1.56)	0.23	1.3 (0.50–3.32)	0.58
Smoking	1.59 (0.66–3.82)	0.29	2.85 (1.06–7.64)	0.03	2.16 (1.01–5.00)	0.01
Diabetes	3.9 (1.2–12.3)	<0.001	2.31 (0.61–8.66)	0.21	1.28 (0.46–3.53)	0.63
Parental CAD	1.15 (0.46–2.8)	0.76	1.39 (0.42–4.5)	0.57	1.49 (0.57–3.90)	0.41
Obesity	1.71 (0.67–4.35)	0.25	1.27 (0.32-4.93)	0.72	0.89 (0.33–2.40)	0.82
Use of statins	0.44 (0.207–0.927)	0.03	0.79 (0.22–2.72)	0.70	2.84 (1.06–7.62)	0.03
Use of nitrates	0.65 (0.25–1.67)	0.38	2.22 (0.60–8.46)	0.22	2.18 (1.05–4.55)	0.04
Use of beta-blockers	0.68 (0.27–1.71)	0.41	0.57 (0.14–2.25)	0.42	0.56 (0.22–1.42)	0.23
Use of ACE inhibitors	1.067 (0.48–2.36)	0.83	2.12 (0.76–6.11)	0.14	1.32 (0.57–3.07)	0.51
Use of Ca antagonists	0.40 (0.146–1.11)	0.07	0.72 (0.19–2.75)	0.63	2.98 (0.98–7.78)	0.05
Use of diuretics	0.41 (0.143–1.35)	0.61	0.55 (0.16–1.45)	0.7	0.60 (0.21–1.50)	0.81

OR, odds ratio; CI, confidence interval; IMT, intima–media thickness; ABI, ankle–brachial index; CAD, coronary artery disease; Obesity, a body mass index > 27 kg/m^2. The cut-offs for IMT > 0.7 mm, ABI < 0.94 and Gensini score > 17 correspond to the first tertile of IMT, ABI and Gensini score.

Table 4 Comparison of patients on statins to those without statin therapy

Variable	Statins + *n* = 79	Statins – *n* = 105	*P*-value
Heart rate (beats/min)	71.9 ± 13.5	70.8 ± 13.9	ns
Age (years)	61.6 ± 10.6	61.5 ± 10.9	ns
Cholesterol (mg/dl)	212 ± 59	205 ± 49	ns
LDL-cholesterol (mg/dl)	128 ± 44	129 ± 37	ns
Triglycerides (mg/dl)	132 ± 76	119 ± 65	ns
HDL-cholesterol (mg/dl)	45.8 ± 18	46.1 ± 14.9	ns
BMI (kg/m^2)	28 ± 3.1	27.2 ± 3.5	ns
Hypertension (n)	55	64	ns
Previous myocardial infarction (n)	59	48	$P = 0.003$
Gensini score	50.2 ± 41.3	28.5 ± 31.2	$P < 0.001$
Systolic blood pressure (mmHg)	116 ± 17.5	127 ± 17.9	$P < 0.001$
Diastolic blood pressure (mmHg)	71.2 ± 10.8	73.6 ± 12.9	ns
Mean blood pressure (mmHg)	85.2 ± 11.7	90.4 ± 13.5	$P = 0.003$
Augmentation pressure (mmHg)	6.4 ± 6.2	8.7 ± 7.6	$P = 0.019$
Augmentation index (%)	19.1 ± 15.2	24 ± 18.5	$P = 0.038$
Central systolic pressure (mmHg)	104 ± 15	113 ± 16	$P = 0.001$
Central diastolic pressure (mmHg)	71.9 ± 10.8	74.4 ± 13	ns
Central mean pressure (mmHg)	85 ± 11.7	90 ± 13.5	$P = 0.003$
Central pulse pressure (mmHg)	32.1 ± 11.4	39.3 ± 13.4	$P < 0.001$

Arterial wave reflection and atherosclerosis of the peripheral arteries

Patients with IMT > 0.7 mm (first tertile) had higher AI compared to patients with IMT < 0.7 mm (24 ± 17 versus 17 ± 16%, $P = 0.03$). Additionally, patients with ABI < 0.94 (first tertile) had higher AI compared to patients with ABI > 0.94 (23 ± 18 versus 18 ± 13%, $P < 0.05$). There was no difference in AI values between patients categorized according to the tertiles of Gensini score (ns).

By logistic regression analysis, a 10% increase in AI was associated with 3.5% increase in the odds of having an abnormal IMT [adjusted-odds ratio 1.035; 95% confidence interval (CI), 1.005–1.066; $P = 0.021$] or with a 8% increase in the odds of having an abnormal ABI (adjusted-odds ratio 1.08; 95% CI, 1.024–1.146, $P = 0.005$) among age, gender, heart rate, height, mean blood pressure, traditional atherosclerotic risk factors, obesity and medication (Table 3).

The cut off values for IMT (> 0.7 mm) and ABI (< 0.94) used in our analysis have been reported as the upper normal limits for these markers, by other investigators [17–21].

No relation was found between the Gensini score and AI (Table 3). Augmentation index did not differ in patients with one, two or three coronary vessels diseased or in patients with single versus those with multi-vessel disease (NS). Conversely, patients with multi-vessel disease compared to those with single vessel disease had lower peripheral diastolic (77 ± 10 versus 72 ± 12 mmHg, $P < 0.05$) and mean blood pressure

(92 ± 10 versus 87 ± 12 mmHg, $P < 0.05$) and were receiving a higher percentage of more than two vaso-active drugs [110/133 (82%) versus 31/51 (61%), $P < 0.05$] and statins [77/133 (58%) versus 16/51 (32%), $P < 0.05$].

Arterial wave reflection and medication

By regression analysis, treatment with statins or nitrates was independently associated with lower augmentation index values ($\beta = -0.14$, $P = 0.008$ and $\beta = -0.15$, $P = 0.007$ respectively). Patients on statins ($n = 79$) or nitrates ($n = 63$) compared to those without did not differ regarding heart rate, age, carotid intima–media thickness, ankle-brachial index, BMI, cholesterol, triglycerides, LDL and HDL cholesterol (Table 4). Peripheral systolic (116 ± 17.5 versus 127 ± 17.9 mmHg, $P < 0.001$) and mean pressure (85.2 ± 11.7 versus 90.4 ± 13.3 mmHg, $P < 0.05$) were lower in the group receiving statins. Conversely, patients on nitrates ($n = 63$) compared to those without did not differ in peripheral blood pressure (ns).

However, a greater number of patients on statins were receiving angiotensin-converting enzyme (ACE) inhibitors [41/79 (52%) versus 37/105 (35%), $P < 0.05$], beta-blockers [58/79 (74%) versus 58/105 (55%), $P < 0.05$] and nitrates [55/79 (69%) versus 58/105 (55%), $P < 0.05$] compared to the group not receiving statins. Additionally, a greater number of patients on nitrates were receiving β-blockers [49/63 (77%) versus 52/121 (43%), $P < 0.05$] and ACE inhibitors [32/63 (51%) versus 40/121 (33%), $P < 0.05$] compared to the group not receiving nitrates.

Discussion

In the present study we demonstrate that enhanced arterial wave reflection as measured by augmentation of the central aortic pressure is associated with the severity of extracoronary atherosclerosis in the carotid arteries and arteries of the lower extremities in patients with documented CAD. These findings suggest that atheromatous changes of the peripheral arterial tree may influence arterial wave reflection and thus, the systemic arterial stiffness.

Arterial wave reflection and atherosclerosis

Pulse wave analysis is a reproducible non-invasive method for assessing augmentation index, a measure of the contribution made by the reflected pressure waves to the ascending aortic pressure waveform, providing an estimate of systemic arterial stiffness [11,12]. In the present study, severe atherosclerosis of the peripheral arteries assessed by increased carotid intima–media thickness (> 0.7 mm, first tertile) and low ankle–brachial index (< 0.94, first tertile) was associated with increased augmentation index suggesting a link between severe peripheral artery atherosclerosis and enhanced arterial wave reflection.

The relation of arterial wave reflection to atherosclerosis is not clear. Results from the ARIC study suggest that higher intima–media thickness of the common carotid artery in middle-aged populations is not related to worse stiffness, except for the thickest 10% of the arteries [21]. In our study we have shown for the first time that atherosclerosis of the carotid and lower limb arteries is associated with increased arterial wave reflection as measured by augmentation index in patients with CAD. Furthermore, we demonstrated that a 10% increase of augmentation index was associated with an 8% increase in the odds of having atherosclerosis in the peripheral arteries. Thus, augmentation index may be used as marker of the atherosclerotic process in the peripheral vessels of patients with CAD. Data from monkeys [22] also indicate that pulse wave velocity measurements can be used to predict the severity of diffuse asymptomatic atherosclerosis.

The Rotterdam study [15] demonstrated a significant association of the carotid to femoral artery pulse wave velocity with atherosclerosis of the carotid and peripheral arteries in elderly subjects aged over 60 years. In our study, we extend these findings by showing that the association between arterial wave reflection and extracoronary atherosclerosis is independent of age, gender and traditional atherosclerotic risk factors in patients with CAD.

As reported in our previous studies [17,18], IMT and ABI were associated with the number of diseased coronary arteries or Gensini angiographic score independently of age, gender, medication and atherosclerotic risk factors. Studies have also shown that augmentation index assessed invasively in the aorta [3] or non-invasively in the carotid arteries [4] was associated with the risk for cardiovascular disease. Recently, Weber *et al.* [9] have shown that increased augmentation index is associated with presence of CAD in patients under the age of 60 years. In the present study, patients with multi-vessel CAD had similar indices of arterial wave reflection compared to those with single vessel disease. Additionally, there was no relation between Gensini score derived from angiography and parameters of pulse wave analysis. McLeod *et al.* have also reported the lack of a significant correlation between augmentation index and extent of coronary atherosclerosis assessed by intravascular ultrasound [23]. However, a number of factors may influence augmentation index independently of changes in arterial stiffness, namely age, female gender, heart rate and blood pressure [4] which were also confirmed in the present study. In our study, patients with multi-vessel CAD on coronary angiography had a lower peripheral blood pressure than patients with single vessel CAD likely because they were receiving more vaso-active medications and statins [24]. Thus, it is possible that treatment with vaso-active medication and statins has reduced blood pressure and thus, eliminated differences in pulse wave analysis parameters between patients with single versus those with multi-vessel CAD. Alternatively, it may be possible that coronary angiography may have underestimated the amount of coronary atherosclerosis, which would have been more accurately determined by other techniques such as intravascular ultrasound.

Hyperlipedaemia, statins and arterial wave reflection

The relation of blood lipids to arterial wave reflection is of interest; Wilkinson *et al.* [14] using pulse wave analysis, showed increased systemic arterial stiffness and central pulse pressure in asymptomatic subjects with hypercholesterolemia despite similar peripheral blood pressure. Other studies in patients with or without familial hypercholesterolemia have reached rather conflicting results [25–27].

In our study, increased augmentation index, a measure of enhanced wave reflection reflecting the overall arterial stiffness was independently related to presence of hyperlipidaemia or no use of statin treatment. In agreement with our findings, Muramatsu *et al.* [28] have shown that pravastatin administered to hypercholesterolaemic patients for 6 months caused a significant lowering of pulse wave velocity and reduction of peripheral resistance in patients achieving a greater than 15% fall in cholesterol levels; this improvement appears to be related to improvement in peripheral haemodynamics and not to changes in the elasticity of the aorta. In our study, the use of statins was associated with better augmentation index in addition to lower central arterial blood pressure. Thus, our results suggest that the beneficial effects of statins on aortic pressure waveform may be linked to the reduction of blood pressure. Other investigators have also reported that statins had a direct hypotensive effect [24] and reduced large artery stiffness in addition to blood pressure in normocholesterolaemic patients with stage I isolated systolic hypertension [29]. As arterial stiffness is dependent on arterial pressure, any reduction in pressure by statins leads to passive decrease in arterial stiffness and therefore it may partly account for the changes in arterial wave reflection observed in our study.

Alternatively, the simultaneous use of vaso-active medication by a larger number of patients on statins compared to those not receiving lipid-lowering treatment may have improved blood pressure leading to the reduction of augmentation index.

Conclusion

In summary, augmentation index, a pulse wave analysis parameter is related to extracoronary atherosclerosis in patients with CAD independently of atherosclerotic risk factors and medication.

References

1 Benetos A, Rudnichi A, Safar M, Guize L. Pulse pressure and cardiovascular mortality in normotensive and hypertensive patients. *Hypertension* 1998; **32**:560–564.

2 Franklin S, Khan S, Wong N, Larson M, Levy D. Is pulse pressure useful in predicting risk for coronary artery disease? The Framingham Heart Study. *Circulation* 1999; **100**:354–360.

3 Hayasshi T, Nakayama Y, Tsumura K, Yoshimaru K, Ueda H. Reflection in the arterial system and the risk of coronary heart disease. *Am J Hypertens* 2002; **15**:405–409.

4 Nurnberger J, Keflioglou-Scheiber A, Opazo Saez AM, Wenzel RR, Philipp T, Schafers RF. Augmentation index is associated with cardiovascular risk. *J Hypertens* 2002; **20**:2407–2414.

5 Blacher J, Demuth K, Guerin A, Safar M, Moatti N, London G. Influence of biochemical alterations in patients with end-stage renal failure. *Arterioscler Thromb Vasc Biol* 1998; **18**:535–541.

6 Stefanadis C, Wooley C, Bush C, Kolibash A, Boudoulas H. Aortic distensibility abnormalities in coronary artery disease. *Am J Cardiol* 1987; **59**:1300–1304.

7 Gatzka C, Cameron J, Kingwell B, Dart A. Relation between coronary artery disease, aortic stiffness and left ventricular structure in a population sample. *Hypertension* 1998; **32**:575–578.

8 Megnien JL, Simon A, Denarie N, Del-Pino M, Gariepy J, Segond P, Levenson J. Aortic stiffness does not predict coronary and extracoronary atherosclerosis in asymptomatic men at risk for cardiovascular disease. *Am J Hypertens* 1998; **11**:293–301.

9 Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, Eber B. Arterial stiffness, wave reflections and the risk of coronary artery disease. *Circulation* 2004; **109**:184–189.

10 Kobayashi K, Akishita M, Yu W, Hashimoto M, Ohni M, Toba K. Interrelationship between non-invasive measurements of atherosclerosis: Flow mediated dilation of brachial artery, carotid intima media thickness, pulse wave velocity. *Atherosclerosis* 2004; **173**:13–18.

11 O'Rourke MF, Kelly RP. Wave reflection in the systemic circulation and its implications in ventricular function. *J Hypertens* 1993; **11**: 327–337.

12 Chen C, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, Kass DA. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation* 1997; **95**:1827–1836.

13 Brooks B, Molyneaux L, Yue D. Augmentation of central arterial pressure in type 1 diabetes. *Diabetes Care* 1999; **22**:1722–1727.

14 Wilkinson I, Prasad K, Hall I, Thomas A, MacCallum H, Webb DJ, *et al.* Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. *J Am Coll Cardiol* 2002; **39**:1005–1011.

15 van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, *et al.* Association between arterial stiffness and atherosclerosis The Rotterdam Study. *Stroke* 2001; **32**:454–460.

16 Herrington DM, Kesler K, Reiber JC, Davis W, Brown WV, Helms R, *et al.* Arterial compliance adds to conventional risk factors for prediction of angiographic coronary artery disease. *Am Heart J* 2003; **146**:662–667.

17 Papamichael C, Lekakis J, Stamatelopoulos K, Papaioannou TG, Alexizaki MK, Cimponeriu AT, *et al.* Ankle-brachial index as a predictor of the extent of coronary atherosclerosis and cardiovascular events in patients with coronary artery disease. *Am J Cardiol* 2000; **86**:615–618.

18 Lekakis J, Papamichael C, Cimponeriu A, Stamatelopoulos KS, Papaioannou TG, Kanakakis J, *et al.* Atherosclerotic changes of extracoronary arteries are associated with the extent of coronary atherosclerosis. *Am J Cardiol* 2000; **85**:949–952.

19 Bots ML, Dijk JM, Oren A, Grobbee DE. Carotid intima–media thickness, arterial stiffness and risk of cardiovascular disease: current evidence. *J Hypertens* 2002; **20**:2317–2232.

20 Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease The San Luis Valley Diabetes Study. *Circulation* 1995; **91**:1472–1479.

21 Riley W, Evans G, Sharrett A, Burke G, Barnes R. Variation of common carotid artery elasticity with intimal-medial thickness: the ARIC study. Atherosclerosis Risk in Communities. *Ultrasound Med Biol* 1997; **23**:157–164.

22 Farrar D, Bond G, Riley W, Sawyer J. Anatomic correlates of aortic pulse wave velocity and carotid artery elasticity during atherosclerosis progression and regression in monkeys. *Circulation* 1991; **83**:1754–1763.

23 McLeod A, Uren N, Wilkinson I, Webb DJ, Maxwell SR, Northridge DB, Newby DE. Non-invasive measures of pulse wave velocity correlate with coronary arterial plaque load in human. *J Hypertens* 2004; **22**:363–368.

24 Sposito A, Mansur A, Coelho O, Nicolau J, Ramires J. Additional reduction in blood pressure after cholesterol–lowering treatment by statins (lovastatin or pravastatin) in hypercholesterolemia patients using angiotensin-converting enzyme inhibitors (enalapril or lisinopril). *Am J Cardiol* 1999; **83**:1497–1499.

25 Kool M, Lustermans F, Kragten H. Does lowering of cholesterol levels influence functional properties of large arteries? *Eur J Clin Pharmacol* 1995; **48**:217–223.

26 Lehman E, Watts G, Fatemi-Langroudi B, Gosling R. Aortic compliance in young patients with heterozygous hypercholesterolemia. *Clin Sci* 1992; **83**:717–721.

27 Cameron J, Jennings G, Dart A. The relationship between arterial compliance, age, blood pressure and serum lipid levels. *J Hypertens* 1995; **13**:1718–1723.

28 Muramatsu J, Kobayashi A, Hasegawa N, Yokouchi S. Hemodynamic changes associated with reduction in total cholesterol by treatment with HMG-CoA reductase inhibitor pravastatin. *Atherosclerosis* 1997; **130**:179–182.

29 Ferrier K, Muhlmann M, Baguet JP, Cameron JD, Jennings GL, Dart AM, Kingwell BA. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. *J Am Coll Cardiol* 2002; **39**:1020–1025.