Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 39, No. 6, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)01723-0

Increased Central Pulse Pressure and Augmentation Index in Subjects With Hypercholesterolemia

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OBJECTIVES The goal of this study was to investigate the relation between serum cholesterol, arterial stiffness and central blood pressure.

BACKGROUND Arterial stiffness and pulse pressure are important determinants of cardiovascular risk. However, the effect of hypercholesterolemia on arterial stiffness is controversial, and central pulse pressure has not been previously investigated.

METHODS Pressure waveforms were recorded from the radial artery in 68 subjects with hypercholesterolemia and 68 controls, and corresponding central waveforms were generated using pulse wave analysis. Central pressure, augmentation index (AIx) (a measure of systemic stiffness) and aortic pulse wave velocity were determined.

RESULTS There was no significant difference in peripheral blood pressure between the two groups, but central pulse pressure was significantly higher in the group with hypercholesterolemia (37 ± 11 mm Hg vs. 33 ± 10 mm Hg [means ± SD]; $p = 0.028$). Augmentation index was also significantly higher in the patients with hypercholesterolemia group (24.8 ± 11.3% vs. 15.6 ± 12.1%; $p < 0.001$), as was the estimated aortic pulse wave velocity. In a multiple regression model, age, short stature, peripheral mean arterial pressure, smoking and low-density lipoprotein cholesterol correlated positively with AIx, and there was an inverse correlation with heart rate and male gender.

CONCLUSIONS Patients with hypercholesterolemia have a higher central pulse pressure and stiffer blood vessels than matched controls, despite similar peripheral blood pressures. These hemodynamic changes may contribute to the increased risk of cardiovascular disease associated with hypercholesterolemia, and assessment may improve risk stratification. (J Am Coll Cardiol 2002;39:1005–11) © 2002 by the American College of Cardiology Foundation

Arterial stiffening is an inevitable part of the aging process in nearly all societies (1,2), and it is associated with a rise in pulse pressure (3). The importance of pulse pressure as a predictor of cardiovascular mortality has been demonstrated by several recent population-based and interventional studies (4–7) and has focused attention on arterial stiffness as a key determinant of cardiovascular risk. "Premature arterial stiffening" occurs in association with several important cardiovascular risk factors including hypertension, diabetes mellitus and cigarette smoking (8), which are also associated with endothelial dysfunction (9). Whether arterial stiffening represents a marker of occult atheroma, or endothelial dysfunction, or is more directly involved in the process of atherosclerosis remains unclear (10).

Hypercholesterolemia is a major risk factor for cardiovascular disease, and it is also associated with endothelial dysfunction (11). However, there are conflicting data concerning the relationship between hypercholesterolemia and *local* arterial stiffness (12). Moreover, the effect of hypercholesterolemia on *systemic* arterial stiffness has only been investigated in one previous study (13), and central blood pressures were not assessed. We hypothesized that hypercholesterolemia would be associated with increased *systemic* arterial stiffness and central pulse pressure, and the aim of this study was to test this hypothesis in a group of otherwise healthy individuals with hypercholesterolemia and matched controls using the technique of pulse wave analysis (PWA). We have previously demonstrated that PWA is a reproducible, noninvasive method for assessing central blood pressure and augmentation index (AIx) (14)—a measure of the contribution that wave reflection makes to the arterial pressure waveform. The amplitude and timing of the reflected wave ultimately depend on the stiffness of the small (preresistance) vessels and large arteries and thus, AIx provides a measure of *systemic* arterial stiffness.

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Manuscript received January 13, 2000; revised manuscript received December 7, 2001, accepted December 21, 2001.

Abbreviations and Acronyms

AIx = augmentation index
DPTI = diastolic pressure time integral
FH = familial hypercholesterolemia
HDL = high-density lipoprotein
LDL = low-density lipoprotein
PMAP = peripheral mean arterial pressure
PWA = pulse wave analysis
TTI = tension time index

METHODS

Sixty-eight patients with hypercholesterolemia, defined as a total serum cholesterol ≥6.5 mmol/l, were recruited from the cardiovascular risk clinics at the Western General Hospital in Edinburgh and the University Hospital of Wales in Cardiff and from general practices local to both hospitals. Concurrently, normocholesterolemic controls (total serum cholesterol < 6.5 mmol/l) were recruited from the same sources and community databases of volunteers held at both hospitals and selected such that, as a group, their distribution of age, gender and weight closely matched the patient group. Approval for the study was obtained from the respective Local Research Ethics Committees, and informed consent was obtained from each participant. Patients with elevated blood pressure (brachial artery blood pressure >160/100 mm Hg), treated hypertension, diabetes mellitus (British Diabetic Association criteria) or a clinical history of cardiovascular disease were excluded, as were subjects receiving any medication. Cigarette smokers were allowed to participate, having abstained for at least 4 h.

Blood pressure measurement. Systolic and diastolic blood pressure were recorded in duplicate in the dominant arm using a validated oscillometric technique (HEM-705CP, Omron Corporation, Tokyo, Japan) (15). Peripheral mean arterial pressure (PMAP) was calculated by integration of the pressure waveform using the sphygmoCor version 6.1 software (AtCor Medical, Sydney, Australia).

Measurement of arterial stiffness and central blood pressure. Pulse wave analysis was used to determine systemic arterial stiffness (sphygmoCor version 6.1 software) as previously described (14). A high-fidelity micromanometer (SPC-301, Millar Instruments, Houston, Texas) was used to obtain accurate recordings of the peripheral pressure waveforms by flattening, but not occluding, the radial artery of the dominant arm using gentle pressure (16). Data were collected directly into a microcomputer and, after 20 sequential waveforms had been acquired, an averaged peripheral waveform was generated. A corresponding averaged central pressure waveform was then generated using a validated transfer function (17–20), and, from this, augmentation, AIx, ascending aortic pressure and heart rate were then determined using the integral software.

Augmentation represents the difference between the second and first systolic peaks of the central pressure waveform, and AIx is defined as augmentation expressed as a percentage of the pulse pressure (Fig. 1) and is a measure of *systemic* arterial stiffness. The tension time index (TTI), the area under the systolic portion of the pressure waveform per minute (the systolic pressure-time integral), an index of systolic stress and the diastolic pressure-time integral (DPTI) were also determined (21,22). The aortic pulse wave velocity was estimated by calculating the time between the foot of the pressure wave and the inflection point, which provides a measure of the timing of the reflected wave, as described previously (23,24).

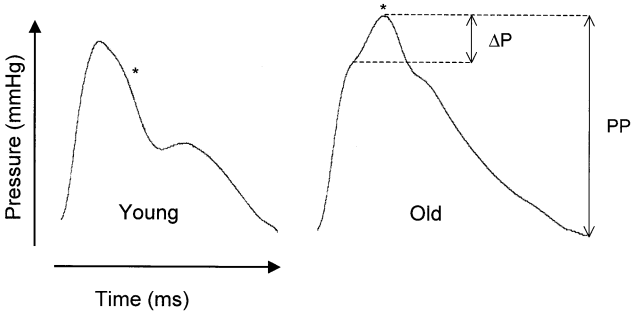

Figure 1. Representative ascending aortic waveforms from a young and older subject (Murgo type "C" and "A" waves, respectively); note the prominence of the second systolic peak (*) in the older individual. Augmentation index is defined as the difference between the second and first systolic peaks (ΔP) expressed as a percentage of the pulse pressure (PP).

Study protocol. After 5 min seated rest in a quiet room, blood pressure was measured. Augmentation, AIx and central arterial pressure were then determined using PWA. All measurements were made in duplicate and mean values used for analysis. Venous blood was then drawn from the antecubital fossa for measurement of plasma glucose, total serum cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol and triglycerides. Finally, height and weight were recorded and body mass index calculated.

Data analysis. Data were analyzed using unpaired, two-tailed Student *t* tests and multiple regression analysis (SPSS software package, version 10, SPSS Inc., Chicago, Illinois). Unless stated otherwise, all results are presented as means ± SD. Significance was defined as $p < 0.05$.

RESULTS

Sixty-eight subjects with hypercholesterolemia, aged 51 ± 10 years (range: men 29 to 77 years, women 39 to 73 years), and 68 control subjects, aged 51 ± 10 years (range: men 25 to 75 years, women 32 to 74 years), were entered into the study. There was no significant difference in age, gender, height, weight or the number of smokers between the two groups, but serum LDL cholesterol and triglycerides were significantly higher in the hypercholesterolemic group (Table 1).

A summary of the peripheral and central hemodynamics is presented in Table 2 and Figure 2. Peripheral blood pressure did not differ between the groups, although the

Table 1. Subject Characteristics

	Number (n)	Men (n)	Age (yrs)	Height (m)	Weight (kg)	Smokers (n)	Cholesterol			TG (mmol/l)	Glucose (mmol/l)
							Total (mmol/l)	LDL (mmol/l)	HDL (mmol/l)		
Hypercholesterolemics	68	25	51 ± 10	1.70 ± 0.08	77.5 ± 14.4	24	7.1 ± 0.5	4.7 ± 0.7†	1.3 ± 0.4	2.2 ± 1.4*	5.1 ± 1.0
Controls	68	25	51 ± 10	1.73 ± 0.10	78.8 ± 13.0	21	5.0 ± 0.7	2.8 ± 0.7	1.4 ± 0.5	1.6 ± 0.8	5.2 ± 0.7

All values are expressed as means ± SD. There were no significant differences between the groups for any parameter, unless stated. *$p < 0.05$; †$p < 0.001$ (unpaired Student *t* test).

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.

control group had a higher resting heart rate. Augmentation, AIx and central pulse pressure were significantly higher in the subjects with hypercholesterolemia compared with controls, and there was a trend towards a higher central systolic pressure in the hypercholesterolemic group. The difference in AIx between the two groups persisted after correction for height and heart rate (18.4 ± 7.6 vs. 23.1 ± 6.1, $p = 0.004$). The TTI (2,296 ± 380 vs. 2,320 ± 438, $p = 0.7$) and DPTI (3,743 ± 559 vs. 3,613 ± 455, $p = 0.2$) were similar in both groups. There were fewer Murgo type "A" waves (23) in the control subjects compared with the subjects with hypercholesterolemia (40 vs. 57) and more type "B" (20 vs. 10) and "C" (8 vs. 1) waves ($p = 0.003$ for trend; chi-square).

Data from all 136 subjects were used to construct two multiple regression models with AIx and estimated aortic pulse wave velocity as the dependent variables. Age, gender, height, heart rate, PMAP, smoking history, LDL cholesterol, HDL cholesterol and triglycerides were entered into the models as known or likely determinants of arterial stiffness. Age, short stature, PMAP, smoking and LDL cholesterol, but not HDL cholesterol or triglycerides, correlated positively with AIx, and there was an inverse correlation with heart rate and male gender (Table 3). The model explained ~62% of the variability in AIx observed in the study ($p < 0.001$). Substituting augmentation for the dependent variable did not make a significant difference to the correlations in the regression model, neither did the addition of plasma glucose or changing the method of analysis to stepwise regression. Estimated aortic pulse wave velocity correlated positively with LDL cholesterol and smoking and inversely with male gender and height (Table 4).

DISCUSSION

A number of studies have investigated the relationship between hypercholesterolemia and arterial stiffness. In animals, hypercholesterolemia, induced by a cholesterol-rich diet, results in an initial reduction in arterial stiffness, followed by a progressive increase over time (25,26), which can be reversed by lowering serum cholesterol (26,27). In humans, a variety of techniques have been used to assess vascular stiffness in vivo, with conflicting results. Lehmann et al. (28) demonstrated increased distensibility, as determined by aortic pulse wave velocity, in a group of young patients with heterozygous familial hypercholesterolemia (FH) but, in contrast, reported reduced aortic distensibility in adults with FH (12). Others have also observed reduced radial artery compliance in adults with FH compared with controls (29). However, Toikka et al. (30) reported no difference in aortic or carotid compliance between asymptomatic adults with FH and controls.

In subjects without FH, most (30–33), but not all (13), studies have reported an inverse relationship between either LDL cholesterol or total cholesterol and aortic compliance. Differences in the vessels studied, patient selection and small sample sizes are likely to account for these discrepant findings. Indeed, Kool et al. (34) reported reduced arterial distensibility in some, but not all, arteries in individuals with hypercholesterolemia. However, all of these studies, with one exception (13), have focused on the stiffness of easily accessible arterial beds or even one small segment of an artery, and not on *systemic* arterial stiffness, which has a major influence on the interaction between the arterial tree and the left ventricle (35). Indeed, the shape of the central pressure waveform partly determines left ventricular workload (35). Therefore, assessing systemic stiffness may be of more clinical importance than measuring compliance within an isolated vascular bed. Moreover, the effect of hypercholesterolemia on central blood pressure has not been previously investigated.

In this study we recorded peripheral pressure waveforms using applanation tonometry and generated corresponding

Table 2. Hemodynamics

	HR (min^{-1})	PSBP (mm Hg)	PDBP (mm Hg)	PPP (mm Hg)	AIx (%)	Aug (mm Hg)	T_R (ms)	CSBP (mm Hg)	CDBP (mm Hg)	CPP (mm Hg)	PPP:CPP (Ratio)
HC	70 ± 9	132 ± 15	84 ± 11	49 ± 12	24.8 ± 11.3	9.9 ± 5.9	140 ± 13	122 ± 17	85 ± 12	37 ± 11	1.34 ± 0.25
Controls	74 ± 12	131 ± 15	84 ± 11	47 ± 13	15.6 ± 12.1	5.8 ± 5.3	145 ± 11	118 ± 17	85 ± 11	33 ± 10	1.45 ± 0.24
Significance (p Value)	0.026	0.6	1.0	0.5	< 0.001	< 0.001	0.013	0.1	0.9	0.028	0.012

All values are expressed as means ± SD.

AIx = augmentation index; Aug = systolic augmentation; CDBP = central diastolic blood pressure; CPP = central pulse pressure; CSBP = central systolic blood pressure; HC = hypercholesterolemics; HR = heart rate; PDBP = peripheral diastolic blood pressure; PPP = peripheral pulse pressure; PSBP = peripheral systolic blood pressure.

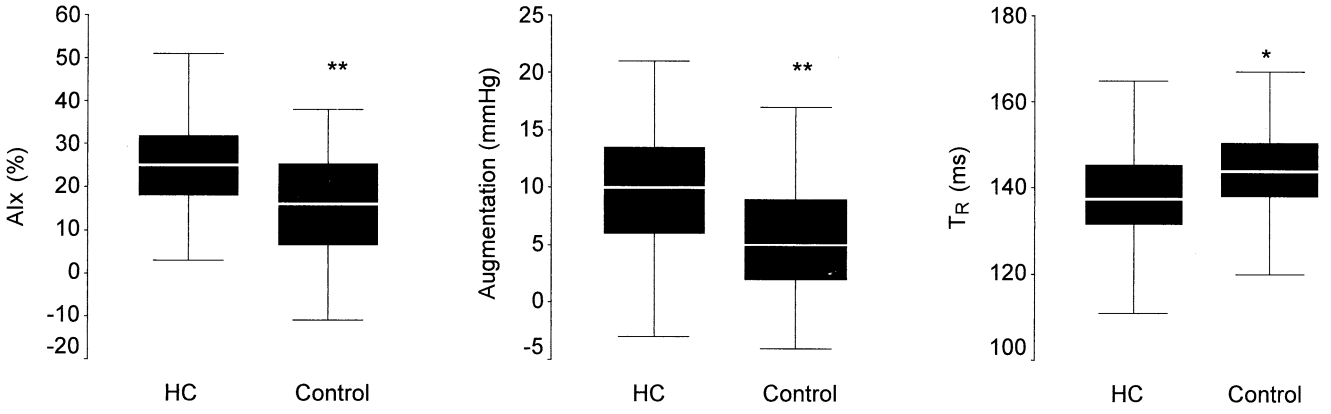

Figure 2. Box and whisker plots for augmentation index (AIx), augmentation and estimated aortic pulse wave velocity (T_R) for the hypercholesterolemia (HC) and control subjects. **Solid horizontal lines** = median values; **error bars** = 95% confidence intervals; **shaded area** = interquartile range. n = 163; *p = 0.01; **p < 0.001.

central arterial pressure waveforms using PWA. The main novel findings were an increased AIx and central pulse pressure in individuals with hypercholesterolemia compared with matched normocholesterolemic controls (Fig. 2). The AIx is a measure of the contribution made by the reflected pressure wave to the ascending aortic pressure waveform (36) and, thus, provides a measure of *systemic* arterial stiffness (37). Therefore, the present data demonstrate that hypercholesterolemia is associated with increased *systemic* arterial stiffness; this conclusion is supported by the higher frequency of Murgo type "A" waves among the subjects with hypercholesterolemia. Importantly, aortic pulse wave velocity, estimated from the timing of the reflected wave, was also increased in the subjects with hypercholesterolemia, indicating increased *aortic* stiffness and that the observed changes in AIx were not solely due to differences in wave reflection.

A number of factors, including gender, heart rate and height are known to influence AIx, independently of changes in stiffness (22,38). However, none of these variables, other than heart rate, differed significantly between the two groups. Moreover, after correction for heart rate and height, AIx remained significantly higher in the hypercholesterolemic group. Furthermore, in the multiple regression model, which included known confounding variables, LDL, but not HDL, cholesterol was a significant independent determinant of AIx (Table 3). The model accounted for ~65% of the observed variability of AIx, which compares favorably with other published multiple regression models (22,32). In addition, we also confirmed the positive relation of age, female gender, short stature, PMAP and low heart rate with AIx (22) and here, for the first time, demonstrated that chronic smoking is associated with an increased AIx (Table 3). We and others have previously demonstrated that individuals with diabetes mellitus (39) and insulin resistance (40) have a higher AIx than matched controls and that insulin per se can influence arterial stiffness (41). However, there was no relation between AIx and serum glucose in this present study. The most likely explanation for this is that we actively excluded patients with diabetes mellitus and, therefore, only studied individuals within a rather narrow range of serum glucose concentrations.

The multiple regression model investigating the determinants of estimated aortic pulse wave velocity confirmed that

Table 3. Results of the Multiple Regression Analysis With Augmentation Index as the Dependent Variable

Parameters	Units	Regression Coefficient	SE	Beta	Significance
Gender	male	−8.98	2.13	−0.34	<0.001
Age	years	0.45	0.08	0.38	<0.001
Heart rate	min^{-1}	−0.40	0.07	−0.33	<0.001
PMAP	mm Hg	0.198	0.061	0.20	0.001
LDL cholesterol	mmol/l	2.18	0.71	0.20	0.003
Height	m	−20.89	10.67	−0.16	0.043
Smoker		4.076	1.536	0.15	0.009
HDL cholesterol	mmol/l	3.41	2.03	0.12	0.1
Triglycerides	mmol/l	1.34	0.78	0.12	0.1

Multiple regression analysis using all 136 subjects. R^2 value for the entire study group = 0.651, $p < 0.001$.

The regression coefficient provides the slope of the regression line relating each parameter to augmentation index, and the coefficient beta provides a measure of the relative strength of the association independent of the units of measurement. Parameters listed in descending value of beta.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; PMAP = peripheral mean arterial pressure; SE = standard error.

Table 4. Results of the Multiple Regression Analysis With Estimated Aortic Pulse Wave Velocity (T_R) as the Dependent Variable

Parameters	Units	Regression Coefficient	SE	Beta	Significance
Gender	male	8.80	2.51	0.38	0.001
LDL cholesterol	mmol/l	−1.63	0.84	−0.17	0.046
PMAP	mm Hg	−0.15	0.08	−0.17	0.06
Heart rate	min^{-1}	−0.16	0.08	−0.17	0.06
Smoker		−4.22	2.14	−0.17	0.050
Age	yrs	−0.17	0.09	−0.16	0.08
Height	m	13.45	12.60	0.12	0.037
HDL cholesterol	mmol/l	0.50	2.34	0.02	0.8
Triglycerides	mmol/l	−0.43	0.92	−0.04	0.6

Multiple regression analysis using all 136 subjects. R^2 value for the entire study group = 0.364, $p < 0.001$. Parameters listed in descending value of beta.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; PMAP = peripheral mean arterial pressure.

LDL cholesterol was independently associated with aortic stiffening. Height was inversely related to estimated pulse wave velocity, which is to be expected, as we did not correct for path length but simply used the arrival of the reflected wave as a measure of aortic pulse wave velocity. Therefore, for a given pulse wave velocity, taller subjects with a longer aortae will have a prolonged transit time.

Peripheral pulse pressure, a surrogate measure of arterial stiffness and important predictor of cardiovascular mortality (4,5,42), did not differ significantly between the two groups. However, we have demonstrated, for the first time, increased *central* pulse pressure in subjects with hypercholesterolemia compared with controls and a reduction in the degree of pressure amplification. Systolic pressure varies throughout the arterial tree due to wave reflection and differences in vessel stiffness. Normally, there is an amplification of pulse pressure from the central to peripheral arteries, but the degree of amplification depends on a number of factors including heart rate (38) and posture (43). Therefore, peripheral pulse pressure does not always predict central pulse pressure, which is important because central, not brachial artery, pressure best defines left ventricular workload and, thus, left ventricular mass—an important and independent predictor of cardiovascular mortality (44). Moreover, carotid pulse pressure correlates more closely with carotid intima-media thickness than brachial pulse pressure (45) and predicts restenosis after angioplasty (46). However, whether measurement of central pulse pressure will improve risk stratification remains to be proven. Nevertheless, we have demonstrated that simply assessing brachial artery pressure does not reliably predict central hemodynamics, which may explain the lack of correlation between peripheral blood pressure and serum cholesterol in a recent study (47).

Whether structural changes in the arterial wall alone are responsible for the increase in arterial stiffness reported in this and other studies is unclear. Although we did not include subjects with a history of vascular disease or manifest evidence of atheroma, we cannot exclude the possibility of occult atheroma in the hypercholesterolemic group being responsible for the observed arterial stiffening. However, mounting evidence suggests that there is a degree of functional regulation of stiffness by the vascular endothelium (48,49). Hypercholesterolemia is strongly associated with endothelial dysfunction and reduced nitric oxide bioavailability (11,49), which may lead to a degree of functional and, therefore, potentially reversible arterial stiffening. Indeed, in animal models of hypercholesterolemia, cholesterol lowering appears to reduce arterial stiffness (26,27). In humans, HMG-CoA reductase (statin) therapy has also been associated with a reduction in aortic pulse wave velocity within six months (50), but not any improvement in femoral, carotid or brachial artery distensibility within eight weeks (34). Finally, although we assessed arterial stiffness and central pressures noninvasively using PWA rather than directly, the transfer function involved has been validated. However, aortic pulse wave velocity was estimated from the timing of the reflected pressure wave rather than measured using a foot-to-foot methodology.

In summary, we have shown increased *systemic arterial* and *aortic* stiffness and, for the first time, central pulse pressure in asymptomatic patients with hypercholesterolemia. Stiffness was independently correlated with LDL but not HDL cholesterol. Large-scale studies are now required to investigate further the influence of hypercholesterolemia on central arterial pressure and left ventricular load. Multicenter studies investigating the effect of various therapeutic interventions on arterial stiffness, including cholesterol-lowering and folate supplementation in hypercholesterolemic subjects (Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine [SEARCH]), are currently ongoing (51), and these will serve not only to provide data concerning the importance of systemic arterial stiffness as a predictor of outcome but will also determine the effects of therapeutic intervention. Mechanistic studies are also required to investigate the relationship between cholesterol, arterial stiffness and endothelial function and may serve to elucidate the role of the endothelium in regulation of arterial stiffness.

Acknowledgments

We thank Mr. B. van der Arend and Mr. M. van der Steen for their technical assistance.

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