Relation Between Coronary Artery Disease, Aortic Stiffness, and Left Ventricular Structure in a Population Sample

Christoph D. Gatzka, James D. Cameron, Bronwyn A. Kingwell, Anthony M. Dart

Abstract—To elucidate the relationship between coronary artery disease (CAD), aortic stiffness, and left ventricular structure, we recruited 55 subjects (33 men; average age, 63 ± 1 years) with previously unknown CAD from a healthy general population sample, as well as 55 control subjects matched for gender, age, and serum cholesterol level. We measured arterial blood pressure and the systolic expansion of the transverse aorta and left ventricular structure by echocardiography. Aortic stiffness was higher in CAD patients than in controls, with a brachial pulse pressure of 59 ± 3 versus 52 ± 2 mm Hg and stiffness indices of $E_p = 212 ± 26$ versus $123 ± 13$ kN/m² and $\beta = 16 ± 2$ versus $9 ± 1$ (all $P<0.01$). Mean arterial pressure was similar in both groups during the measurements (95 ± 2 versus 93 ± 2 mm Hg, $P=\text{NS}$). Most CAD patients (61%) were in the highest stiffness quartile defined by the normal control values ($P<0.05$ versus control). Left ventricular mass index was also higher in CAD patients than in matched controls (139 ± 5 versus 123 ± 4 g/m², $P<0.05$). We conclude that aortic stiffness and left ventricular mass are increased in subjects newly diagnosed as having CAD. This might explain previously reported associations of an increased mortality, particularly from CAD, found among subjects with elevated pulse pressures. (Hypertension. 1998;32:575-578.)

Key Words: aorta ■ arterial compliance ■ coronary artery disease ■ ventricular function, left

It has been shown recently that pulse pressure, a measure closely related to aortic stiffness, predicts future all-cause, cardiovascular, and especially coronary mortality in the general population.1 A number of factors may be responsible for an increase in mortality in association with an increase in aortic stiffness. It increases left ventricular pulsatile work and hence leads to left ventricular hypertrophy, with a higher demand for coronary blood flow.2 In addition, coronary perfusion is changed unfavorably, with a reduced supply due to a decreased diastolic blood pressure.3

However, if coronary artery disease (CAD) were associated at baseline with an increase in aortic stiffness, then the relation between pulse pressure and subsequent increased coronary mortality might just reflect this association. This notion is supported by previous work in younger patients and patients after myocardial infarction.4–5 To address this issue in a more general manner, we determined aortic stiffness and left ventricular structure in a case-control study in subjects with and without CAD. Subjects were drawn from a general population sample and matched for age, gender, and total cholesterol, since the latter has been found to be related to arterial stiffness in patients with CAD.6–8

Methods

Subjects
Consecutive volunteer screenees attending the Health 2000 Diet and Cancer Study of the Anti-Cancer Council of Victoria were invited to self-complete a modified Rose chest-pain questionnaire.9 The Health 2000 Study is a cohort study whereby some 50 000 Melbourne inhabitants are to be followed up to examine the relationship between diet and the incidence of various forms of cancer. The aim of the screening process was to identify subjects with chest pain due to ischemic heart disease that had not been previously recognized. Initial questions in the survey identified subjects who knew of a previous diagnosis of myocardial infarction and/or angina. Subsequent questions identified the presence of exertional chest pain (the site of which was also marked on a cartoon figure). A total of 5160 questionnaires were returned. Those subjects who were aware of a previous diagnosis of myocardial infarction and/or angina were excluded from further participation. The remaining 760 subjects, whose responses indicated that they experienced exertional chest pain plausibly due to myocardial ischemia, were invited to undergo a clinical interview and ECG stress test; only 50% of invited subjects attended. Subjects who had an ECG indicative of a prior myocardial infarction or significant ST deviation at rest were excluded from further participation. The ECG stress test was performed according to a modified Bruce protocol on a treadmill. A total of 57 subjects, who developed ≥1.5 mm ST-segment depression, were classified as positive cases. Of these subjects with a positive stress test, 55 agreed to participate in this study.

Gender-, age-, and cholesterol level–matched control subjects were recruited from among questionnaire respondents who indicated that they had no past history of myocardial infarction or angina and did not currently experience chest pain. Control subjects did not undergo an ECG stress test because of the low specificity of the test in this cohort with a low pretest probability of disease. Criteria for matching were age ±2 years and total serum cholesterol ±1 mmol/L.

Investigations
On the day of the study, subjects arrived in the morning after an overnight fast. Cases were investigated within days of the positive
Data for CAD Patients and Control Subjects Matched for Gender, Age, and Serum Cholesterol

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender*</td>
<td>33 men, 22 women</td>
<td>33 men, 22 women</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y&lt;sup&gt;†&lt;/sup&gt;</td>
<td>63±1</td>
<td>62±1</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72±2</td>
<td>73±2</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166±1</td>
<td>167±1</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>26.0±0.4</td>
<td>25.8±0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

| Biochemical data       |          |          |       |
| Triglycerides, mmol/L  | 1.53±0.09 | 1.65±0.14 | NS |
| Cholesterol, mmol/L*   | 5.66±0.13 | 5.70±0.12 | NS |
| HDL cholesterol, mmol/L| 1.16±0.04 | 1.21±0.06 | NS |
| LDL cholesterol, mmol/L| 3.79±0.12 | 3.72±0.11 | NS |

| Echocardiography data  |          |          |       |
| IVS, mm                | 11.4±0.3 | 10.6±0.3 | NS |
| PW, mm                 | 11.3±0.2 | 10.7±0.2 | <0.05 |
| LVM, g                 | 250±11   | 228±9    | NS |
| LVMI, g/m<sup>2</sup>  | 139±5    | 123±4    | <0.05 |

| Aortic stiffness       |          |          |       |
| SBP, mm Hg             | 133±4    | 130±3    | NS |
| Mean arterial pressure, mm Hg | 95±2          | 93±2    | NS |
| DBP, mm Hg             | 74±2     | 77±2     | NS |
| Pulse pressure, mm Hg  | 59±3     | 52±2     | <0.01 |
| Aortic D<sub>s</sub>, mm | 29.2±0.7 | 30.2±0.5 | NS |
| Aortic D<sub>p</sub>, mm | 27.7±0.7 | 28.0±0.5 | NS |
| E<sub>p</sub>, kN/m<sup>2</sup> | 212±26 | 123±13 | <0.01 |
| β                      | 16±2     | 9±1      | <0.01 |

*Matched variables.

ECG stress test. Height and weight were recorded, and a fasting blood sample was drawn.

Afterward, echocardiography was performed with a Hewlett-Packard 77020A phased-array echo-Doppler System. Transverse aortic measurements were made from the suprasternal notch as previously described. Systolic (SBP) and diastolic (DBP) arterial pressures (mean of 3 readings) used in this analysis were recorded at the brachial artery by sphygmomanometry immediately after completion of the suprasternal view while the subjects were still recumbent. Mean arterial pressure was calculated by adding 1/3 of the pulse pressure to DBP. All echo-Doppler measurements were performed by a single operator who was unaware of the categorization of subjects as cases or controls. Subsequent measurements were made on screen with electronic calipers, again without knowledge of the case/control status of the subject. Interventricular (IVS) and left ventricular posterior wall thickness (PW) were measured from leading edge to leading edge at end diastole. Left ventricular internal diameter (LVID) was measured at end diastole. Left ventricular mass (LVM) was determined as LVM = 0.6 + 0.832 × [(LVID + PW + IVS)/2 − LVID]<sup>2</sup> g. For subjects in whom only either the IVS or PW could be accurately determined, the available measurement was doubled and used in the formula. Minimum end-diastolic (D<sub>e</sub>) and maximum systolic (D<sub>s</sub>) diameters for the transverse aortic arch were measured with the M-mode beam perpendicular to the aortic wall. The aortic stiffness indices E<sub>p</sub> and β were computed as E<sub>p</sub> = (SBP−DBP) × D<sub>e</sub>/((D<sub>s</sub>−D<sub>e</sub>) N/m<sup>2</sup>) and β = (ln SBP−ln DBP) × D<sub>e</sub>/(D<sub>s</sub>−D<sub>e</sub>). Five measurements of all variables were obtained for each subject, and the mean was used in calculations. Coefficients of variation for repeated measurements in the present study were 2.3% and 1.9% for posterior and left ventricular septal wall thickness and 2.3% for diastolic LVID, respectively.

Adequate images were not obtained in all cases because of technical difficulties in image acquisition, but these failure rates were similar in both groups. Thus, LVM was obtained in 39 cases and 40 controls and aortic measurements in 39 cases and 42 controls.

**Statistical Analysis**

All data are expressed as mean±SEM except where indicated otherwise. Statistical comparisons were made using Student’s t and χ² tests as appropriate; 2-tailed probabilities for a separate variance estimate are given where applicable. Because E<sub>p</sub> and β data are skewed, nonparametric tests were used to compare groups. The analysis by quartiles was restricted to subjects older than 55 years with a mean arterial pressure <107 mm Hg as suggested by previous work. All other subgroups (ie, those younger than 55 years or with a mean arterial pressure >107 mm Hg) contained too few subjects for a meaningful analysis. Data were complete for 28 CAD patients and 30 controls for the analysis by quartile. Values were considered significant if P<0.05. All computations were done using SPSS software for Windows, version 7.0.

**Results**

CAD patients and controls were matched for gender, age, and serum cholesterol levels (Table). No significant differences were found for weight, height, or body mass index. Both CAD patients and controls had similar values for triglycerides and HDL and LDL cholesterol. Only a small proportion of
CAD patients and controls were current cigarette smokers (3 in each group). More CAD patients than controls were taking antihypertensive medication (36% versus 7%, P<0.01). Left ventricular mass index and posterior wall thickness were higher in CAD patients than in controls.

At the time of the measurement of aortic stiffness (during echocardiography in the recumbent position), mean arterial pressure was almost identical between CAD patients and control subjects (95±2 versus 93±2 mm Hg, P=NS), thereby not confounding the stiffness measurements. Pulse pressure, however, was significantly higher in the CAD patients than in the controls. The average aortic diameter was slightly larger in controls than in CAD patients (this difference was not significant). CAD patients had markedly stiffer aortas than did asymptomatic controls: both aortic stiffness indices, \( E_p \) and \( \beta \), were significantly higher in CAD patients than in controls.

When CAD patients and control subjects were divided into quartiles defined by aortic stiffness measured in the controls (Figure), 61% of CAD patients were found to be in the highest stiffness quartile (\( P<0.05 \)).

**Discussion**

The major finding of this case-control study was that the proximal aorta is stiffer in patients with newly diagnosed CAD than in matched control subjects. In keeping with this, we have shown that CAD patients have a very high likelihood of being in the highest quartile of stiffness when quartiles are defined by measurements in subjects presumably free of CAD. Left ventricular wall thickness was also higher in CAD patients than in controls.

Our finding of an increased aortic stiffness in patients with CAD is in keeping with previous smaller studies.3,7,10,12 Another study has shown that proximal aortic stiffness is increased progressively with the number of diseased coronary blood vessels in patients investigated after myocardial infarction.7 This finding might account for the increased coronary mortality associated with an increased pulse pressure found in male subjects drawn from a similar general population sample. That study classified subjects according to quartiles of pulse pressure, similar to our classification (Figure). When limited to subjects older than 55 years with a mean arterial pressure <107 mm Hg, subjects in the highest stiffness quartile had a relative risk of 1.9 of dying from CAD compared with the rest of the cohort.2 Interestingly, that study found that no such association existed for cerebrovascular mortality. Hence, the higher prevalence of CAD in subjects with a higher aortic stiffness as demonstrated in our study might account for this additional CAD mortality.

The diagnosis of CAD in our study was based on clinical criteria, ie, if subjects presented with typical exertional angina and had a positive exercise test. Although not part of the study protocol, we were subsequently able to determine that within 24 months of their participation, 60% of the CAD subjects were known to have undergone coronary angiography in the course of their routine clinical management, which in turn demonstrated hemodynamically significant stenoses in 78% of those investigated. A further 10% of those investigated had evidence of coronary disease of lesser magnitude. Of all 55 CAD subjects, 39% had had a revascularization procedure (coronary artery bypass graft or angioplasty or both) performed within 24 months. Hence, we conclude that the selection criteria used did indeed in the main correctly identify subjects with previously undiagnosed CAD. Notwithstanding this, as well as the possibility that “angiographically negative” case subjects experienced myocardial ischemia due to other causes (eg, coronary spasm, microvascular disease), it is possible that the CAD group contained some cases inappropriately so classified. However, this seems unlikely to have seriously confounded our results.

The measures of aortic stiffness used in this study require determination of minimal and maximal aortic diameters, together with sphygmomanometrically measured brachial pressures as a surrogate for intra-aortic pressure. Although the property of pulse pressure amplification at more distal arterial sites is well recognized, this generally has been demonstrated for comparison between femoral and proximal aortic sites where it is evident for young but not older subjects.13 The age of participants in the present study, together with the use of brachial pressures, makes it unlikely that the assumption of pressure equivalence will have introduced significant error. Indeed, a recent study in which brachial systolic and diastolic pressures were used to calibrate subclavian arterial waveforms registered by applanation tonometry found no significant difference between calibrated subclavian waveforms and those recorded from the proximal aorta.14 Another study compared invasive with noninvasive measurements and found excellent correlation between both measures independent of whether subjects had CAD or not.12

The variability of echocardiographically determined indices of aortic stiffness has been found previously to be <10% for interobserver comparisons and also for measurements repeated at 4-week intervals.7,15 In addition, pulse pressure measurement is independent of echocardiographic assessments. In our study, the pulse pressure data are consistent with the aortic stiffness measurement. This argues against the results observed here being an artifact introduced by potential
confounding factors in the measurement of aortic root diameter by echocardiography.

Differences between the CAD patients and control subjects were evident in regard to blood pressure and the number of subjects taking antihypertensive medication. These factors may be expected to have opposing effects in that hypertensive medication may not affect aortic stiffness similarly, there were too few subjects to permit analysis by class of medication. The difference in blood pressure between CAD patients and controls was small, however, and unlikely to account for the marked difference in $E_R$ and $\beta$ between CAD patients and control subjects.

Echocardiographic left ventricular hypertrophy has been found to be predictive of future cardiovascular events in hypertensive subjects, in those with CAD, and in disease-free subjects.\textsuperscript{16–21} The left ventricular hypertrophy seen in the CAD patients compared with controls might reflect the effect of a higher input impedance associated with increased aortic stiffness, a different average cardiac load over 24 hours, or growth factors such as insulin, which were not assessed in this study.\textsuperscript{22,23}

In conclusion, we have shown in a case-control study that proximal aortic stiffness as well as left ventricular mass is increased in subjects with newly detected CAD in a general population sample; patients with CAD are likely to be in the highest quartile of aortic stiffness distribution. This might contribute to previously reported associations between pulse pressure and an increased subsequent mortality, particularly from CAD.

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