Radial artery hypertrophy occurs in coronary atherosclerosis and is independent of blood pressure

Alison J. MACKAY*, Carlene A. HAMILTON*, Kenneth McARTHUR†, Geoffrey BERG†, Anne-Isabelle TROPEANO‡, Pierre BOUTOUYRIE‡, John L. REID* and Anna F. DOMINICZAK*

*Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow G11 6NT, Scotland, U.K., †Department of Cardiothoracic Surgery, Western Infirmary, Glasgow G11 6NT, Scotland, U.K., and ‡Service Cardiovasculaire, Hôpital Broussais, 96 rue Didot, F-75674 Paris cedex 14, France

ABSTRACT

Endothelial dysfunction, believed to underlie the structural changes of atherosclerosis, is a systemic phenomenon. Despite this, the radial artery has been considered as devoid of atherosclerosis and is commonly used as a conduit in coronary artery bypass grafting (CABG). Recently, histological study has shown intimal hyperplasia and other structural changes consistent with early atherosclerosis in the radial artery. The objective of the present study was to determine if structural changes in the radial artery could be detected in vivo in patients with coronary atherosclerosis. Using high resolution echo-tracking, measurements of radial artery internal diameter, wall thickness and wall cross-sectional area were made in 25 patients awaiting CABG and in 20 controls. Digital and brachial blood pressures were also recorded. Mean arterial pressures did not differ between the patient and control groups. All measures of wall thickness were greater in the patient than the control group. Neither current arterial pressures nor past history of hypertension correlated with wall thickness. Using a model of analysis of covariance, coronary artery disease was the best single predictor of intima-media thickness, \( R^2 = 48\% \), \( n = 44 \), \( P < 0.0005 \). We concluded that increased radial artery wall thickness can be demonstrated in vivo in patients with coronary atherosclerosis. This is a novel observation which seems to be independent of blood pressure, and is consistent both with the hypothesis of systemic endothelial dysfunction leading to systemic structural changes and also to the recent histological evidence for atherosclerotic changes in this vessel.

INTRODUCTION

Atherosclerosis of conduit vessels supplying heart, brain, kidneys and peripheral vascular beds results in significant morbidity and mortality due to ischaemia of these territories. The ‘response-to-injury’ hypothesis of atherosclerosis [1] suggests that one or several systemic insults, such as hypercholesterolaemia [2], hypertension [3], diabetes [4] and hyperhomocysteinaemia [5] result in dysfunction of the anti-atherosclerotic properties of the vascular endothelium [6]. This dysfunction, in turn, leads to development of structural changes. The features of atherosclerosis are an initial accumulation of lipid-laden macrophages and T lymphocytes within the intima. Within this layer there next occurs a proliferation of smooth muscle cells with macrophages interspersed. Finally, complex fibrous plaques containing vascular smooth muscle cells, and a core of lipid and necrotic

Key words: vasculature, pathophysiology, ultrasound, atherosclerosis, hypertension, radial artery, hypertrophy.

Abbreviations: CABG, coronary artery bypass grafting; MID, mean internal diameter; PWT, posterior wall intima-media thickness; BMI, body-mass index; HMG-CoA reductase, 3-hydroxy-3-methylglutaryl-CoA reductase; CI, confidence interval.

Correspondence: Dr A. J. Mackay (e-mail alisonjmackay@hotmail.com).
debris encroach on the lumen of the vessel [7,8]. As there is evidence of endothelial dysfunction in coronary, cerebral and upper limb regions [9–11], with upper limb circulations correlating well with coronary arteries [12], many consider endothelial dysfunction to be a systemic phenomenon [13]. We consider that, as a consequence of this, one might expect to find atherosclerosis as a systemic phenomenon. However, the regions supplied by the radial artery are generally spared the symptoms of the structural lesions of atherosclerosis and the radial artery is commonly used as a graft for coronary artery bypass grafting (CABG) [14]. Recently, a histological study of arterial sections removed from patients with advanced atherosclerosis identified structural changes of atherosclerosis in radial arteries. Ruengsakulrach et al. [15] reported histopathological findings from paired samples of radial arteries and internal thoracic arteries obtained from 150 patients undergoing CABG. Structural changes attributable to atherosclerosis were found more frequently in the radial artery than in the internal thoracic artery, with intimal hyperplasia in 94% of radial arteries and in 69% of internal thoracic arteries; calcification was present in 13.3% of radial arteries and none was found in internal thoracic artery; atherosclerotic plaques or overt stenoses were observed in 5% of radial arteries and in 0.7% of internal thoracic arteries. It is notable that the finding of intimal hyperplasia, rather than more advanced lesions, was highly prevalent, suggesting an early stage of atherosclerotic development.

The study of radial artery dimensions in vivo is possible using very-high-resolution ultrasound echo-tracking devices, allowing internal diameter and intima-media thickness to be measured directly and wall cross-sectional area to be calculated. This therefore permits accurate assessment of combined intima and medial thickness in vivo without, however, distinguishing between these layers in the same way that histological examination would allow.

We designed a study to test the hypothesis that, in patients with confirmed coronary atherosclerosis and, by assumption, underlying endothelial dysfunction, structural changes in the radial artery, consistent with early atherosclerotic changes in this vessel, could be detected non-invasively.

**METHODS**

**Patients and controls**

The study protocol was approved by the Western Infirmary Ethics Committee as conforming to the principles outlined in the declaration of Helsinki, and all subjects gave informed written consent to participation. Patients with angiographically proven coronary artery disease, who were awaiting CABG, were recruited by letter and telephone. Those with diabetes were excluded. We sought controls matched for age and sex but free of cardiovascular disease. These healthy volunteers were recruited by advertisement. By necessity the patient and control groups differed in terms of prevalence of cardiovascular risk factors. Data on age, sex and cardiovascular risk factors are shown in Table 1.

The control group was deemed free of vascular disease on the basis of clinical history, physical examination and electrocardiographic findings. Coronary angiography was not performed in this group. In contrast with their controls, concurrent vascular disease was prevalent within the patient group, with one case of renal artery stenosis, six subjects with peripheral vascular disease and two with evidence of cerebrovascular disease. A history of treated hypertension was given by 12 individuals in the patient group, although their blood pressures at the time of study did not differ from the never-hypertensive patients. The mean ± S.D. duration of treatment of hypertension was 7.79 ± 4.67 years, range 4–20 years.

Lipid subfractions were measured in the patient group. As shown in Table 1, the mean ± S.D. fasting total cholesterol concentration was 5.5 ± 1.0 mmol/l. In keeping with their pathology, the patients were also prescribed multiple vasoactive drugs in different combinations. The total numbers of patients using any one class of drug are as follows: aspirin, n = 25; long acting nitrates, n = 20; calcium-channel antagonists, n = 15; beta-blockers, n = 18 and potassium-channel openers, n = 3. Angiotensin-converting enzyme (‘ACE’) inhibitors were prescribed for four patients, with the indication being hypertension in three of the four. The most frequently prescribed combination of drugs was aspirin + nitrate + beta-blocker + calcium-channel antagonist, a combination being taken by nine of 25 in this group. As stated above, 12 had been prescribed an HMG-CoA reductase (3-hydroxy-3-methylglutaryl-CoA reductase) inhibitor. None of the controls was taking any vasoactive medication, although hormone replacement preparations were prescribed for four females in this group. Body size was similar in the two groups, as judged by weight, height and body-mass index (BMI) measurements.

**Arterial measurements**

A high-resolution echo-tracking device (NIUS O2; Aaslab, Neuchatel, Switzerland) was used for arterial measurements. This utilizes both Doppler and A-mode ultrasound to make continuous measurements of arterial structure throughout the cardiac cycle. After comfortably restraining the non-dominant arm of the supine subject in a moulded arm-rest, an aqueous gel was applied to the anterior surface of the wrist to prevent any pressure being applied by the transducer over the artery. The 10 MHz ultrasound probe was then positioned over the radial artery, using Doppler ultrasound to accurately place it perpendicular to the axis of the artery, with its height adjusted to correspond to the focal distance of 11 mm.
It was situated between 1–3 cm proximal to the crease of the wrist, choosing the site which gave the clearest ultrasound signal. As the diameter of the radial artery is constant in this part of the arm, this amount of flexibility in position does not alter results to any significant degree [17,18]. The stereotactic arm supporting the probe was screwed into place. To monitor the echoes obtained from the artery walls with A-mode ultrasound, the final probe positioning was completed by fine adjustment of the micrometric screws in x, y and z planes. The operator then detected and ‘tagged’ with electronic markers, oscilloscopic signals from the blood–intima interface of the anterior wall and the interfaces between blood and intima, and intima and adventitia of the posterior wall. The operator was blinded to the scale between blood and intima, and intima and adventitia of the posterior wall. The electronic markers were followed throughout the cardiac cycle, resulting in measurements of internal diameter and wall thickness at the full range of pressure changes in the artery. This method has been extensively validated [20–22] and is accepted as a highly accurate means of measuring structure and stiffness of arterial material [29]. Reproducibility, assessed in our laboratory using the methods described above, in which two repeated measurements were made 15 min apart in 12 healthy volunteers, resulted in coefficients of variance of 2.1% for mean internal diameter (MID) and 5.6% for posterior wall intima-media thickness (PWT). We further assessed the inter-observer variation by submitting 17 ‘blinded’ arterial traces to two experienced operators (P. B. and A.-I. T.). For this analysis, the coefficient of variance was 0.4% and 6.7% for MID and PWT respectively.

### Blood pressure measurement

Digital artery pressure of the middle finger of the hand ipsilateral to the radial artery being measured was recorded concurrently with NIUS echo-tracking measurements. The arterial pressure was measured continuously using a digital photoplethysmograph (Finapres). In addition to digital pressures, brachial artery blood pressure was recorded with the subject relaxed and recumbent, using a standard sphygmomanometer, and the mean of three sequential readings was obtained. There is well recognized heterogeneity between peripheral and more central pressure recordings, with peripheral pressures being consistently higher than those obtained more centrally [27]. This is due, in part, to the phenomenon of pressure wave reflection from distant sites (particularly resistance arterioles [28]). The effect of reflected waves augmenting the incident pressure wave is greatest in distal arteries, and is dependent to an extent on the intrinsic compliance of arterial material.

### Study protocol

All subjects attended at 09.00 after a 12 h fast. Morning medication was taken as usual by the patient group as it was felt unethical to withhold medication from this group. Details of medical history were documented before each subject underwent a full physical examination in which particular attention to the cardiovascular system was paid. The examination included, in addition to blood pressure measurement performed in accordance with current British Hypertension Society guidelines, the recording of a 12-lead ECG in the controls as an extra screen for occult ischaemic heart disease. Prior to the arterial measurements, the subject was given time to settle into the surroundings of the examination room; a darkened, quiet, temperature-controlled environment. NIUS recordings were made over 30–60 s periods, with simultaneous digital artery pressure recordings. According to standard procedure, the most technichally satisfactory 10 s of each recording, as judged by smooth contour of arterial diameter, wall thickness and blood

### Table 1 Clinical details of patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 25)</th>
<th>Controls (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (M/F)</td>
<td>15/10</td>
<td>10/10</td>
</tr>
<tr>
<td>Mean age (range in parentheses)</td>
<td>62 (41–73)</td>
<td>50 (40–63)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.66 ± 0.1</td>
<td>1.58 ± 0.37</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.6 ± 12.3</td>
<td>70.8 ± 11.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9 ± 3</td>
<td>25.5 ± 2.7</td>
</tr>
<tr>
<td>Number of current/ex smokers</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Number with treated hypertension</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Fasting total cholesterol</td>
<td>5.5 ± 1.0 mmol/l</td>
<td>Not known</td>
</tr>
<tr>
<td>Brachial blood pressure (mmHg)</td>
<td>132 ± 24/76 ± 10</td>
<td>131 ± 13/77 ± 9</td>
</tr>
<tr>
<td>Digital blood pressure (mmHg)</td>
<td>142 ± 39/52 ± 12</td>
<td>129 ± 22/61 ± 14</td>
</tr>
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pressure wave forms, was sampled to allow generation of measures of arterial structure. MID, defined as the distance between anterior wall blood–intima interface and posterior wall blood–intima interface, was measured directly, as was PWT, which is the distance between the posterior wall blood–intima interface and the intima–adventitia interface. Wall cross-sectional area was calculated as $\pi (Re^2 - Ri^2)$, where Re is the mean internal radius + PWT and Ri is the mean internal radius. Wall/lumen ratio was subsequently calculated as the ratio of PWT/MID, expressed as a percentage. The same operator made all the measurements in the present study. During the positioning of the probe and the recording and selection of the trace, the operator was blinded to arterial dimensions. Systolic and diastolic blood pressure, measured by the Finapres during the same 10 s period, were also recorded.

**Statistics**

Two-way ANOVA was used to compare blood pressure and structural data between sexes and between patient and control groups. Confidence intervals were calculated for differences between patient and control means. An analysis of covariance, adjusted for patient–control difference, was then used to determine factors predicting wall thickness.

**RESULTS**

Mean systolic and diastolic blood pressures did not differ between the patient and control groups, whether measured by sphygmomanometer or photoplethysmograph (Table 1). The greater S.D. for systolic pressures in the patient group compared with those of controls was because two female patients had pulse pressures greater than normal when measured by photoplethysmograph (digital blood pressure 202/30 and 233/34 respectively), although their brachial blood pressures were close to the group mean (105/85 and 136/76 respectively).

Mean total fasting cholesterol for the patient group was 5.5 ± 1.0 mmol/l (Table 1). The lipoprotein subfractions for this group (means ± S.D.) were: triglycerides, 1.87 ± 1.0 mmol/l; very-low-density lipoprotein, 1.03 ± 0.5 mmol/l; low-density lipoprotein 3.28 ± 0.86 mmol/l; high-density lipoprotein, 1.22 ± 0.3 mmol/l; and the cholesterol/high-density lipoprotein ratio was 4.73 ± 0.7. Total cholesterol > 5.2 mmol/l was measured in 16 patients, of whom eight had already been prescribed an HMG-CoA reductase inhibitor. A further four patients, whose total fasting cholesterol range was 3.45–4.52 mmol/l, were also taking an HMG-CoA reductase inhibitor. Division of the patient group into those prescribed HMG-CoA reductase inhibitors and those not taking the drug showed no difference in mean (± S.D.) cholesterol levels (5.3 ± 1.1 mmol/l and 5.7 ± 0.8 mmol/l respectively). BMI (Table 1) did not differ significantly between patients and controls.

MID was greater in males than females in both patient [P < 0.00005; 95% confidence interval (CI) 1.83, 2.48] and control groups (P < 0.00005; 95% CI 1.65, 2.29), reflecting the larger size of men’s arms. However, there was no difference in resting internal diameter between patient and control groups. Results of directly measured MID and PWT and calculated wall cross-sectional area and wall/lumen ratio are shown in Figure 1. There was no effect of gender on measurements of posterior wall dimensions, therefore measurements from both sexes were combined. All measurements of wall thickness were greater in the patient than the control group (PWT, P < 0.00005, 95% CI 0.095, 0.174; wall cross-sectional area, P < 0.00005, 95% CI 1.03, 1.89; wall/lumen ratio, P < 0.00005, 95% CI 2.4, 6.6). In summary, the structural findings demonstrated an increase in intima-media thickness without obvious reduction of lumen diameter.

Although mean blood pressure did not differ between patients with treated hypertension and those that had
never been hypertensive, in order to determine the effect of previously treated hypertension, the analysis was repeated omitting the sub-group of 12 individuals with a past history of hypertension. This did not alter either the mean results or their levels of significance.

Statistical analysis for correlation between structural findings and clinical parameters was undertaken. No significant correlation was found between systolic or diastolic pressures, whether obtained with sphygmomanometer or photoplethysmograph, and any of the three measures of wall thickness when the results of all 45 subjects were analysed. Similarly, analysis of mean arterial pressure (Finapres derived) in the patient group failed to show a positive correlation with PWT, wall cross-sectional area, or wall/lumen ratio. Furthermore, a history of treated hypertension did not correlate with wall hypertrophy. None of the measures of lipid subfractions in the patient group showed significant correlation with any of the structural measurements.

Mean internal diameter was positively correlated with males (Pearson correlation coefficient, 0.469; \( P = 0.001; n = 45 \)) and more strongly with height (\( r = 0.511; P = 0.0005; n = 45 \)).

We then applied a model of analysis of covariance adjusted for obvious patient-control differences, using 15 possible predictors of wall thickness: systolic and diastolic pressures, obtained both using photoplethysmograph and sphygmomanometer, past history of hypertension, age, sex, ever having smoked, height, weight, BMI, co-existent renal, peripheral or cerebral vascular disease and presence of coronary artery disease. The presence of coronary artery disease was found to be the best single predictor of wall cross-sectional area (\( R^2 = 44\%; P = 0.0005; n = 44 \)), and the second best predictor was weight, with a combined \( R^2 \) of 59\%; \( P = 0.0005; n = 44 \). For PWT, the variable with the strongest positive predictive value was the presence of coronary artery disease (\( R^2 = 48\%; P = 0.0005; n = 44 \)). The second best predictor was BMI, giving a combined \( R^2 \) of 56\% (\( P = 0.006 \)). For wall/lumen ratio, the presence of coronary artery disease was again the strongest predictor (\( R^2 = 34\%; P = 0.0005; n = 39 \)), with an \( R^2 \) of 44.4\% (\( P = 0.006; n = 39 \)) when combined with height.

**DISCUSSION**

The salient finding of this study is that greater intima-media thickness of radial arteries of patients with coronary atherosclerosis compared with healthy control subjects is detectable in vivo using ultrasound echotracking. As radial arteries from patients with advanced atherosclerosis have never been studied non-invasively in vivo before, this is a novel observation. Furthermore, the finding is consistent with the recent demonstration of histological changes of atherosclerosis in radial arteries. We propose that, in patients with coronary atherosclerosis, the radial artery should not be assumed to be free of structural changes but that early atherosclerotic changes should be considered likely. The extent of any structural abnormalities might be evaluated when considering these arteries as donor grafts for coronary artery bypass surgery.

The finding of intima-media hypertrophy outwith the coronary circulation in patients with coronary atherosclerosis is not a novel observation. This phenomenon is well recognized in the carotid arteries of patients with atherosclerosis, to the extent that carotid intima-media thickness is used as a marker for coronary risk in studies [30–33]. Carotid intima-media thickening is also found in individuals with single risk factors, such as hyperlipidaemia [34], hyperhomocysteinaemia [35] and diabetes [36], as well as those with essential hypertension [37] and is considered in these subjects to be a marker of presymptomatic atherosclerosis.

Radial artery intima-media hypertrophy has been demonstrated previously in individuals with essential hypertension [38]. In contrast with the pathological findings of intimal hypertrophy in atherosclerosis, the structural changes of hypertension are seen in the medial layer, in which smooth muscle cells hypertrophy and proliferate, resulting in thick-walled vessels with no external diameter increase, but a narrowing of the internal lumen [39]. The term ‘remodelling’ has been used to describe these structural changes when they occur in the resistance vasculature [40]. It is suggested that such remodelling is a response by smooth muscle cells of the vascular media to the increased tensile stress which hypertension places on the arterial wall. Structural adaptations are thought to be the result of homoeostatic mechanisms which maintain pressures at the level of resistance arteries [41]. However, in the present study, the differences between the arteries of the patient group and those of the controls was unrelated to any past or present measure of arterial pressures, reducing the likelihood of the structural phenomenon resulting from direct pressure-related mechanical forces. Although it is arguable that including a sub-set of treated hypertensives in the patient group may have affected the findings, their exclusion did not alter the results or the level of significance which was achieved. Furthermore, as treatment had reduced previously elevated blood pressures to those of the control group, one would expect to see regression to normal of any pressure-related wall changes, as demonstrated in the study of Girerd et al. [42].

Although there are very few studies investigating vascular function of radial and brachial arteries in subjects with advanced atherosclerosis, the functional effects of individual biological variables and cardiovascular risk factors have been studied in upper limb conduit arteries [2,5,43,44]. Work has concentrated on the analysis of
endothelium-mediated vascular function, disruption of which predisposes towards structural abnormalities. Impaired vasodilation to flow, an NO-dependent response, has been shown in the brachial arteries both of children with familial hyperlipidaemia [2] and of elderly individuals with hyperhomocysteinaemia [5]. Studies in smokers have shown both reduced basal nitric oxide bioavailability in the resistance circulation [45] and altered wall properties in conduit vessels [43]. Greater arterial stiffness has been shown in the radial artery wall of those with Type I diabetes [44], and impaired NO-mediated vasodilation has been demonstrated in the resistance vessels of a group with Type II diabetes [46].

A study of radial artery functional properties in vitro has been undertaken in samples from patients similar to those in the present study. In internal thoracic arteries, basal vasorelaxation appeared to be entirely NO-mediated, whereas within the radial artery there was evidence for both NO-dependent and -independent vasorelaxation [47].

It is likely that the brachial arteries of the individuals we studied with advanced coronary atherosclerosis would show significant endothelial dysfunction. However, whereas this vessel is continuous with and has structural similarities to the radial artery, the evidence for dichotomy of results amongst peripheral vessels makes any extrapolation speculative.

Atherosclerotic disease has been demonstrated, albeit to a limited extent, within this vascular region. Kane-ToddHall et al. [48] studied histological specimens of radial artery, internal mammary artery and long saphenous vein from patients undergoing CABG. They classified the degree of stenosis, extent of intimal thickening and presence or absence of medial calcification in order to quantify the severity of atherosclerotic change present. Although their conclusion was that pre-existing vascular disease in donor arteries was not severe, their findings, and those of Ruengsakulrach et al. [15], are consistent with the presence of early atherosclerotic changes. Considering these observations, and the absence of any evidence for hypertension contributing to the structural changes noted in the present study, we hypothesize that the greater intima-media measurements of our patient group are due to hypertrophy of the intimal layer. However, the limits of ultrasound technology, which do not allow differentiation between intima and media, prevent this being established in an entirely non-invasive study. A study correlating histopathology with results in vivo from the same patient would establish if this is the case and add to our understanding of this phenomenon.

Although the control group differed from the study group slightly in age and sex ratio, both of these variables were included in the analysis of covariance and did not show any predictive value. Although it is possible that some of the control group may have had silent atherosclerosis, this would serve rather to under- than over-estimate the differences between patients with atherosclerosis and the healthy population.

Polypharmacy was unavoidable for the patient group and it is likely that the resting degree of vasoconstriction or dilatation of the vessels was affected. This, in turn, will have had some effect on the measured PWT. For this reason, we consider the wall cross-sectional area result to be the most reliable under these experimental conditions. As the matter of the arterial wall is incompressible, this result is constant irrespective of the degree of vasodilation or constriction of the arterial smooth muscle [20,49]. Vasodilator drugs may be the explanation too behind the surprising failure to find encroachment of the vascular lumen, a feature noted by Ruengsakulrach et al. [15] yet missing from our results. However, as it is recognized that the histological fixation techniques used for vessels with early atherosclerotic change results in over-estimation of the degree of luminal encroachment [50], it is important not to attempt too many comparisons between different investigational techniques. It is hard to speculate whether long-term drug therapy has affected arterial structure in these patients. There is evidence in rat models of hypertension that betablockade may reduce medial thickening [51], and in vitro work with these compounds suggests reduction of smooth muscle cell proliferation [52]. Long acting calcium-channel antagonists have caused regression of increased media/lumen ratio in gluteal resistance vessels of hypertensive humans, as have angiotensin-converting enzyme inhibitors and angiotensin-II-receptor antagonists [53–55]. However, the structural effects of anti-anginal agents in individuals who are normotensive have not been investigated.

In conclusion, this is the first report that radial artery intima-media hypertrophy may be detected non-invasively in patients with coronary atherosclerosis. Its presence is likely to be independent of blood pressure effects, which allows us to hypothesize that it may be due to endothelial dysfunction. These observations suggest that structural changes of atherosclerosis are more widespread than formerly believed and this knowledge could be further utilized in the assessment of potential donor arteries.

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