Association of increased carotid intima-media thickness with the extent of coronary artery disease

A Kablak-Ziembicka, W Tracz, T Przewlocki, P Pieniazek, A Sokolowski, M Konieczynska

Objective: To investigate (a) the relation between intima-media thickness (IMT) in carotid arteries and the extent of coronary artery disease (CAD); and (b) whether IMT is predictive of coronary atherosclerosis. The coexistence of severe extracranial atherosclerosis in patients with CAD was also analysed.

Methods: Coronary angiography and carotid ultrasound evaluation were performed in 558 consecutive patients (438 men), with a mean (SD) age of 58.8 (9.2) years and suspected CAD. Mean IMT was measured at both carotid arteries and expressed as the mean aggregate value. The relation between IMT and severity of CAD was determined.

Results: A significant correlation between mean IMT and advancing CAD (p < 0.0001) was found. Four independent predictors of CAD were found in the discriminant analysis: age (p = 0.0193), hyperlipidaemia (p < 0.0001), smoking (p = 0.0032), and IMT (p < 0.0001). A significant increase in IMT was observed among patients with one, two, and three vessel CAD. A log normal distribution of IMT values showed that if mean IMT was over 1.15 mm, patients had a 94% probability of having CAD, with sensitivity of 65% and specificity of 80% in the patients with a high risk of CAD. The number of critically stenosed extracranial arteries increased with advancing CAD. None of the patients with normal coronary arteries had severe stenosis of the extracranial arteries. Severe carotid, vertebral, or subclavian stenosis was found in 16.6% of patients with three vessel CAD.

Conclusions: IMT increases with advancing CAD. Patients with mean IMT over 1.15 mm have a 94% likelihood of having CAD, and the coexistence of CAD with severe stenosis of aortic arch arteries is relatively high and was found in 16.6% of patients with three vessel CAD.

Coronary artery disease (CAD) remains the main cause of death in developed countries, despite several prevention programmes widely pursued across Europe, the United States, and other countries.

Since treadmill testing and transthoracic echocardiography can have limited specificity and sensitivity in diagnosing CAD, other methods are required. This applies especially to patients with atypical angina or with typical angina accompanied by a negative treadmill test and echocardiography, at the same time reflecting an overall need for an introduction of new complementary diagnostic instruments. The development of Doppler ultrasound machines, advanced operating software, and high resolution transducers facilitates comprehensive analysis of the intima-media thickness (IMT) in the peripheral vessels—that is, the carotid and femoral arteries. Thickening of the intima-media is commonly recognised as the initial stage in the development of atherosclerosis.

Myocardial infarction or other acute coronary syndromes are the first symptom of CAD in more than 50% of all patients with cardiovascular disease. Thus, early detection of CAD may well prove to be instrumental in introducing effective treatment and may contribute to reducing mortality, for example, through plaque stabilisation and more aggressive control of atherosclerotic risk factors.

The impact of hypertension, diabetes mellitus, hyperlipidaemia, cigarette smoking, age, and sex on IMT has already been well established. However, the association between IMT and atherosclerosis of the coronary arteries requires further investigation.

Furthermore, concomitant severe carotid and vertebral atherosclerosis may increase the risk of peri-procedural stroke in patients undergoing coronary artery bypass grafting or percutaneous procedures for CAD. In these patients, Doppler ultrasound examination offers the potential for simultaneous intervention in both carotid and coronary arteries.

The present study aimed at investigating whether an increase in IMT is related to the severity of CAD, as well as whether IMT may be instrumental in identifying patients with or without CAD. The frequency of concomitant severe carotid and vertebral artery atherosclerosis in patients with CAD was also investigated.

PATIENTS AND METHODS

We examined 558 consecutive patients (438 men, 120 women), with a mean (SD) age of 58.8 (9.2) years (range 40–81), admitted with suspected CAD from November 2000 to July 2001.

Coronary angiographies and ultrasound quantification of IMT in the carotid arteries were obtained for all patients.

High resolution B mode, colour Doppler, and pulse Doppler ultrasonography of both carotid arteries were performed with an ultrasound machine (ALOKA 5500 SSD; ALOKA Co, Tokyo, Japan) equipped with a 7.5 MHz linear array transducer. Patients were examined in the supine position with the head tilted backwards. After the carotid arteries were located by transverse scans the probe was rotated 90° to obtain and record a longitudinal image of the anterior and posterior walls. The maximum IMT was measured at the near and far walls of the common carotid artery, the bifurcation, and the internal carotid arteries and was expressed as a mean aggregate value. The IMT was assessed as normal if it did not exceed 1 mm. With regard to the incidence of plaque (defined as a focal thickening of the intima-media complex thickness

Abbreviations: CAD, coronary artery disease; IMT, intima-media thickness
greater than 1.3 mm), its maximum diameter was assessed and included in further analysis.

Furthermore, the grade of stenosis in the carotid and vertebral arteries was assessed through the increase in the peak systolic and end diastolic velocities (according to the criteria of Hood et al15), with a view to establishing the frequency of concomitant CAD and severe carotid and vertebral atherosclerosis. The carotid and vertebral atherosclerosis was considered severe when the grade of stenosis was \( \geq 70 \% \). When Doppler ultrasound indicated severe stenosis of the carotid or vertebral artery, the actual grade of stenosis was confirmed by standard angiography.

All scans were obtained by the same experienced sonographer, who had no prior knowledge of the patients’ clinical and angiographic characteristics.

The changes in mean IMT were analysed for patients with angiographically normal coronary arteries, one vessel CAD, two vessel CAD, and three vessel CAD.

Coronary angiography was performed in the catheterisation laboratory by means of COROSCO (Siemens AG, Munich, Germany), equipped with Quantcor QCA version 2.0 quantitative coronary analysis software. All angiographies were performed by the Selindger technique through femoral artery access. Patients with at least one lesion \( \geq 50 \% \) within the main branches of the coronary arteries were considered to have significant CAD. Patients with minimal atherosclerotic lesions (\(<50\%\)) in coronary arteries were not included.

**Statistical analysis**

Four groups of patients were considered in the analysis: patients without atherosclerotic lesions on coronary angiograms and patients with one, two, and three vessel CAD. The distribution of IMTs in these groups was evaluated according to IMT quartiles. To establish the independent value of IMT in predicting CAD we used multivariable discriminant analysis. The relation between mean IMT values and the severity of CAD was determined by one way analysis of variance. Furthermore, non-parametric estimation of carotid mean IMT distributions was assessed with simple histograms based on a theoretical log normal distribution of IMT values in the patients with CAD and the patients without CAD. The positive predictive values, sensitivity, and specificity were calculated to visualise the discriminating power of IMT.

**Table 1** Clinical and angiographic characteristics of the studied patients

<table>
<thead>
<tr>
<th></th>
<th>No CAD (n = 95)</th>
<th>CAD (n = 463)</th>
<th>(p) Value (\chi^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCS class II, III, or IV</td>
<td>81 (85.3%)</td>
<td>438 (94.0%)</td>
<td>0.0023</td>
</tr>
<tr>
<td>ECG ischaemic changes</td>
<td>22 (23.2%)</td>
<td>288 (61.8%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive treadmill test</td>
<td>58 (61.0%)</td>
<td>331/419(79.0%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Segmental contractility abnormalities on echocardiography</td>
<td>15 (15.8%)</td>
<td>328 (70.4%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age (years) [mean]</td>
<td>55.7 (8.3)</td>
<td>59.3 (9.25)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Men</td>
<td>66 (69.5%)</td>
<td>372 (80.3%)</td>
<td>0.0188</td>
</tr>
<tr>
<td>Obesity (BMI (&gt;30) kg/m²)</td>
<td>23 (24.2%)</td>
<td>94 (20.3%)</td>
<td>0.0859</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53 (55.8%)</td>
<td>287 (61.9%)</td>
<td>0.5458</td>
</tr>
<tr>
<td>NIDDM</td>
<td>12 (12.6%)</td>
<td>91 (19.7%)</td>
<td>0.1755</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>37 (38.9%)</td>
<td>298 (64.4%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>55 (57.9%)</td>
<td>390 (84.2%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>12 (12.6%)</td>
<td>305 (65.9%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal coronary arteries</td>
<td>95 (100%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>One vessel CAD</td>
<td>NA</td>
<td>154 (33.2%)</td>
<td>NA</td>
</tr>
<tr>
<td>Two vessel CAD</td>
<td>NA</td>
<td>104 (22.5%)</td>
<td>NA</td>
</tr>
<tr>
<td>Three vessel CAD</td>
<td>NA</td>
<td>205 (44.3%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

BMI, body mass index; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; NA, not applicable; NIDDM, non-insulin dependent diabetes mellitus.
RESULTS

On coronary angiography 95 (17.0%) patients had normal coronary arteries. One vessel CAD was diagnosed in 154 (27.6%), two vessel CAD in 104 (18.7%), and three vessel CAD in 205 (36.7%) patients.

Table 1 shows selected characteristics of the study groups. We observed significant differences between the studied groups of patients without CAD and with CAD in the majority of examined factors. However, typical atherosclerosis risk factors and symptoms of CAD were relatively prevalent in patients without significant coronary lesions.

The mean measured IMT calculated for patients with normal coronary arteries was 1.01 (0.19) mm, with one vessel CAD was 1.15 (0.20) mm, with two vessel CAD was 1.26 (0.27) mm, and with three vessel CAD was 1.47 (0.34) mm (fig 1). A significant, nearly linear correlation between IMT and advancing CAD (p < 0.0001) was found. Patients with one, two, and three vessel CAD had significantly higher IMT than did patients without CAD (p = 0.0044, p < 0.0001, respectively). We observed significant differences in IMT between patients with one and two vessel CAD (p = 0.0025), as well as between two and three vessel CAD (p < 0.0001).

Table 2 shows the distribution of patients according to IMT quartiles. Among patients without CAD 86% had IMTs in the first and second quartiles (< 1.04 mm and ≤ 1.2 mm) and 81% with three vessel CAD had IMTs in the third and forth quartiles (> 1.2 mm and > 1.4 mm). Patients with more advanced CAD had a higher prevalence of intima-media complex thicknesses in the two upper quartiles. However, 21% of patients without significant CAD had IMTs in the third and forth quartiles, which is connected with the presence of plaque formation. Similarly, 4.4% of patients with three vessel CAD had IMTs in the lowest quartile.

To establish the independent value of IMT in predicting CAD we used discriminant analysis. To find how IMT behaves as a predictor of CAD severity in the presence of other important risk factor we included age, sex, hypertension, diabetes, hyperlipidaemia, cigarette smoking, and IMT in analysis. After a stepwise selection procedure we found four independent predictors of CAD in the final discrimination function: age (p = 0.0193), hyperlipidaemia (p < 0.0001), smoking (p = 0.0032), and IMT (p < 0.0001).

We also created theoretical log normal distributions of IMT for patients with and without CAD, first by drawing simple histograms, then by using them as the basis for drawing mean IMT distribution curves (fig 2). We took 1.15 mm as the cut off point. For that value we calculated the discriminating power of mean IMT measurements for patients with and without CAD. Notably, the theoretical distributions of IMT showed that patients with a mean IMT over 1.15 mm had a 94% probability of having CAD, with a sensitivity of 65% and specificity of 80%.

Furthermore, we sought the cut off points that would facilitate the allocation of patients into one, two, and three vessel CAD categories (fig 3). However, because of the overlapping distributions of IMT, this allocation procedure proved inadequate (fig 4).

We found that the number of critically stenosed carotid and vertebral arteries increased with advancing CAD (table 3). Among patients with normal coronary arteries none had severe stenosis of the aortic arch arteries, whereas we found severe stenosis of the internal carotid, vertebral, or subclavian artery in six (3.8%) of the patients with one vessel CAD. Furthermore, we found a critical stenosis of these arteries in nine patients (8.7%) with two vessel CAD and in 34 patients (16.6%) with three vessel CAD (analysis of variance p = 0.0001).

DISCUSSION

Association between IMT of the carotid arteries and prevalence of CAD

Our study group consisted of patients admitted to the department with suspected CAD. The majority of our patients had additional risk factors, a positive treadmill test, segmental hypokinesis or akinesis on echocardiography, ischaemic changes on ECG, or symptoms suggesting angina in functional class II or more. However, despite the high likelihood of CAD 17% (95 patients) of these patients appeared not to have atherosclerotic lesions within their coronary arteries.

B mode ultrasonography of the carotid arteries, mainly thanks to the sufficient visualisation of carotid wall structures, offers the potential for effective evaluation of early atherosclerotic changes, such as thickening of the intima-media complex and non-significant carotid plaques, and brings into focus the possibility of monitoring atherosclerotic progress in peripheral arteries. This imaging technique may also hold some potential for predicting atherosclerotic lesions in vital arteries, such as coronary arteries or the aorta.

Many investigators have evaluated associations between the risk factors and mean IMT, as well as between the changes in risk factor levels and progression or regression in the thickness of the intima-media complex in the carotid arteries. They found that the thickness of the intima-media complex increases with age, sex, hypertension, diabetes mellitus, hyperlipidaemia, and many other factors.

Other studies compared IMT with the incidence of clinically symptomatic CAD and the extent or incidence of
increased intima-media thickness and extent of CAD 

Table 2 Distribution of mean intima-media thickness (IMT) in 558 patients with and without CAD

<table>
<thead>
<tr>
<th>Patients</th>
<th>Lower quartile</th>
<th>Second quartile</th>
<th>Third quartile</th>
<th>Upper quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 (28.4%)</td>
<td>11 (11.6%)</td>
<td>2 (2.1%)</td>
<td>95 (57.9%)</td>
<td>22 (47.3%)</td>
</tr>
<tr>
<td>17 (16.3%)</td>
<td>36 (34.6%)</td>
<td>22 (21.2%)</td>
<td>104 (29.3%)</td>
<td>30 (14.6%)</td>
</tr>
<tr>
<td>9 (4.4%)</td>
<td>69 (33.7%)</td>
<td>97 (47.3%)</td>
<td>205 (9.4%)</td>
<td>30 (14.6%)</td>
</tr>
</tbody>
</table>

Table 3 Coronary artery status and severe stenosis (≥70%)

<table>
<thead>
<tr>
<th>No of stenosed coronary arteries (≥50%)</th>
<th>Patients</th>
<th>Patients with stenosis</th>
<th>Stenoses of SA (≥70%)</th>
<th>Stenoses of VA (≥70%)</th>
<th>Stenoses of ICA (≥70%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>95 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1</td>
<td>104 (9.8%)</td>
<td>4 (3.8%)</td>
<td>11 (8.6%)</td>
<td>3 (2.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>2</td>
<td>305 (34.1%)</td>
<td>23 (6.9%)</td>
<td>3 (2.4%)</td>
<td>3 (2.4%)</td>
<td>39 (2.4%)</td>
</tr>
<tr>
<td>Total (patients with CAD)</td>
<td>463 (10.6%)</td>
<td>7 (7.7%)</td>
<td>7 (7.7%)</td>
<td>47 (10.6%)</td>
<td></td>
</tr>
</tbody>
</table>

ICA, internal carotid artery; SA, subclavian artery; VA, vertebral artery.
with more advanced CAD might have had some influence on IMT, but these factors are also associated with higher risk of atherosclerosis.

Regrettably, the extent of CAD cannot be predicted solely by the advancement of atherosclerosis in the carotid arteries. All attempts at allocating patients into groups with one, two, and three vessel CAD failed in our study as they did in the study of Adams et al.24 However, increasing mean IMT is strongly associated with more advanced CAD.

The significance of severe carotid and vertebral stenosis in patients with CAD

Our study indicates that advancing CAD is related to a gradually increasing rate of concomitant severe atherosclerosis in the extracranial arteries. Of 463 patients with at least one vessel CAD, 49 (10.6%) had coexisting stenosis of the extracranial arteries of ≥ 70%, whereas none of 95 patients without CAD had significant stenosis of the extracranial arteries. Furthermore, among patients with two and three vessel CAD, severe stenosis of the extracranial arteries was found in 8.6% and 16.6% of patients, respectively. Also, other investigators have found a high incidence of carotid and symptomatic coronary heart disease, estimated at 10–20%, among patients with two and three vessel CAD.

Among patients for whom coronary artery bypass grafting the coexisting severe stenosis of carotid or vertebral arteries increases the periprocedural risk of stroke.26 Early diagnosis of concomitant carotid stenosis may affect the revascularisation strategy. Some patients may benefit from simultaneous coronary and carotid operations.14 Optionally, patients at high risk with advanced but stable CAD may require prior intervention in the carotid arteries followed by coronary intervention.27–31

Conclusions

We found, firstly, that IMT increases with advancing CAD; secondly, that patients with a mean IMT over 1.15 mm have a high likelihood (94%) of CAD (ultrasound examination of the carotid arteries can effectively predict atherosclerosis of the coronary arteries; and thirdly, that there is relatively high coexistence of CAD with severe aortic arch arteries stenosis. Ultrasound examination of the carotid and vertebral arteries should be considered for patients with advanced CAD who will be undergoing coronary artery bypass grafting.

Authors’ affiliations
A Kablak-Ziembicka, W Tracz, T Przewlocki, P Pieniazek, M Konieczynska, Department of Cardiac and Vascular Diseases, The John Paul II Hospital, Krakow, Poland
A Sokolowski, Krakow University of Economics, Krakow, Poland

REFERENCES