

Carotid and femoral atherosclerotic lesions in patients with coronary heart disease confirmed by angiography

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Abstract

Introduction: Clinically evident atherosclerosis is preceded by preclinical changes in the arterial wall. These changes are characterised by increased thickness of the intima-media complex (IMT).

Aims: A complex ultrasound assessment of the peripheral vessels as well as an attempt to find ultrasound parameters correlating with the burden of atherosclerotic lesions of the coronary arteries.

Methods: 231 patients who underwent both coronary angiography and ultrasound examination of the following arteries: common carotid artery (CCA), carotid bulb and common femoral artery (CFA) were enrolled. The IMT value, presence of plaque and Doppler blood flow parameters were evaluated. Selected clinical and biochemical risk factors of atherosclerosis were assessed. Two groups of patients were analysed: 200 patients with coronary artery disease confirmed by angiography (study group), and 31 patients with normal coronary arteries (control group).

Results: Significantly higher values of the IMT in the peripheral arteries were observed in patients with coronary artery lesions than in those without (CCA – 0.91 vs 0.61mm, carotid bulb – 1.31 vs 0.67 mm, CFA – 1.38 vs 0.63 respectively, $p < 0.0001$). Atherosclerotic plaques were present only in patients with coronary artery disease. Additionally, IMT values of the CCA, carotid bulb and CFA were significantly higher in patients with severe coronary artery disease (three vessel disease) than in patients with lesions in one or two coronary arteries.

Conclusions: Patients with coronary lesions present with increased IMT values and higher plaque occurrence. Complex ultrasound evaluation of different peripheral arteries (CCA, carotid bulb and CFA) may be used as part of the cardiovascular risk stratification.

Key words: atherosclerosis, peripheral artery ultrasound, intima-media thickness

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Introduction

Atherosclerosis is a generalised process that involves various blood vessels. It affects many arteries, leading to the symptoms of target organ ischaemia. Clinically evident atherosclerosis is preceded by preclinical arterial wall changes. These changes are characterised by increased thickness of the internal and medial membrane of the arterial wall (intima-media thickness – IMT), or by attenuation of blood-flow induced reactivity of the artery (flow-mediated dilatation – FMD). These parameters can be easily

assessed using ultrasound [1]. Ultrasound has the advantage of being a noninvasive and reproducible technology. The following superficial arteries are easily accessible for ultrasound examination: carotid, brachial and femoral artery.

Increased thickness of the arterial intima-media complex is commonly seen in early stages of atherosclerosis and when present it correlates well with the prevalence of classic cardiovascular risk factors, as well as with the presence of clinical symptoms [2-4]. IMT measurements may help to select

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high risk patients and evaluate the efficacy of the therapy used [5]. Furthermore, an aggressive preventive strategy reduces IMT progression in patients with peripheral vascular disease. Held et al. have shown that the risk of ischaemic heart disease (IHD) could be estimated based on the evidence of atheromatous plaques and common carotid artery IMT assessment [1]. It is however not clear yet whether IMT correlates with IHD progression. Some investigators showed the presence of such a relationship, whereas others indicated the low clinical relevance of the carotid artery IMT measurements which results from their insufficient sensitivity and specificity [6]. Also, there is no single peripheral vessel ultrasound parameter that could be used as a cardiovascular risk predictor.

The aim of the study was to perform a complex ultrasound assessment of the peripheral vessels (the carotid and femoral artery). Ultrasound parameters showing the best correlation with atherosclerosis burden were searched for. The sensitivity and specificity of ultrasound parameters of peripheral artery atherosclerotic changes in patients with confirmed coronary artery disease by angiography were assessed.

Methods

Patients

The study group was recruited from consecutive patients hospitalised in the Department of Cardiology, Medical University of Białystok from 2001 to 2003, who underwent coronary angiography due to symptoms of IHD.

Inclusion criteria consisted of male gender, age between 18 and 65 years, completed coronary angiography as well as transthoracic echocardiography and ultrasound examination of the carotid and femoral arteries. Selected clinical and biochemical risk factors of atherosclerosis progression were assessed. Patients with known diabetes mellitus, symptomatic peripheral vascular disease or severe hypertension (retinal changes – stage III and IV, left ventricular hypertrophy evidenced by wall thickness of 1.5 cm or more by echocardiography) were excluded.

Following these criteria 231 patients were enrolled. According to the angiographic findings patients were divided into two groups: a study group of 200 patients with confirmed coronary artery disease, and a control group of 31 patients, in whom no significant coronary lesions were found. A significant coronary lesion was defined as lumen stenosis of more than 50%. Depending on the number of vessels involved, the changes were classified as single, two, or three vessel disease. There were 85 patients with single vessel disease, 58 patients with two vessel disease and 57 patients with significant three vessel disease. Detailed characteristics of the two groups are given in Table I.

The control group consisted of younger patients, smoking less frequently, with lower diastolic blood pressure, higher HDL cholesterol levels, lower triglycerides and fibrinogen levels, and lower platelet counts. Impaired fasting glucose, impaired glucose tolerance and diabetes were also significantly less frequent in this group. LV ejection fraction assessed by echocardiography was significantly higher in the control group.

Clinical evaluation included blood pressure measurements, resting ECG recording, exercise stress test, transthoracic echocardiography, coronary angiography, and carotid and femoral artery ultrasound examination. Total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride and fibrinogen plasma levels and platelet counts were measured. An oral glucose tolerance test was also performed. Indications for coronary angiography were established based on the assessment of clinical symptoms and work-up results (according to the Polish Cardiac Society guidelines). Standard angiographic projections and femoral access were used.

Ultrasonography

Examination of the carotid and femoral arteries was performed with an ultrasound device (Sonos 5500) equipped with a 3-11 MHz linear-array high-resolution transducer, using dedicated software for B-mode analysis, as described elsewhere [7]. The following parameters were measured: 1. intima-media thickness (IMT), 2. the presence of atheromatous plaques in the vessel, 3. Doppler blood flow parameters.

The common carotid artery (CCA) was scanned along a 10 mm-long segment from the carotid bulb. The common femoral artery (CFA) was examined along a 10 mm-long segment proximal to the origin of the deep femoral artery. In some patients images of the internal carotid artery (ICA) were of inadequate quality, resulting in the ICA being excluded from further analysis. IMT measurements were made for the distal wall, because the IMT assessment for the proximal wall is complicated by the higher echo density of the adventitia than of the media and intima. The distance between the first clearly delineated bright line (the lumen/intima interface) and second bright line (the media/adventitia interface) of the distal wall was measured as the IMT. For each analysed segment of the vessel two IMT measurements were taken and an average calculated. Maximum IMT values were used for further calculations. A plaque was defined as IMT of more than 1.3 mm. The CCA and CFA blood flow Doppler parameters were evaluated with the sample gate placed in the middle of the vessel lumen at an angle corrected to 60°. The blood flow velocity spectrum was recorded, and then the pulsatility index (PI) and resistance index (RI) were calculated, based on the following formulae:

Table I. Patient characteristics

	Study group (n=200)	Control group (n=31)	p<
Age [years]	52.8±8.4	45.9±10.5	0.001
Smoking [n]	137 (68.5%)	11 (35.5%)	0.001
BMI [kg/m ²]	27.6±3.8	26.8±3.3	NS
Systolic BP [mmHg]	142.7±20.6	136.1±19.9	NS
Diastolic BP [mmHg]	92.1±13.4	85.6±11.5	0.05
Total cholesterol [mg%]	181.7±37.1	174.0±32.9	NS
LDL – cholesterol [mg%]	112.2±33.5	104.0±28.9	NS
HDL – cholesterol [mg%]	38.3±8.6	44.5±13.5	0.05
Triglycerides [mg%]	156.0±65.0	120.3±36.2	0.01
Impaired fasting glucose* (n)	8 (4%)	0 (0%)	
Impaired glucose tolerance* (n)	65 (32.5%)	5 (16.1%)	=0.0001
Diabetes (n) *	39 (19.5%)	1 (3.2%)	
Fibrinogen [mg%]	423.2±110.8	364.8±124.4	0.01
Platelet count [thou./mm ³]	231.8±80.3	198.1±54.1	0.05
Ejection fraction (%)	46.2±8.3	52.0±13.3	0.01

* Impaired glucose control diagnosed during hospitalisation, based on the OGTT

PI = $V_{max} - V_{min} / V_{mean}$ (V_{max} – maximum velocity, V_{min} – minimum velocity, V_{mean} – mean velocity);
 RI = $V_{max} - V_{ed} / V_{max}$ (end diastolic velocity, V_{ed}).

All patients gave their written consent for participation in the study. The study protocol was approved by the local Ethics Committee.

Statistical analysis

The mean values and standard deviations for quantitative variables and also the quantitative and percentage distribution for qualitative variables were calculated. Pearson's correlation coefficient was calculated for categorical variables of normal distribution, and Spearman's correlation coefficient for variables not satisfying normal distribution criteria. To

compare the groups, statistical analysis for variables of normal distribution, estimated using the Kolomogorow compatibility test, was carried out using the unpaired Student's test and Mann-Whitney test for variables inconsistent with a normal distribution. A comparison of qualitative variables between the groups was performed using the Chi² test. A p value of <0.05 was considered statistically significant.

The statistical analysis was carried out using SPSS 8.0 PL and Statistica 6.0 PL software.

Results

Significant differences in the IMT values measured in the CCA, carotid bulb and CFA between the two groups were observed (Figure 1). In the control group, the borderline IMT value (75th percentile) was 0.68 mm in the CCA, 0.74 mm in the carotid bulb and 0.71 mm in the CFA.

In patients with significant coronary artery disease, IMT values above the 75th percentile were as follows: for the CCA – 1.0 mm, carotid bulb – 1.52 mm, CFA – 1.74 mm. Thus, the IMT value of the peripheral vessels was significantly higher in the study group than in the control group. Arbitrarily accepting an upper limit of 95% confidence interval for the mean value in a group of healthy individuals as the cut-off point, the sensitivity and specificity of the IMT measurements in the CCA were 91% and 65% respectively, in the carotid bulb 98% and 68%, and in the CFA 92% and 74%.

Blood flow Doppler parameters (RI and PI) measured in the CCA and CFA are shown in Table II. There was no

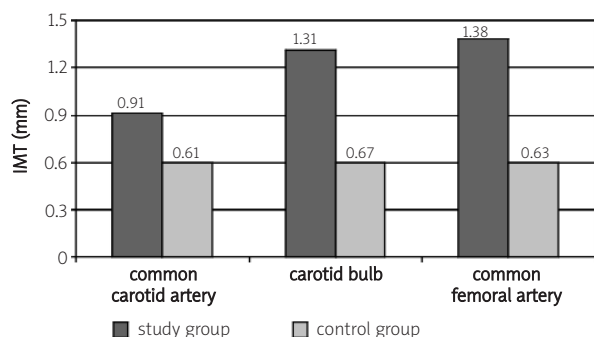


Figure 1. Comparison of IMT values between study group patients and controls (all differences significant with $p < 0.0001$)

Table II. Doppler blood flow parameters in the peripheral vessels

CCA	Study group	Control group	p
RI	0.73±0.06	0.72±0.09	NS
PI	1.73±0.83	1.71±0.58	NS
CFA	Study group	Control group	p
RI	0.97±0.04	0.98±0.05	NS
PI	5.94±2.24	6.23±2.68	NS

Table III. Plaque occurrence in the peripheral arteries and severity of coronary lesions

Patients with coronary artery disease:	Plaque occurrence in the peripheral vessels		
	common carotid artery	Carotid bulb	common femoral artery
1 vessel	6 (7%)	29 (34%)	27 (32%)
2 vessels	1 (2%)	18 (31%)	33 (57%)
3 vessels	6 (11%)	31 (54%)	40 (70%)

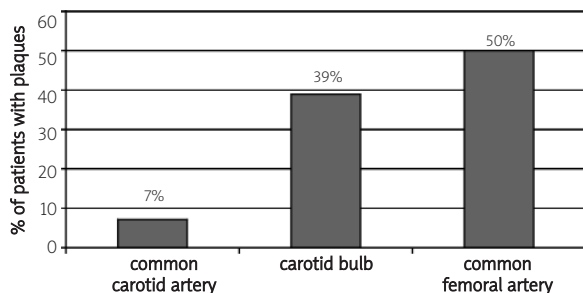


Figure 2. Plaque occurrence in the CCA, carotid bulb and CFA in the study group patients

significant difference between the study and the control group with respect to these parameters.

Plaques in the carotid bulb and in the CFA were found only in the study group patients (Figure 2).

The relationship between IMT values for peripheral arteries and the severity of coronary lesions is presented in Figures 3-5. IMT values for the CCA, carotid bulb and CFA were significantly higher in patients with three vessel disease than in patients with lesions in one or two vessels.

The relationship between the occurrence of the plaques in peripheral arteries and the severity of coronary lesions is shown in Table III. The plaques in the CCA were significantly more frequent in patients with three vessel disease than in patients with lesions in two vessels. Also, plaque occurrence in the carotid bulb was significantly higher in patients with three vessel disease than in patients with single or two vessel disease. The mean plaque number per patient

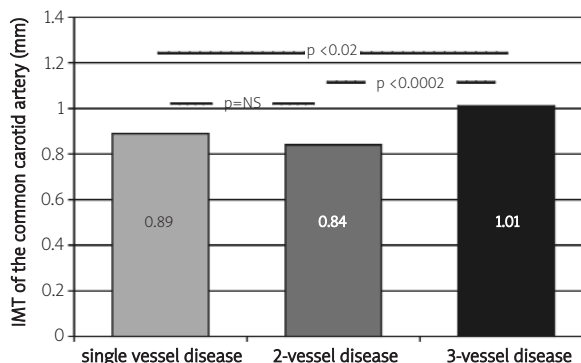


Figure 3. CCA IMT measurements and coronary artery lesions

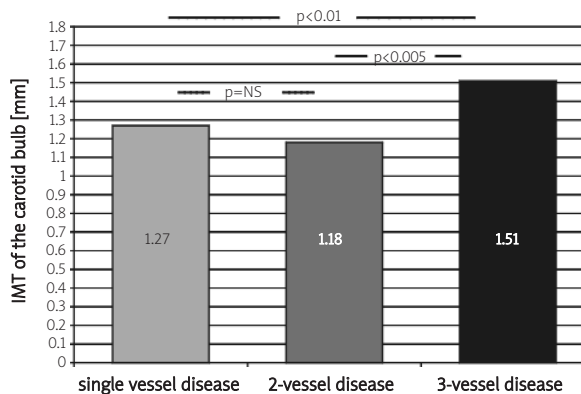


Figure 4. Carotid bulb IMT measurements and coronary artery lesions

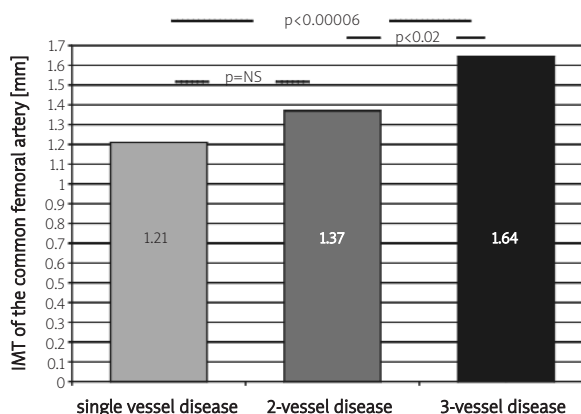


Figure 5. CFA IMT measurements and coronary artery lesions

with single vessel disease was 0.73, with two vessel disease 0.93, and with three vessel disease 1.35.

Discussion

The majority of studies published so far have assessed only CCA IMT; in some of them carotid bulb IMTs were also evaluated, while only in a few reports were CFA IMT measurements presented. Our study revealed that atherosclerotic lesions were more severe in the CFA than in the carotid arteries. Thus, an isolated CCA IMT measurement may be an inadequate parameter of systemic atherosclerosis [8], because its sensitivity and specificity are too low to identify patients with significant coronary artery disease and healthy subjects [6].

It has been demonstrated that a complex evaluation of CCA and carotid bulb IMTs increases the predictive value of these measurements [9]. Thus, in our opinion, based on the results reported here, IMT in another arterial region should be measured, e.g. in the carotid bulb and internal carotid artery proximal segment (ICA), as nonlinear blood flow facilitates plaque formation in these areas [10]. In some patients ICA wall imaging is difficult; thus, this parameter was excluded from the analysis in our study, and ultrasound evaluation was added to CFA IMT measurement.

Another difficult problem with ultrasound examination is to differentiate whether an increased CCA IMT value is the result of intima thickening, reflecting local atherogenesis, or of media thickening, which is a consequence of arterial wall hypertrophy [8]. To avoid the uncertainty, patients with severe hypertension were excluded from the study.

The results of our IMT measurements are consistent with those reported by Hulthe et al. [11]. However, unlike in their study, the occurrence of CCA plaques significantly correlated with the severity of atherosclerotic lesions in the carotid bulb and CFA. This may suggest that ultrasound IMT assessment in several arterial regions possibly increases the diagnostic value of the method. Hulthe et al. reported an association between IMT of the carotid bulb and the severity of coronary lesions [11]. A similar association for CCA and CFA IMTs was not observed in their study [11]. Unlike other investigations [11], the results of our study seem to indicate a significant correlation between various vessel segment IMTs, e.g. CCA, carotid bulb and CFA. These IMTs significantly correlated with plaque occurrence. The absence of plaques in the control group could be attributed to the fact that these patients were at a low cardiovascular risk.

In order to improve the diagnostic value of peripheral vessel ultrasound, apart from IMT measurements and plaque occurrence, the following blood flow Doppler parameters were assessed: pulsatility index (PI) and resistance index (RI). The normal RI value measured in the carotid artery should remain within the range of 0.55-0.75. Increased values usually indicate peripheral

stenosis of the artery, and pulsatility index decreases with vessel lumen diameter reduction [12]. In our study no significant differences in blood flow Doppler parameters (PI and RI indices) for the CCA and CFA between the study and the control group were found. This may support the hypothesis that IMTs reflect the severity of preclinical atherosclerosis, when blood flow turbulence and Doppler parameter changes are still absent.

This study revealed significantly higher peripheral artery IMTs in patients with significant coronary heart disease than in patients with normal coronary angiograms. Additionally, CCA, carotid bulb and CFA IMTs were significantly higher in patients with severe IHD (three vessel disease) than in patients with single or two coronary vessels involved. This finding confirms the value of peripheral artery IMT measurements as predictors of coronary atherosclerosis severity.

It should be emphasized that the results of studies investigating the relationship between CCA IMTs and the severity of coronary atherosclerosis are inconclusive. A significant correlation between CCA IMT and coronary lesions was reported by Wofford et al. [13]. A similar relationship was demonstrated in a large group of over 500 patients by Kabłak-Ziembicka et al [14]. Their results are consistent with our findings. However, others, including Adams et al. [6] and Pasiński et al. [15], found only a weak correlation between the common carotid artery IMT and the presence and severity of coronary artery disease. On the other hand, they demonstrated significant correlations between common femoral artery IMT as well as peripheral artery plaque occurrence and coronary atherosclerosis [15]. Others suggested that common carotid artery IMTs were significantly higher only in patients with severe coronary artery lesions (90%) [16], as well as in relation to the number of vessels involved [17]. Raso et al. [17] reported that an increase of IMT of the CCA was associated with the number of stenotic coronary arteries, even after adjusting for such risk factors as age, gender, smoking, hypertension, hypercholesterolaemia and diabetes mellitus. The described differences may have been a result of selection bias and the complexity of ultrasound examinations.

In the AXA study, which included healthy subjects, a CCA IMT value above the 75th percentile was regarded abnormal in the oldest age category, i.e. above 50 years. The corresponding value was ≥ 0.70 mm [18]. In another study the mean IMT of the CCA in asymptomatic male patients was 0.68 mm [19]. These findings are consistent with our control group results. Carotid bulb IMT appeared to be the most sensitive parameter of coronary atherosclerosis prediction; however, as mentioned above, a complex evaluation of different arterial regions is recommended.

The value of our study is limited by the small size and heterogeneity of the control group. Because coronary angiography is an invasive diagnostic procedure, the control group included only patients with appropriate clinical indications. They differed from the study patients significantly in many aspects.

Conclusions

1. Significantly higher CCA, carotid bulb and CFA IMT values were found in patients with confirmed coronary artery disease than in patients without coronary lesions. Atherosclerotic plaques were found only in patients with coronary artery disease.
2. Higher peripheral vessel IMTs in patients with three vessel disease than in patients with single or two vessels involved indicate that IMT may reflect the severity of atherosclerosis.
3. As the assessment of a single parameter has been shown not to be of definite value in cardiovascular risk stratification, complex ultrasound evaluation of different peripheral arteries should be used.

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Ocena zmian miażdżycowych w tętnicy szyjnej i udowej u chorych z potwierdzoną koronarograficznie chorobą wieńcową

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Streszczenie

Wstęp: Jawną klinicznie miażdżycę poprzedza faza zmian przedklinicznych dotyczących ściany naczynia. Zmiany te charakteryzuje pogrubienie błony wewnętrznej i środkowej ściany tętnicy (ang. *intima-media thickness* – IMT).

Cel pracy: kompleksowa ocena ultrasonograficzna (USG) naczyń obwodowych oraz próba znalezienia wskaźników w badaniu USG, korelujących ze stopniem nasilenia miażdżycy w tętnicach wieńcowych.

Metodyka: Badaniem objęto 231 chorych poddanych koronarografii, którzy mieli równocześnie wykonywane badanie ultrasonograficzne naczyń: tętnicy szyjnej wspólnej (TSW), opuszki TSW i tętnicy udowej wspólnej (TUW). Oceniano IMT, obecność blaszek miażdżycowych oraz dopplerowskie parametry przepływu. Określano wybrane parametry kliniczne i biochemiczne ryzyka rozwoju miażdżycy. Analizowano 2 grupy chorych: 200 osób z potwierdzoną koronarograficznie chorobą wieńcową (grupa badana) i 31 pacjentów bez zmian w naczyniach wieńcowych (grupa kontrolna).

Wyniki: Wykazano znamienne większą wartość kompleksu IMT w tętnicach obwodowych u pacjentów ze zmianami w naczyniach wieńcowych w porównaniu do osób z prawidłową koronarografią (odpowiednio TSW -0,91 vs 0,61 mm, opuszka TSW -1,31 vs 0,67 mm, TUW -1,38 vs 0,63, $p < 0,0001$). Także blaszki miażdżycowe częściej występowały u pacjentów grupy badanej. Nie stwierdzono ich obecności w grupie kontrolnej. Dodatkowo, wartość IMT w TSW, opuszce TSW i w TUW była znamienne większa u chorych z zaawansowaną chorobą wieńcową (zmiany trójnaczyńniowe) w stosunku do pacjentów ze zwężeniem jednej czy dwóch tętnic wieńcowych.

Wnioski: Chorzy ze zmianami w naczyniach wieńcowych wykazują pogrubienie kompleksu intima-media oraz częstsze występowanie blaszek miażdżycowych. Dla stratyfikacji ryzyka sercowo-naczyniowego celowa jest ocena ultrasonograficzna różnych naczyń obwodowych (TSW, opuszka TSW i TUW).

Słowa kluczowe: miażdżycy, badanie ultrasonograficzne tętnic obwodowych, kompleks błona wewnętrzna-błona środkowa (IMT)

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