Clinical Research

Ultrasound screening of multifocal atherosclerosis: markers for coronary heart disease

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Background and Objective The frequency of multifocal atherosclerosis (MFA) in patients with coronary heart disease (CHD) has not been thoroughly studied. The purpose of our study was to perform ultrasound screening for MFA in patients with coronary atherosclerosis and make evaluation of the sensitivity and significance of different atherosclerosis markers. Methods Using Color Duplex Ultrasound (CDU), we studied 32 clinically healthy persons and 87 patients of the city of B with clinical data for CHD where we also performed coronaryography. Results In patients with coronary atherosclerosis we found high frequency of carotid atherosclerosis (93%) and peripheral artery disease (PAD) (81%). We established verifiable thickening of the intima-media (IMT) of the common carotid artery (CCA) and common femoral artery (CFA) in patients with CHD. There is a correlation between the frequency of carotid and femoral stenoses and CHD proven by coronaryography. Patients with CHD had a high relative risk to develop carotid (RR = 5) and peripheral atherosclerosis (RR = 3.5) and high frequency of asymptomatic stenoses and thromboses of the internal carotid artery (86.9%) and femoral artery (78.3%), as well as aneurisms of the abdominal aorta (8.1%). Markers for CAD with high sensitivity were the atherosclerotic plaques of ICA (0.93) and CFA (0.81) as well as IMT of the CFA (0.84). Conclusions MFA are common among patients with CHD. Ultrasound diagnosis is the method of choice for simultaneous non-invasive screening of carotid, peripheral and MFA and provides sensitive markers for coronary atherosclerosis. The most sensitive and specific markers for CHD are the combination of the IMT and atherosclerotic plaques of CCA, ICA and CFA (100% sensitivity and 0.92 specificity). (J Geriatr Cardiol 2009; 6:31-37)

Key words Color Duplex; coronary heart disease; peripheral artery disease; carotid; femoral artery; atherosclerosis

Atherosclerosis is one of the most serious and socially consequential conditions. It is a leading cause of mortality in the developed countries. Its basic forms are the coronary, cerebro-vascular and peripheral disease. One of the main characteristics of atherosclerosis is its multifocality. The treatment of atherosclerosis presents a diagnostic and therapeutic problem because different affected areas are usually investigated by different types of specialists—cardiologists, neurologists, angiologists, and gastroenterologists. Another important problem is the fact that in many of the patients with coronary atherosclerosis, carotid pathology and peripheral arterial disease (PAD), the condition progresses asymptomatically for a very long time. Probably only less than half of the patients develop clinical manifestations such as angina, transient ischemic attack (TIA) and claudicatio intermittens. In cases when an attack (a heart attack, stroke, visceral or peripheral attack) has already occurred and the patient has survived its acute phase, the treatment is extremely difficult and functional impairment of the organs and limbs is usually unavoidable.

Ultrasound screening holds a tremendous advantage over other diagnostic methods. It can be carried out on a large scale and in a non-invasive way on risk groups within ambulatory clinical institutions. Moreover, the carotid pathology and PAD, as well as the affected abdominal aorta and its visceral branches, can be screened simultaneously. Such an examination has a high diagnostic potential. Unfortunately, coronary atherosclerosis is practically inaccessible through such non-invasive investigation. The only reliable diagnosis here is achievable through coronary angiography, but the indication for its implementations is usually a clinically coronary heart disease (CHD), which considerably limits the circle of patients screened for coronary atherosclerosis. The familiar risk factors—hypertension, dislipidemia, diabetes, smoking, stress—don’t guarantee a presence of an atherosclerotic process. Because of this, a number of new markers for coronary atherosclerosis have been recently introduced.

In the last decades it is the changes in the intima-media thickness (IMT) of the carotid and, less frequently, the femoral artery, that have been used as a marker for coronary atherosclerosis. A number of multi-center studies have established a correlation between the increase over 1 mm of the IMT of common carotid artery (CCA), internal carotied artery (ICA) and common femoral artery (CFA) and the occurrence of coronary atherosclerosis. It has been established that there is a correlation between the increase in IMT and the frequency of the cardio-vascular complications. This makes IMT not only a marker of coronary sclerosis but also a risk factor for the development of

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a heart attack or stroke. According to other studies, however, IMT of the femoral artery is more sensitive as a marker than IMT of the common carotid artery. Still others claim that the carotid plaque is a much more sensitive marker than IMT.

The aim of the current study is to carry out ultrasound screening of multifocal atherosclerosis in the cases of patients with coronary atherosclerosis and, consequently, provide an evaluation of the sensitivity and potential of the different markers of atherosclerosis.

**Patient and methods**

**Patients**

A total of 119 patients (90 male and 29 female) with an average age of 61.4 ±10.9 were examined. The patients were divided into two groups. Group A comprised of 32 patients (18 males and 14 females, at an average age of 60.4 ±9.8 years) who had been clinically healthy, with no indications of atherosclerosis and risk factors including hypertension, diabetes, dislipidemia, smoking and a family history of such conditions. Group B included 87 patients (72 males and 15 females, at an average age of 61.4 ±11.2 years), with clinical indications of CHD.

The patients from groups A and B were examined anamnestically and clinically for the following risk factors of atherosclerosis: arterial hypertension, diabetes, dislipidemia, family history (of heart attacks, strokes, and vascular gangrene), obesity, stress, as well as for an additional factor-a belief in God. A history concerning possible coronary conditions, cerebrovascular disease (CVD) - TIA, stroke, chronic PAD, operations, and stenting, was taken into account as well.

**Color Dupplex screening**

Atherosclerotic plaques, stenoses and thromboses of a. carotis comunis (CCA), a. carotis interna (ICA) and a. femoralis communis (AFC) were examined by Color Dupplex Ultrasound (CDU). The degree of stenosis was measured in terms of European carotid surgery trial (ECST). The IMT of CCA and AFC was measured employing standard methods by means of measuring IMT of the distal vascular wall, in a 10 mm-long section before the bifurcation. Screening for aneurysms of the abdominal aorta (AAA) was also performed and the maximum diameter of the aorta was measured.

**Pulsed wave Doppler examination**

Using pulsed wave Doppler the systolic pressure of a. tibialis anterior, a. tibialis posterior and ankle-brachial index (ABI) was measured in all patients.

**Coronary angiography**

Coronary angiography was performed in all patients from group B. Analyzed was the degree of coronary stenoses/thromboses, along with the number of branches affected.

**Statistics**

All statistical analyses were done by a 2-sided test. Continuous variables were described as a mean ± standard deviation (SD), and categorical data were described with frequency and percentage. A 2-sided probability P value <0.05 was considered statistically significant.

**Results**

**Clinical characteristics of group B patients**

Coronary angiography showed coronary stenosis in 74 patients which consist group B1 (85% of the subjects in group B), while 13 patients (group B2) had no coronary stenosis. Risk factors of atherosclerosis and history of patients with and without coronary stenosis were shown in Tab 1.

It was found that among patients with angiographically proven coronary stenosis 50% had undergone a heart attack and 32% a coronary bypass or stenting, and over 80% of the patients had a history of advanced coronary atherosclerosis. 12% reported cardiovascular diseases (CVD) and 17% reported PAD.

A much higher frequency of risk factors of atherosclerosis, including diabetes, dislipidemia, smoking and hypertension, was found in patients with proven coronary stenosis rather than in those without coronary stenosis. Of interest is the factor “belief in God”, which is more frequent in patients without coronary stenosis than in those with coronary stenosis. The relative risk (RR) of development of coronary atherosclerosis in the case of non-believers is 1.4, (CI 95% CI 0.76-2.58).

**IMT parameter, stenosis, and thrombosis of the common carotid and femoral artery**

As shown in Tab 2, statistically significant increase of IMT in the two examined arteries was found in patients with coronary stenosis when compared to the control group and those patients in group B with negative coronographies.

In patients with proven coronary stenosis, high frequency of carotid and femoral atherosclerotic pathology was found (stenoses -93.2% in ICA and 81% in CFA; thromboses- 9.4 % in ICA and 16.2% in AFC ). All thromboses of the carotis were only diagnosed within our screening and 6 out of 7 (85.7%) had been developed asymptotically. The high frequency of carotid pathology affecting almost 100% of the patients with coronary stenoses was in no way reflected in the history of cerebral-vascular disease.

**Ankle-brachial index**

The values of ankle-brachial index (ABI) in the subjects of group A and those in group B without coronary stenosis were normal, (1.03±0.15 and 1.02±0.16, respectively), while in subjects from group B with proven
Table 1  Clinical characteristics of group B patients (n, %)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Patients with coronary stenosis (n=74) B1 group</th>
<th>Patients without coronary stenosis (n=13) B2 group</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypertension</td>
<td>72 (97.2)</td>
<td>11 (84.6)</td>
</tr>
<tr>
<td>diabetes</td>
<td>18 (24.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>dislipidemia</td>
<td>62 (83.7)</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>smoking</td>
<td>43 (58.1)</td>
<td>6 (46.1)</td>
</tr>
<tr>
<td>obesity</td>
<td>43 (58.1)</td>
<td>7 (53.8)</td>
</tr>
<tr>
<td>family history</td>
<td>37 (50)</td>
<td>6 (46.1)</td>
</tr>
<tr>
<td>stress</td>
<td>17 (22.9)</td>
<td>3 (23.0)</td>
</tr>
<tr>
<td>belief in God</td>
<td>26 (35.1)</td>
<td>7 (53.8)</td>
</tr>
</tbody>
</table>

History

CHD                  | 74 (100)                                        | 0 (0)                                            |
angina               | 13 (17.5)                                       | 0 (0)                                            |
heart attack          | 37 (50)                                         | 0 (0)                                            |
Coronary stenting    | 14 (13.5)                                       | 0 (0)                                            |
PAD                  | 13 (17.5)                                       | 0 (0)                                            |

Table 2  IMT parameter, stenosis, and thrombosis of the common carotid and femoral artery in patients of the 2 groups

<table>
<thead>
<tr>
<th>Group A (n=32)</th>
<th>Group B</th>
<th>Patients with coronary stenosis (n=74)</th>
<th>Patients without coronary stenosis (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT (mm, mean±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA</td>
<td>0.78±0.13</td>
<td>1.21±0.26</td>
<td>0.79±0.14</td>
</tr>
<tr>
<td>CFA</td>
<td>0.81±0.14</td>
<td>1.46±0.41</td>
<td>0.85±0.16</td>
</tr>
<tr>
<td>Stenosis (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA</td>
<td>0</td>
<td>14 (18.9)</td>
<td>0</td>
</tr>
<tr>
<td>ICA</td>
<td>0</td>
<td>69 (93.2)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>CFA</td>
<td>0</td>
<td>60 (81)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Thrombosis (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>0</td>
<td>7 (9.4)</td>
<td>0</td>
</tr>
<tr>
<td>AFS</td>
<td>0</td>
<td>12 (16.2)</td>
<td>0</td>
</tr>
</tbody>
</table>

*p<0.001

Coronary stenosis, the index was considerably reduced (0.76±0.21; P<0.001 compared to that of group A patients).

Maximum diameter of the abdominal aorta and aortic aneurysm

Using Color Duplex, the abdominal aorta of all patients under the renal arteries was examined. The mean maximum diameter of the aorta was 17±4 mm in group A subjects, which was smaller than that of patients with proven coronary stenosis in group B1 (23±8 mm, P< 0.001), but not significantly different from those without coronary stenosis in group B2 (18±5). Aortic aneurysm was found in 6 patients (8.1%) in patients with proven coronary stenosis.

Diagnostic ability of some markers for coronary heart disease

The sensitivity, specificity and other characteristics of IMT, as well as the presence of plaques of ICA and CFA and ABI, were established on the basis of the frequency and the correlation between the parameters examined by means of Color Duplex in the case of groups B1 and B2. The parameters shown in tables 3 can be used as markers for coronary atherosclerosis.
The sensitivity of IMT of CCA as a marker of atherosclerosis is unexpectedly low-0.36, while its specificity is relatively high-0.84. The accuracy of the method is low, its relative risk close to normal. Higher is the sensitivity of IMT of CFA-0.91, the accuracy of the method being-0.88, RR-2.0 ABI is a marker with a very low sensitivity-0.24, but with a high specificity-0.99. As a marker for coronary atherosclerosis, the plaque of ICA has a high sensitivity-0.93, specificity-0.69, high accuracy-0.89, RR =2.6. The plaque of AFC as a marker has relatively lower sensitivity but higher specificity. The combination of markers considerably increases the potential for screening for coronary atherosclerosis. The presence of plaques on the inner carotid and the common femoral artery is a marker with 0.97 sensitivity, 0.84 specificity, 0.95 accuracy of the method, and RR at 6.3. A combination of markers determined-thickening of IMT of ICA and CFA over 1 mm., combined with the presence of plaques on ICA and CFA - almost certainly indicates the presence of coronary atherosclerosis: sensitivity-1.0, specificity-0.92, positive predictive value-0.98, negatively predicted value-0.99, accuracy of the method-0.98, very high values of RR - > 10.

The changes in the abdominal aorta - found more often in the case of patients in group B1 (with proven coronary atherosclerosis) than in the case of patients in groups A and B2 - can be added to the aforementioned markers. In the case of 26 patients from group B1 - 35% - dilatation of AA exceeding 2 cm was found much more frequently than in the case of patients from the other groups. It was established, while studying the potential of this parameter as a marker for coronary atherosclerosis, that its sensitivity is relatively low-0.35, but its specificity is high-0.99, the accuracy of the method being-0.44, its positive prognostic value-0.86, its relative risk-1.2. Clearly, regardless of its weak sensitivity, the pathological distension of the abdominal aorta can be used as a marker for coronary atherosclerosis.

The data with regards to the high frequency of the risk factors contributing to atherosclerosis (hypertension, diabetes, dislipidemia, smoking, obesity and family history) in the case of patients with coronary atherosclerosis, demonstrated their significant role in the initiation and development of the process. The relatively low percentage of believers in God in the case of group B1-compared to group B2 is a fact that needs closer examination within a larger study. The fact could be explained in terms of the hypothesis that believers adapt more easily to stress than non-believers.

The statistically verified thickening of IMT of CCA and CFA in the case of the group of patients with coronary atherosclerosis-in contrast to the group of patients without coronary atherosclerosis-proves the link between the changes in IMT and coronary atherosclerosis. Such pathological changes have been established by a number of studies investigating the problem. IMT of CCA is more frequently used as a marker and risk factor for coronary atherosclerosis. There are, however, studies investigating the two arteries-the common carotid artery and the common femoral artery - in which it has been asserted that IMT of CFA is the more sensitive marker. Many studies prove the existence of a correlation between the pathological increase in IMT of CCA and the frequency of heart attack and stroke, the patients having been monitored for a period of 3 to 9 years. In most studies, a high frequency of the relative risk of coronary and cerebro-vascular incidents has been established.

**Discussion**

There is an increased risk of myocardial attack and brain stroke in the case of asymptomatic patients with thickening of IMT over 1 mm, and in the case of women, this risk is more pronounced. The Rotterdam study proves also that each increase in IMT with 0.16 mm increases the relative risk of heart attack and stroke 1.4 times. Similar studies have been carried out with regard to IMT of CFA as well as with regard to the two arteries. The significance of IMT as a predictor of coronary and cerebro-vascular complications, and a risk factor and marker for coronary and multifocal atherosclerosis, has been proven. Nevertheless, some authors point out that the increase in the IMT cannot be at-
tributed with absolute certainty to the initial atherosclerotic changes in the intima since the thickness of the media is measured as well. Besides, the thickening of the intima can be due to an intimal hyperplasia and intimal hypotrophy, two compensatory reactions to hemodynamic stress. This phenomenon is more clearly evidenced in the area of arterial bifurcation and can only provoke the development of intimal hypertrophy or the development of atherosclerotic plaque. Hence our assertion that it cannot be stated with certainty that the changes in IMT are due to early atherosclerosis. The two changes-IMT and the atherosclerotic plaque-may have a partly common pathogenesis.

Some studies have proven the direct correlation between the thickening of IMT and the development of atherosclerotic plaque of the carotid artery.\textsuperscript{10}

In summary, we can say that the changes in IMT of the carotid and common femoral artery have to do with coronary atherosclerosis and are a risk factor and predictor of the development of coronary and cerebro-vascular complications. But are these changes a sensitive marker of coronary atherosclerosis really?\textsuperscript{11}

Our data did not corroborate such supposition. Only 27 patients (36\%) from group B1 with advanced atherosclerosis-turned out to have had pathological changes in IMT exceeding 1 mm. The sensitivity of the method as a marker of atherosclerosis is low-0.36, the relative risk at 1.1. Much higher is the sensitivity of IMT of CFA, the relative risk involved being 2.0. This finding has been corroborated by other authors.\textsuperscript{8,9,17}

Studying ABI, as a risk factor, predictor and marker of coronary atherosclerosis\textsuperscript{13,14} we found its sensitivity very low: only 0.24, but the specificity was very high-0.99. A number of researches confirm the existence of a correlation between pathological ABI and coronary atherosclerosis, and the role of the pathological ABI as a risk factor and predictor of coronary and cerebro-vascular complications\textsuperscript{5,13,17,19,20}

This is due to the fact that the values of ABI bellow 0.9 are determined only in the cases of hemodynamic stenoses or thromboses in the peripheral arteries of the lower limbs, and are usually the results of PAD caused by atherosclerosis. Consequently, ABI and IMT should not be used as independent markers of coronary atherosclerosis.

A very high frequency of atherosclerotic pathology was established in studying the group of patients with coronarographically proven atherosclerosis in terms of atherosclerotic plaques, stenoses and thromboses of the inner carotid artery and the common femoral artery. When the plaque or the thrombosis of ICA is used as a marker of coronary atherosclerosis, the sensitivity of the method is very high-0.93. When the plaque of CFA is used as a marker of coronary atherosclerosis, the sensitivity of the method is relatively lower, but its specificity is higher. These data are confirmed by studies carried out by other authors. Proceeding from the assumption that atherosclerosis is a multifocal process, it is logical to assume the following. When an advanced atherosclerotic process (plaque) is ascertained in one or two key arteries of the body, it can be assumed with a very high degree of probability that a third group of arteries, the coronary arteries, are affected too. In order for the sensitivity and specificity of the markers to be increased, it is appropriate that the markers are combined. When two markers are used in combination high sensitivity-0.97 and high specificity-0.84 are manifested. The relative risk is high as well.

Because IMT is a specific marker, different from the atherosclerotic plaque, we studied the two types of markers, IMT and plaque of the two arteries (the carotid and common femoral) using a Color Duplex. In this way we achieved a very high sensitivity: (0.99), as well as very high specificity: (0.93), the RR was extremely high for coronary atherosclerosis.

While studying patients with proven coronary atherosclerosis, using ultrasound in order to determine the multifocality of the process, we established a very high frequency of concomitant atherosclerosis with other localizations. Atherosclerotic carotid pathology was found in the case of 93\% of the patients with coronary atherosclerosis. The common femoral artery was afflicted in 81\% of the cases. As a result of the progress in diagnostic methods, it is possible to detect the beginning atherosclerotic changes in the vessels and the high frequency of multifocal atherosclerosis. Most studies, including ours, establish 20-30\% and up to 50\% occurrence of multifocal atherosclerosis. More precise researches with extended criteria for diagnosing the disease-plaque over 2 mm-prove not only the multifocality of the process, but also the near simultaneous damage (on a different level) to the arteries of the body. The three basic forms of atherosclerosis-coronary, cerebro-vascular (carotid) and peripheral (PAD) develop simultaneously. The problem is that the frequency of the asymptomatic forms of atherosclerosis is very high. Six out of the altogether seven (85\%) carotid thromboses, and 25\% of the femoral thromboses diagnosed within our study, had developed asymptotically and were only detected through the screening that we carried out. Aside from thromboses, six of the patients from the group with coronary atherosclerosis, had also developed AAA asymptptomatically. This specificity of atherosclerosis-its long asymptomatic development-makes its timely clinical diagnosis very difficult. As a result, treatment often starts at a stage when serious damage to the organs—due to heart attack, brain stroke, and gangrene—has already occurred. From this point of view it is extremely important that an early diagnosis of atherosclerosis, in its different forms and localizations, is carried out. The screening of the hidden atherosclerotic damages in the case of high-risk patient groups is extremely important as well\textsuperscript{10,12,18,21} In this respect, the ultrasound Doppler diagnostic means-the color Duplex
and PW Doppler – are methods with tremendous potential both in the field of mass screening and the field of precise vascular diagnosing\textsuperscript{6,11,16,18,20-22}. Its diagnostic value is high and its cost negligent. Within one research, the following markers of atherosclerosis can be examined: IMT of CCA and CFA, plaques and stenoses of the two arteries, ABI and the diameter of AA under the renal arteries. All these parameters are diagnose multifocal atherosclerosis-the presence of an atherosclerotic process in the carotid, femoral or peripheral arteries. They can also be used as highly sensitive markers of coronary atherosclerosis and predictors of future complications. As a result, the complex examination of the patient and the use of combined markers can improve considerably the potential of early diagnosis. They also improve our capacity to discover early forms of multifocal atherosclerosis and, in particular, our capacity to screen for coronary atherosclerosis.

The most reliable marker of coronary atherosclerosis is the combination of atherosclerotic plaques of the carotid and femoral arteries, with or without changes in IMT of the two arteries. In addition to these markers ABI should be used also. Thus, an ultrasonic exam can solve several problems with regards to atherosclerosis.

Our study involves the simultaneous screening of the carotid, peripheral and abdominal-visceral form of atherosclerosis, and the beginning or asymptomatic forms of atherosclerosis are detected. By using a whole set of ultrasound markers, we can predict the presence of a hidden form of atherosclerosis-coronary atherosclerosis. Also, the method is appropriate for the handling of mass screening of risk groups. This advantage is extremely important, considering the aforementioned characteristics and specifics of atherosclerosis. And it must be mentioned that the method is relatively inexpensive.

On the basis of the study conducted the following major conclusions can be drawn: 1) Atherosclerosis is a multifocal condition affecting simultaneously the coronary, carotid and peripheral arteries, and occurring clinically as CHD, CVD and PAD. The MFA determined was 81%, and involved simultaneous damage to the coronary, carotid and femoral arteries. 2) The employing of CDS in the case of patients with coronary atherosclerosis led to the establishment of a high frequency of CAD (93%) and PAD (81%), including its early, preclinical forms. 3) There is a correlation between the frequency of occurrence of the carotid and femoral atherosclerotic plaques (stenoses) and the occurrence of the coronary angiographically proven CHD. Patients with CHD stand a high relative risk of developing carotid (RR=5) and peripheral atherosclerosis- PAD (RR=3.5). 4) In patients with CHD high frequency of clinically non-manifested asymptomatic stenoses and thromboses of a. carotis interna (86.9%) and a. femoralis (78.3%), as well as of aneurysms of the abdominal aorta (8.1%), was ascertained by ultrasound. This determines the necessity of screening for MFA in the case of all patients with CHD.

We established a relatively low sensitivity of IMT towards CCA (0.36) and ABI (0.24), and a high specificity as markers for CHD and that highly sensitive markers of CHD are the atherosclerotic plaques of ICA (0.93) and CFA (0.81), as well as IMT of CFA (0.84). The most sensitive and specific markers for CHD are the combination of the examination of IMT and the atherosclerotic plaques of CCA, ICA and CFA (100% sensitivity and 0.92 specificity).

Ultrasound diagnosis is a method of choice for an instantaneous, non-invasive screening of the carotid, peripheral, and multifocal atherosclerosis, and has sensitive markers for coronary atherosclerosis.

The thorough, early diagnosing of MFA employing coronary markers can make treatment with medications and endovascular treatment much more efficient. The mass ultrasound screening of risk groups for atherosclerosis can change dramatically our approach to this serious condition. It would redirect our attention towards the early asymptomatic stages of the condition, thus reducing the high rate of mortality and disability. The future of the treatment of atherosclerosis is in prophylaxis, early diagnosis, timely medication, and endovascular treatment. Such an approach can make coronary, carotid and peripheral vascular surgery a thing of the past.

References


