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The role of ultrasonography in the assessment of preclinical atherosclerosis

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Abstract

The diagnosis of preclinical atherosclerosis represents an important step in the precocious treatment of this important disease. There are various methods that can identify the early structural and functional modification of arterial wall by the exploration of coronary or peripheral arteries. Ultrasound techniques (flow mediated vasodilatation of the brachial artery, intima media thickness and arterial stiffness) are non invasive, relatively simple and rapid methods that are extensively used in research studies. Data of recent years showed their prognostic importance and recommends them for clinical practice.

Key words: preclinical atherosclerosis, ultrasonography, flow mediated vasodilatation, intima media thickness, arterial stiffness

Rezumat

Diagnosticul ateroclerozei preclinice reprezintă un pas important in tratamentul precoce al acestei boli. Exista azi variate metode ce pot identifica modificările structurale şi funcţionale ale pereţilor arteriali, la nivel coronarian şi periferic. Tehnicile ecografice (vasodilataţia arterei brahiale mediată de flux, grosimean intimă-medie, rigidiatea artrială) sunt metode relativ simple şi rapide şi sunt pe larg folosite în ultimii ani în cercetare. Datele acumulate în ultimii ani au dovedit importanţa acestora în prognosticul bolii, fiind recomandate pentru practica clinică.

Cuvinte cheie: aterosceroza subclinică, ecografia, vasodilataţia arterei brahiale mediată de flux, grosimean intimă-medie, rigidiatea artrială

It is increasingly recognised that the traditional risk factors such as age, gender, smoking, blood pressure, total and high-density lipoprotein cholesterol (HDL-C), can explain around 50% of the patient cardiovascular risk [1]. That is why beyond these factors other conditions that are emerging risk factors (hs-C reactive protein, fibrinogen and other markers of inflammation, the metabolic syndrome, hyperhomocysteinemia and instrumental markers of preclinical atherosclerosis) are now the subjects of research activities.

It has been shown that preclinical atherosclerosis increases global cardiovascular risk. Evaluation of atherosclerosis in its preclinical stage can help us to establish individual risk, to stratify patients with a high cardiovascular risk, and to introduce a new strategy of primary prevention in clinical practice. Recent efforts have now focused on preclinical evaluation of atherosclerosis using non-invasive imaging techniques. These methods are used for the assessment of carotid intima-medial thickness and asymptomatic carotid plaques, endothelial function, arterial stiffness, peripheral vascular disease and the morphology of coronary vessels [2].

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The function of vascular endothelium and the endothelial dysfunction

The vascular endothelium once considered a passive structure is, in fact, an important endocrine organ that intervene in the regulation of vascular tone, in thrombotic

and inflammatory processes, in platelet and leukocyte vessel – wall interactions, and in vascular permeability [3,4]. The endothelium plays a very important role in the mechanism of vasodilatation and vasoconstriction. Endothelial nitric oxide (NO) is a potent vasodilator and it has an important role in maintaining the vascular tone. It has also an antiatherogenic effect by inhibiting platelet aggregation, smooth muscle proliferation and expression of adhesion molecules [3,4,5].

Alteration of endothelial function is an early and potentially reversible modification of atherosclerosis [6]. Endothelial dysfunction is characterized by an impaired vasodilatation. This is associated with the classical vascular risk factors such as active and passive smoking [7,8], hypertension [9], obesity [10], diabetes [11], and hypercholesterolemia [12].

Endothelial dysfunction is present even in the absence of atherosclerotic plaques and it persists in symptomatic patients for whom it has also a prognostic significance [13].

Non-invasive measurement of endothelial function reveals the ability of peripheral arteries to dilate secondary to endothelial NO release in response to various exogenous and endogenous stimuli. Endothelial dysfunction is accompanied by a reduction of the quantity of NO released by endothelium decreases. A method used to assess non-invasively the endothelial function is *flow-mediated dilatation in the peripheral circulation*, a high resolution ultrasound technique. According to this method changes in brachial artery diameter and in Doppler velocity are measured after and endothelial dependent stimulation of increased blood flow or after an oral administration of endothelial-independent agonists such as glyceryl trinitrate [6].

In order to determine endothelium-dependent flow-mediated dilation, after baseline measurements of brachial artery diameter and velocity, a cuff of a sphygmomanometer is placed at the wrist or at above the antecubital fossa. The transducer is placed in an area approximately 7 cm proximal to the brachial bifurcation, where the artery can be identified in the longitudinal view. The cuff is inflated to at least 50 mmHg above systolic pressure to occlude arterial inflow. The ischemia caused by the vascular compression causes dilatation of the downstream vessels by an autoregulatory mechanism. The released of the cuff determine a reactive hyperaemia of brachial artery which induces shear stress that causes brachial artery dilatation. The occlusion in maintained usually for 5 minutes. The maximal dilator response occurs at approximately 1 min in healthy subjects [14,15]. The new devices can measure automatically the entire period of vasodilatation response, the peak response, the time to peak response, and the duration of flow mediated dilatation (fig 1, fig 2).

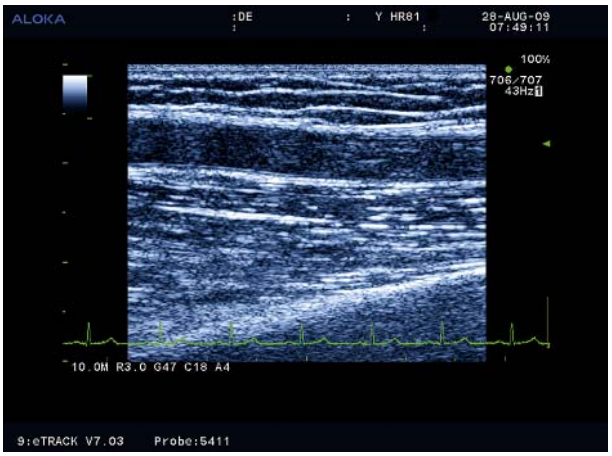


Fig 1. Ultrasound image of the brachial artery at baseline (B-mode image).

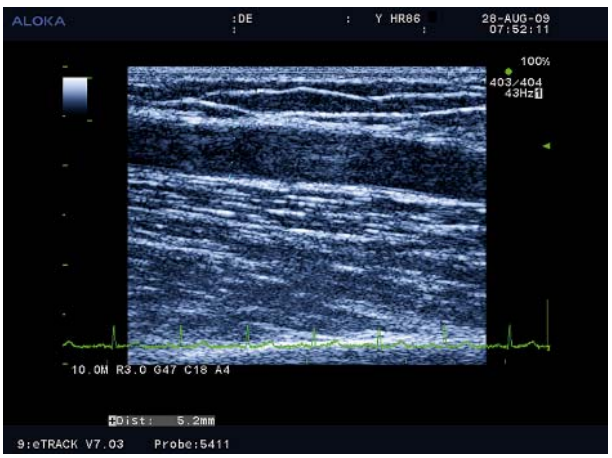


Fig 2. Brahial artery 1 min after cuff release (B-mode image).

It is considered that 70% of the dilation obtained 1 min after cuff release is determined by NO synthesis [16]. The inhibitors of the L-arginine-NO pathway block the dilatation response indicating that this reaction is secondary to NO released [17]. Cuff placement on the distal forearm produces a vasodilator effect greater than 5% and the placement of the cuff above the antecubital fossa is accompanied by a vasodilator response greater than 8%. Many factors can influence the vasodilator response such as age that reduces this response especially above 40 years in men and above 50 in women [2], and baseline diameter, a larger baseline diameter implies a smaller measure of percent change [18].

The method used for the measurement of endothelium-independent vasodilatation consists in the administration of an exogenous NO donor, such as a single high dose 0,4 mg of nitroglycerine spray or sublingual tablet.

The maximal vasodilatation is obtained 3 to 4 minutes after nitroglycerine administration and it reflects the smooth muscle function [19].

The flow-mediated dilation is now widely used as a noninvasive method of assessing the endothelial function and its integrity. Endothelial dysfunction is correlated with the presence of conventional cardiovascular risk factors and the treatment of these risk factors has been shown to improve brachial flow-mediated reactivity [2,20]. Reduced brachial artery flow-mediated vasodilatation is associated with a greater likelihood of coronary artery disease [22].

Flow-mediated dilation has also been used to assess the antiatherogenic effect of some therapeutic options, such as converting enzyme inhibitors [22,23], antioxidants [24], and statines [25].

Endothelial dysfunction is a very important and precocious sign of preclinical atherosclerosis. It precedes the structural changes of arterial wall such as carotid intima-medial thickness and arterial stiffness [21]. At present, assessment of endothelial function is an important research tool to improve our understanding of mechanisms of vascular disease and to determine the impact of novel therapeutic approaches on vascular function.

Carotid intima-media thickness

Another non-invasive method uses high resolution B-mode ultrasonography for the assessment of preclinical atherosclerosis is the measurement of carotid intima-media thickness (IMT).

Carotid atherosclerosis is correlated with coronary artery disease and cardiac risk. The increase in intima-media thickness is an early sign that reflects adaptation to elevated intravascular shear stress [26]. This determination has been used to estimate coronary artery events and the extent of atherosclerosis [27]. Histological studies have shown a close correlation between coronary and carotid modifications of atherosclerosis [28]. The increasing in carotid IMT and the aggravation of carotid atherosclerosis are associated with an increasing risk of important coronary artery lesions [29]. IMT is also an important and independent predictor for cerebrovascular events [30]. However, endothelial dysfunction expressed as impaired brachial artery reactivity may be an earlier predictor of coronary artery disease, with increased carotid IMT appearing at a later stage of atherogenesis [21].

Many methods have been used for the determination of carotid IMT. The intima - media layer is the distance between the media-adventitia interface and the intima–media interface. Measurements can be done at different levels that are all technically acceptable, common carotid, carotid bifurcation and internal carotid (fig 3). All sites appear to have the same value in the prediction of coronary artery events [31]. Most commonly is measured in B-mode, with linear ultrasound transducers between 7.5 and 10 MHz , preferably in the far wall, of the common carotid artery before its bifurcation (Fig.4). However, meta-analysis suggests that the mean maximum carotid IMT calculated from the circumferential scanning of the carotid artery is the most accurate measurement of the carotid atherosclerosis [32].

According to the ESC/ESH 2007 Guidelines on the Management of Arterial Hypertension the reference values for the evaluation of carotid atherosclerosis are:

– *normal IMT under 0,9 mm*
– *increased IMT, values between 0,9 and 1,5 mm*
– *asymptomatic carotid plaques values greater than 1,5 mm*

The ASE Consensus Statement recommended IMT measurements for patients at intermediate cardiovascular risk and in subjects with family history of premature car-

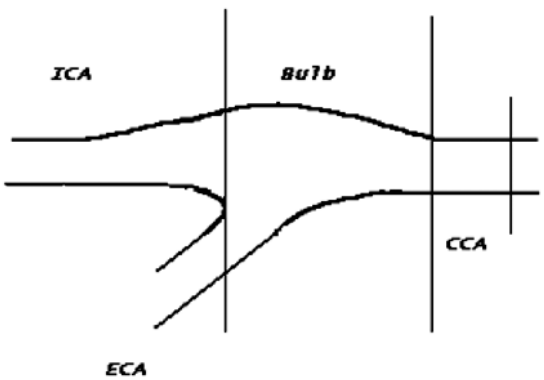


Fig 3. Carotid segments (common carotid, carotid bulb, bifurcation and internal carotid artery) used for the measurement of intima – media distance (vertical lines).

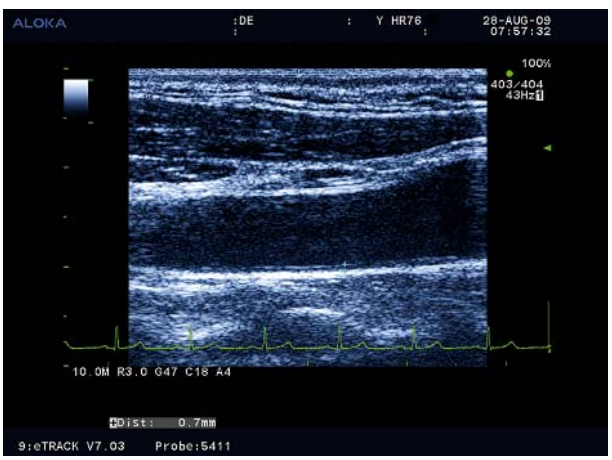


Fig 4. Measurement of intima - media thickness of the posterior wall of the common carotid artery (B-mode image).

diovascular disease in first-degree relatives, individuals younger than 60 years old with severe abnormalities in a single risk factor who otherwise would be not candidates for pharmacotherapy, women younger than 60 years of age with at least two cardiovascular risk factors in all epidemiological and interventional trials dealing with vascular diseases to better characterize the population investigated [33].

Arterial stiffness

Large arteries convert intermittent blood flow to steady flow. During systole aorta expends due to stoke volume and aortic pressure increases (systolic blood pressure). During diastole aortic walls recoil and the pressure is partially maintained (diastolic blood pressure). When an artery becomes stiffen the cushioning function is altered, the systolic blood pressure increases and the diastolic pressure diminishes. Measure of arterial stiffness evaluate the ability of an artery to expand and to contract with each cardiac cycle

Large artery stiffness is primarily determined by the balance between elastin and collagen content of arterial wall. The augmentation of collagen content caused, for example by advanced age, is associated with an increased arterial stiffness. Elevated smooth muscle tone and smooth muscle cell hypertrophy also increase arterial stiffness [34].

The degree of arterial stiffness is correlated with the risk of cardiovascular disease. It has been demonstrated that arterial stiffness is a powerful independent marker of vascular target organ and an independent predictor of cardiovascular morbidity and mortality [35,36,37].

In order to determine arterial stiffness parameters, the ultrasound transducer must direct ultrasound beams perpendicularly to the artery to obtain the optimal reflection from the wall. The maximum and the minimum areas of the vessel are calculated by wall tracking. Blood pressures are measured at the same time, usually in the brachial artery. The correlation between blood pressure and artery variation in diameter is used to determine the parameters of arterial stiffness. One of the most common is the stress–strain elastic modulus (Ep), the ration of stress (the difference in the systolic and diastolic blood pressure) to strain (the percent change in the arterial diameter during the cardiac cycle). It can also measure the arterial compliance and the stiffness index (the logarithm of the ratio of systolic to diastolic blood pressure divided by strain) [38].

The analysis of the pressure waveform allows to determine the augmentation index. Normal arterial pressure waveform is made of an incident wave and a reflected wave from smaller arteries downstream. The augmentation index attempts to measure the height of a reflected wave relative to the incident wave. In individuals with normal compliant arteries, the reflective wave will return during diastole and augment diastolic coronary blood flow (fig 5) [39].

The speed of the advancing wave represents the pulse wave velocity (PWV). The ultrasound device measures a local arterial PWV.

Carotid arterial stiffness is measured at 1 cm proximal to the origin of the bulb. Parameters of arterial stiffness are calculated automatically. A normal carotid artery is shown in the fig 6 obtained with an ALOKA alpha 10 Prosound Premium device.

Arterial stiffness causes an increase in PWV and a premature augmentation of the systolic waveform, forming a late systolic peak that determines left ventricular workload. (fig 7)

An abnormal carotid waveform in a case of arterial stiffness is shown in fig 8 and fig 9.

It has been shown that carotid arterial stiffness has an important value in predicting cardiovascular complications. In ARIC study lower carotid arterial distensibility increased the risk of developing hypertension in the future [40]. In patients with end stage renal disease, carotid stiffness is a predictor of cardiovascular and all-cause mortality [41]. Carotid arterial stiffness is also higher in the metabolic syndrome and markedly higher in type 2 diabetes mellitus patients [42].

Increased common carotid artery stiffness is associated with ischemic stroke independent of conventional risk factors [43]

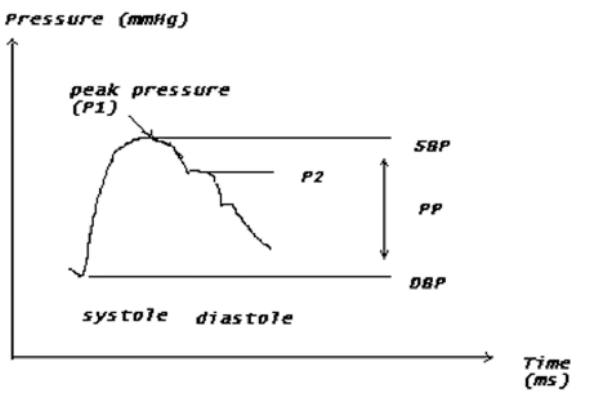


Fig 5. Common carotid pressure wave form of an elastic artery. PP is the pulse pressure – the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). (P2-P1) is the augmentation pressure – the difference between maximal pressure and pressure at the first peak on the pulse wave form. Augmentation index, (AI) is calculated as the ratio between the augmentation pressure and PP and is expressed in percentage: (P2-P1)/PP) x 100.

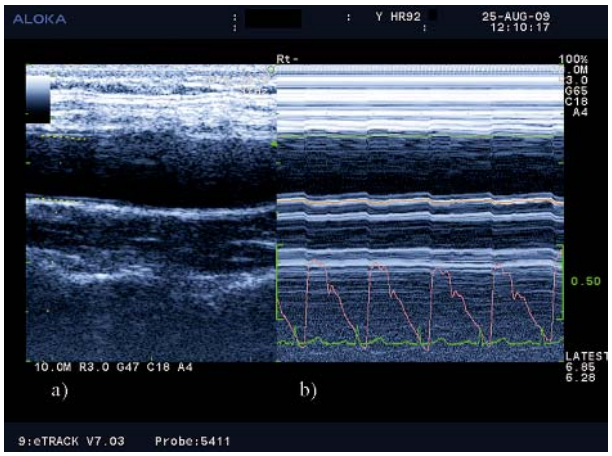


Fig 6. Common carotid artery with normal elasticity: a) the gate tracking in B-mode; b) the tracking in M-mode with 4 normal carotid waves.

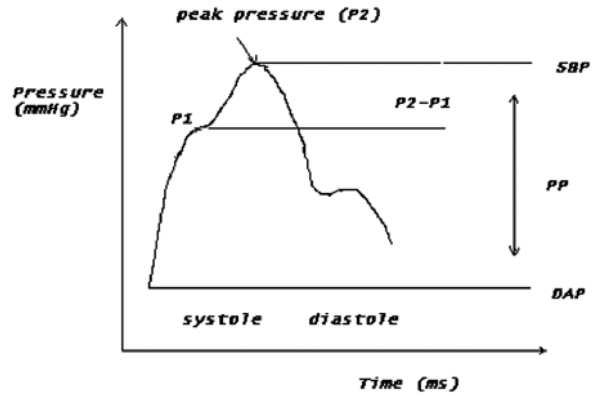


Fig 7. Common carotid pressure waveform – increased artery stiffness. Backwards wave from the periphery returns early to the aorta, during systole, increasing central systolic blood pressure (SBP) and decreasing central diastolic blood pressure (DBP). PP-pulse pressure. (P2-P1) – augmentation pressure.

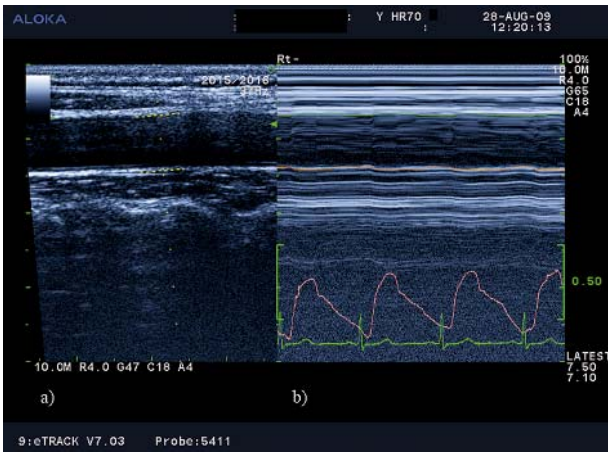


Fig 8. Common carotid artery of a young patient (35 years old) with diabetes mellitus type 1. *a)* the gate tracking in B-mode; *b)* the tracking in M-mode with 3 carotid waves.



Fig 9. Automatic analysis of the selected carotid waves; the stiffness parameters calculated are pathologic.

Carotid artery stiffness is also associated with clasical risk factors for atherosclerosis, such as smoking, proteinuria or low HDL-cholesterol levels [44,45,46].

Conclusions

All the ultrasound methods described before (flow mediated dilatation of brachial artery, intima-media thickness and measures of arterial stiffness), are non invasive, simple and no time consuming techniques useful for the assessment of early peripheral arterial damage.

The ultrasound methods for the determination of preclinical markers of atherosclerosis have shown their diagnostic and predictive values in many clinical studies and they are now increasingly used in clinical practice.

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