

SUBCLINICAL ATHEROSCLEROSIS DIAGNOSIS AND POTENTIAL CLINICAL IMPLICATIONS

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REZUMAT

Markerii aterosclerozei subclinice pot fi considerați fie mecanisme intermediare între factorii majori de risc și ateroscleroză, fie factori direct implicați în apariția complicațiilor bolii aterosclerotice. Odată cuantificați, ei pot modifica riscul evaluat pentru ateroscleroză a unui anumit subiect și aduc informații suplimentare importante pentru managementul bolii. Vom discuta principalii markeri ai aterosclerozei subclinice disponibili în practica clinică de rutină, valoarea lor diagnostică și prognostică, precum și potențialele implicații terapeutice.

Cuvinte cheie: ateroscleroză, disfuncție endotelială, rigiditate arterială, grosime intimă-medie, indice gleznă-brat

ABSTRACT

Markers of subclinical atherosclerosis can be considered either as intermediate mechanisms between most of the major risk factors and atherosclerosis, or as direct risk factors for the complications of the atherosclerotic disease. Once assessed, they can modify the evaluated risk for atherosclerotic disease of a particular subject, adding important information for its best management. We will discuss the main markers of subclinical atherosclerosis ready to be used in routine clinical practice, their diagnosis and prognostic value, and potential therapeutic implications.

Key Words: atherosclerosis, endothelial dysfunction, arterial stiffness, intima-media thickness, ankle-brachial index

INTRODUCTION

Markers of subclinical atherosclerosis have been described in the last decade, and were used mainly as research tools. Since some of them can be now assessed by commercially available devices, they are ready to be used in routine clinical practice. These are: (1) markers of endothelial dysfunction; (2) arterial stiffness; (3) intima-media thickness; and (4) the ankle-brachial index.

MARKERS OF ENDOTHELIAL DYSFUNCTION

The normal endothelium, an autocrine, paracrine, and endocrine organ, plays a key role in the vessel protection against atherosclerosis, by regulating vascular tone, lipid breakdown, inflammation, vessel growth, and thrombogenesis. Conventional risk factors can promote atherosclerosis by inducing endothelial dysfunction, through the decrease of bioavailability of nitric oxide (NO), which is the main mediator of the abovementioned endothelial functions.¹

A dysfunctional endothelium may lose its ability to exert its protective effect on the vascular system, and thus can be an important factor in the development and progression of the atherosclerotic process.^{1,2} This is not surprising, since it is well proved now that atherosclerosis initially involves the infiltration of LDL through the dysfunctional endothelium, followed by their oxidation in the arterial intima. Modification of LDL leads to the release of phospholipids that can

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potentate the dysfunction of the endothelium, with the activation of the inflammatory process and release of growth factors, resulting in vascular smooth muscle cell proliferation and collagen matrix production.³

Endothelial function is most commonly measured non-invasively as the vasodilator response to shear stress in the brachial artery, technique labeled as flow-mediated vasodilatation (FMD). (Fig. 1) Shear stress is induced by releasing a sphygmomanometric cuff after a 5-minutes over-inflation (at least 50 mmHg above systolic pressure in order to occlude the arterial inflow) at the forearm level. This induces a brief high-flow state through the brachial artery (reactive hyperemia), which provokes the endothelium to release nitric oxide with subsequent vasodilatation, that can be imaged and quantified by high-quality ultrasounds technique. Flow-mediated vasodilatation (FMD) is typically expressed as the change in post- shear stress diameter as a percentage of the baseline diameter.¹

Although this technique assesses only the vasomotor function of the endothelium, it is attractive because it is non-invasive and allows repeated measurements.¹ Moreover, there are important data suggesting that forearm endothelial dysfunction is a marker of future cardiovascular events.² (Fig. 2) Since flow-mediated vasodilatation is now an expanding technique, being commercially available on the new-generation echocardiographic machines, we might speculate that assessment of endothelial function will be an important step in the evaluation of the atherosclerotic risk in the near future.

Another marker of endothelial function, indicating the hyperpermeability of endothelium to macromolecules, is the microalbuminuria. An urinary albumin secretion of more than 10 mg/24 h (corresponding to an urinary albumine/creatinine ratio of > 1 mg/mmol) is associated with a significant increase in the risk of atherosclerotic disease in the general population.⁴

Endothelial dysfunction can now be targeted with different therapeutic strategies, such as statins, ACE-inhibitors, nebivolol, etc.¹ However, how much this technique can add to the current risk assessment scores and how it can be used to monitor treatment needs further evaluation.

ARTERIAL STIFFNESS

Endothelial dysfunction and incipient atherosclerosis make arteries to get stiffer and, therefore, increased arterial stiffness is now considered a marker of subclinical atherosclerosis.

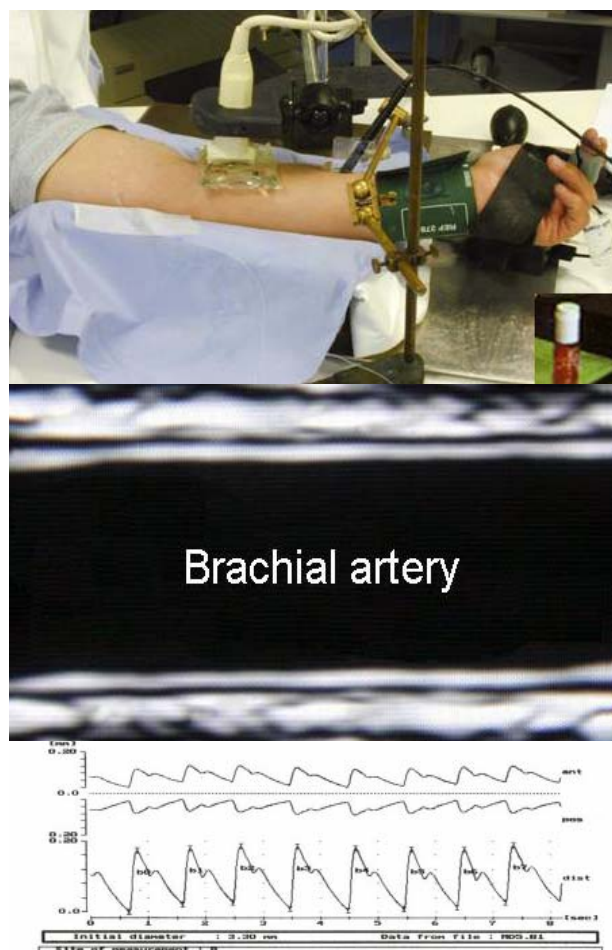


Figure 1. Assessment of endothelial dysfunction by flow mediated vasodilatation (FMD). **Upper panel:** ultrasound probe, positioned using a probe-holder, imaging the brachial artery; shear stress is induced by releasing a sphygmomanometric cuff after a 5-minutes over-inflation (at least 50 mmHg above systolic blood pressure in order to occlude the arterial inflow) at the forearm level. **Mid panel:** high-quality ultrasound image of the brachial artery. **Lower panel:** anterior and posterior wall tracking of the brachial artery, with the beat-to-beat variations of the arterial diameter; diameter is measured at baseline and after reactive hyperemia, and flow-mediated vasodilatation (FMD) is typically expressed as the change in post-shear stress diameter as a percentage of the baseline diameter.

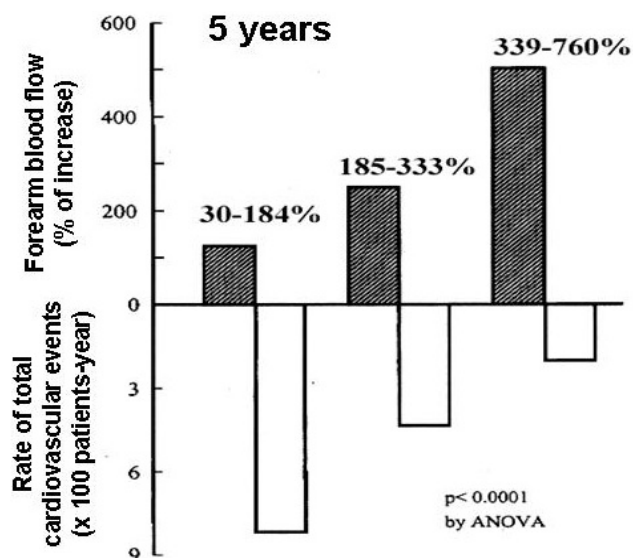


Figure 2. Rate of total (fatal and nonfatal) cardiovascular events and mean values of percent increase in forearm endothelial function, in tertiles.²

Stiffness, or reduced compliance of large arteries, modifies arterial wave reflection timing. Ventricular ejection generates a primary (or forward) pressure wave, which moves away from the heart at a speed labeled pulse wave velocity (PWV). The incident wave is reflected from the arterial tree, generating a backward wave, traveling towards the heart. In young subjects, the pulse wave velocity is low, and so the reflected pulse wave reaches the aorta after the closure of the aortic valve. Therefore, systolic blood pressure in the aorta is unchanged, and the backward wave increases the central diastolic pressure with increase of the coronary perfusion pressure, this being the main physiological mechanism by which coronary perfusion is increased in diastole. In patients with risk factors, such as hypertension or diabetes, pulse wave velocity is increased from 5 up to 20 m/s, causing an early return of the backward wave from the periphery to the aorta. This reach the aorta during left ventricular ejection, adding additional pressure load and increasing central systolic blood pressure, with decreasing of central diastolic pressure and coronary perfusion.^{5,6}

The consequences are represented by increase of left ventricular afterload and ventricular oxygen consumption, associated with a reduced subendocardial coronary blood flow during diastole.⁷ These mechanisms might cause left ventricular dysfunction, since we proved that increased arterial stiffness can cause dysfunction of the subendocardial muscle layers of the left ventricle.⁸ Moreover, large artery stiffness has shown recently to be an independent predictor of all-cause and cardiovascular mortality in patients with hypertension.^{9,10} (Fig. 3) The odds ratio of being in the group at high risk of cardiovascular mortality (> 5% for 10 years) for patients with a pulse wave velocity greater than 13.5 m/s was 7.1 (95% CI 4.5-11.3).¹⁰

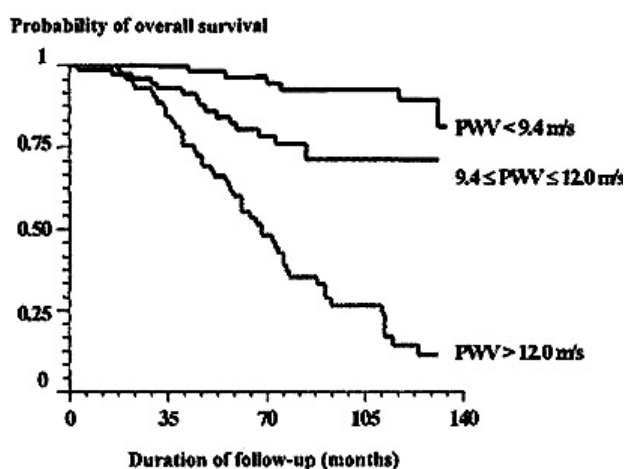


Figure 3. Probability of overall survival in patients with hypertension and end-stage renal disease according to level of pulse wave velocity (PWV) divided into tertiles.¹⁰

Pulse wave velocity is measured usually at the level of the leg, as the distance between two points in the line of travel of the pulse wave, divided by the time delay. Different devices are commercially available. Typical values range from 5 m/s to 20 cm/s.⁵ Recently, new software has been available for the measurement of single-point pulse wave velocity at the level of the carotid artery.⁸ However, this software is still under validation, and more data are needed to implement it in clinical practice.

According to the current guidelines, measurement of arterial stiffness might improve assessment of the global cardiovascular risk, and might prove to be a better therapeutic target than the simple measurement of blood pressure.¹¹ Thus, an important goal of drug treatment of hypertension should be to modify arterial stiffness, independently of the reduction of blood pressure, but there is still uncertainty over the effects of antihypertensive agents on large artery properties. However, a number of studies have suggested that ACE inhibitors (ramipril, quinapril, perindopril, and lisinopril) and, to a lesser extent, some of the calcium channel antagonists, i.e. amlodipine, felodipine, nifedipine, and nitrendipine, can reduce pulse wave velocity, whereas beta-blockers and diuretics have no effects on these parameters.¹² And indeed, a very recent large study has shown that the combination amlodipine + perindopril can significantly lower central aortic pressure by decreasing arterial stiffness than the combination atenolol + thiazide, despite a similar impact on brachial blood pressure, and this was associated with a better outcome on the major endpoints, such as total cardiovascular events/procedures and development of renal impairment.¹³

Long-term nitrates, by increasing the diameter of the peripheral muscular arteries, can delay the reflected wave, and therefore decrease central systolic blood pressure. Recent clinical studies suggested that low-dose nitrates might be beneficial in reducing isolated systolic hypertension when added to ACE-inhibitors or angiotensin receptor blockers.¹⁴ Promising results have been also reported with NO donors, such as the selective beta-blocker nebivolol, but long-term studies are needed in patients with hypertension.¹⁵

INTIMA-MEDIA THICKNESS

Intima-media thickness (IMT) is a marker of subclinical atherosclerosis at the level of the carotid arteries. It is measured by high-frequency (≥ 8 MHz) ultrasound transducers in both carotid arteries, on the distal straight 1 cm of the common carotid arteries,

the carotid bifurcations, and the proximal 1 cm of the internal carotid arteries. The carotid IMT is determined as the average of 12 measurements (both sides 6 measurements each from the near and far wall of each of the three segments). A value > 1.3 mm is considered abnormal.⁴

Subjects without known cardiovascular disease with increased IMT are at increased risk for coronary artery disease and stroke. Thus, a 0.2 mm thicker carotid IMT was associated with a 33% increase in relative risk for myocardial infarction, and a 28% increase in relative risk for stroke.¹⁶ Moreover, a recent study has shown that IMT increases with advancing coronary artery disease, patients with mean IMT over 1.15 mm presenting a 94% likelihood of having coronary artery disease.¹⁷ Meanwhile, in another recent study IMT was independently associated with the risk of stroke, with an odds ratio of 1.68 (95% CI 1.25-2.26).¹⁸

Measurement of IMT has the potential to improve the assessment of global cardiovascular risk. And indeed, it has been demonstrated recently that Framingham risk score increased progressively according to tertiles of IMT. Thus, with increasing IMT, the 10-year Framingham risk score increased gradually between 10% and 20% in the presence of carotid plaques, and between 5% and 20% in the absence of carotid plaques.¹⁸ Furthermore, carotid IMT can be used as a surrogate marker in order to monitor the effects of different drugs, such as statins or calcium-antagonists, on the regression of the atherosclerotic process.¹⁶

ANKLE-BRACHIAL INDEX

Ankle-brachial blood pressure index (ABI) is an easy-to-perform, inexpensive, and reproducible non-invasive test to detect subclinical atherosclerosis.⁴

Technical requirements consist of a regular blood pressure cuff and a Doppler ultrasonic sensor. Systolic blood pressure is measured in the brachial artery in both arms, by use of the Doppler detector in the antecubital fossa. The blood pressure cuff is then applied to the ankle, and the Doppler sensor is used to determine systolic blood pressure at the left and right posterior tibial arteries and dorsalis pedis arteries. The ABI for each leg is calculated as the ratio of the higher of the two systolic pressures (posterior tibial or dorsalis pedis) in the leg, and the average of the right and left brachial artery pressures. In the case a discrepancy of more than 10 mm Hg in blood pressure values is found between the two arms, the higher reading is used for

the ABI. Pressures in each leg should also be measured and ABI calculated separately for each leg. An ABI < 0.9 reflects a $\geq 50\%$ stenosis between the aorta and the distal leg arteries, and progressively lower ABI values indicate more severe obstruction.¹⁹

A recent published study has shown that, after adjustment for all conventional risk factors, a low ABI ≤ 0.9 was independently predictive of the risk of fatal myocardial infarction (OR 1.69, 95% CI 1.06-2.69). Moreover, addition of the ABI increased significantly the accuracy of the predictive model for fatal myocardial infarction, by comparison with a model containing risk factors alone. Therefore, ABI has the potential of being included into the cardiovascular scoring systems, with a view to improving their accuracy, but this should now be examined.²⁰

CONCLUSIONS

Markers of subclinical atherosclerosis can be considered either as intermediate mechanisms between most of the major risk factors and atherosclerosis, or as direct risk factors for the complications of the atherosclerotic disease. Once assessed, they can modify the evaluated risk for atherosclerotic disease of a particular subject, adding important information for its best management. Furthermore, they can be targeted by specific therapeutic strategies.

REFERENCES

1. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. A Report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002;39:257-65.
2. Perticone F, Ceravolo R, Pujia A, et al. Prognostic significance of endothelial dysfunction in hypertensive patients. *Circulation* 2001;104:191-6.
3. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;352:1685-95.
4. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2003;10(Suppl 1):S1-S78.
5. London GM, Guerin A. Influence of arterial pulse and reflective waves on systolic blood pressure and cardiac function. *J Hypertens* 1999;17(Suppl 2): S3-6.
6. O'Rourke MF. Wave travel and reflection in the arterial system. *J Hypertens* 1999;17(Suppl 5):S45-7.
7. Ohtsuka S, Kakiyama M, Watanabe H, et al. Alterations in left ventricular wall stress and coronary circulation in patients with isolated systolic hypertension. *J Hypertens* 1996;14:1349-55.
8. Vinereanu D, Nicolaides E, Boden L, et al. Conduit arterial stiffness is associated with impaired left ventricular subendocardial function. *Heart* 2003;89:449-50.
9. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent

- predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236-41.
10. Blacher J, Guerin AP, Pannier B, et al. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999;99:2434-39.
 11. Safar ME, London GM, for The Clinical Committee of Arterial Structure and Function, on behalf of the Working Group on Vascular Structure and Function of the European Society of Hypertension. Therapeutic studies and arterial stiffness in hypertension: recommendations of the European Society of Hypertension. *J Hypertens* 2000;18:1527-35.
 12. Dart AM, Kingwell BA. Pulse pressure - a review of mechanisms and clinical relevance. *J Am Coll Cardiol* 2001;37:975-84.
 13. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes. Principal results of the conduit artery function evaluation (CAFE) study. *Circulation* 2006;113:published on internet.
 14. Stokes GS, Barin ES, Gilfillan KL. Effects of isosorbide mononitrate and AII inhibition on pulse wave reflection in hypertension. *Hypertension* 2003;41:297-301.
 15. McEniery CM, Schmitt M, Qasem A, et al. Nebivolol increases arterial distensibility in vivo. *Hypertension* 2004;44:305-10.
 16. De Groot E, Hovingh GK, Wiegman A, et al. Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation* 2004;109:III33-8.
 17. Kablak-Ziembicka A, Tracz W, Przewlocki T, et al. Association of increased carotid intima-media thickness with the extent of coronary artery disease. *Heart* 2004;90:1286-90.
 18. Touboul PJ, Labreuche J, Vicaut E, et al. GENIC Investigators. Carotid intima-media thickness, plaques, and Framingham risk score as independent determinants of stroke risk. *Stroke* 2005;36:1741-5.