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Non Invasive Assessment of Cardiovascular Risk Profile: The Role of the Ultrasound Markers

Marco Matteo Ciccone*, Michele Gesualdo, Annapaola Zito, Cosimo Mandurino, Manuela Locorotondo and Pietro Scicchitano
Cardiovascular Diseases Section, Department of Emergency and Organ Transplantation (DETO), University of Bari, Bari, Italy

1. Introduction

Atherosclerosis, with its complications, is the most frequent cause of death all over the world, and it is the underlying cause of about 50% of all deaths in developed countries (1).

Recent studies showed the key role played by inflammation and immune responses in development, progression, and rupture of atherosclerotic plaque (2,3,4). The presence of an immune reaction and/or infective antigens as potential triggers of atherogenesis (5,6) makes atherosclerosis be considered as an autoimmune disease in which the adaptive immune system is targeted against self-antigens modified by biochemical factors such as oxidative stress and hypercholesterolemia (7). These give rise to plaque birth (8,9) and the inflammatory status of the plaque makes the lesions unstable, inducing their abruption and acute thrombotic obstruction. Therefore, it induces impairment in endothelial function in bioactive antiatherogenic or proatherogenic molecules production (10), although other factors could increase such an imbalance: age (11), sex (12), hypertension (13), obesity (14), smoking (15), dyslipidemia (16), diabetes (17), all able to increase oxidative stress and vascular inflammation (18), morphological wall alterations and subsequently progression of atheromatous lesions.

The initial atherosclerosis stages silently and symptom free occur since childhood (19); the clinical expressions (i.e., sudden cardiac death, myocardial infarction, angina pectoris, stroke, aortic aneurysm, renovascular hypertension, and intermittent claudication) involve 2 over 3 men and 1 over 2 women after age 40, and almost 60% of deaths are due to a cardiovascular disease cause (20). Thus, there has been an increase in recognition of the importance of subclinical atherosclerosis, and early detection of this insidious process must be the goal for improving cardiovascular health through prevention, and treatment of risk factors.

Currently, non-invasive risk profile assessments can be evaluated not only with some laboratory parameters, (lipids and systemic inflammation markers as white blood cells,

* Corresponding Author

reactive C protein and erythrocyte segmentation rate), but also with ultrasonographic methods that detect subclinical atherosclerosis. Three internationally validated methods had been adopted in order to evaluate endothelium function: brachial artery flow-mediated vasodilation (FMD) (21,22), antero-posterior abdominal aorta diameter (APAO) (23) and intima-media thickness of the common carotid artery (CCA-IMT) (24,25). Cause of their non-invasiveness, feasibility and cheap cost, these techniques are the best tools for the physicians to assess functional and morphological alterations of the arteries before a cardiovascular event occurs and the feasibility of therapies to reduce atherosclerosis burden (26).

2. FMD technique

The endothelium is a real "organ", endowed with autocrine and paracrine properties and playing an essential role in controlling vasomotion by producing molecules able to modulate blood, such as nitric oxide (NO), the most important vasodilator molecule produced by endothelial cells) (27). Shear stress is the main element able to determine increasing in NO production, its action being exerted perpendicularly to the long axis of the vessel.

Nevertheless, endothelial cells can also produce substances with vasoconstrictor action, as endothelin-1, (27) above all in case of increased age, hyperhomocysteinemia, smoking, diabetes, hypercholesterolemia, and hypertension (28): in these case it could be detected the presence of reduced vasodilating response to endothelial stimuli. Instead, diet and exercise can improve endothelial function (29). Lipid-lowering therapy (30,31), antioxidants (32), estrogen replacement (33) and treatment with angiotensin-converting enzyme inhibition or receptor blockade (34) improve this response.

Thus, endothelial dysfunction is considered the basic pathogenic mechanism of cardiovascular disease (35) and therefore can be considered as an early marker of cardiovascular risk.

In fact, the endothelial dysfunction seems to be the earliest event in the process of atherosclerotic plaque formation, appearing even before structural lesion of the vessel wall (36); for this reason the evaluation of endothelial function could be a useful tool for early stratification of patients at risk for cardiovascular events.

Studies in postmenopausal women suggest that endothelial dysfunction may be a predisposing factor for the development of hypertension (37) and diabetes (38), thus being not only a consequence of risk factors but also a pathogenetic mechanism for their onset.

Moreover, impaired endothelium-dependent vasomotion may contribute to the genesis of cardiovascular events by modulating the stability of plaque and coronary vasospasm. In fact, the analysis of Lerman and Zeiher (39) showed that endothelial dysfunction, assessed both at coronary and peripheral level, is significantly predictive of cardiovascular events independently of the presence of traditional cardiovascular risk factors.

3. Procedure description

A non-invasive method to assess endothelium-dependent flow-mediated vasodilation (FMD) was developed in the 1990s: it consisted in inducing endothelial cells to release NO

(40,41) through mechanical stimulation originating from increasing in vessel wall "shear stress". It is usually performed at brachial artery level by high-frequency ultrasonographic imaging (21).

It is performed in a quiet, temperature-controlled (22–24°C) room, early in the morning and it adopts a high resolution ultrasonograph connected to an image analysis system and a sphygmomanometer cuff applied around the forearm to create a flow stimulus in the brachial artery. The examination requires the patients to be supine, at rest, fast for at least 8 to 12 hours before the study; all vasoactive medications (calcium channel blockers, ß-adrenergic blocking agents, nitrates and converting enzyme inhibitors) should be withheld for at least 4 half-lives, if possible. Moreover, subjects should avoid substances that might impair FMD such as caffeine, high-fat foods, and vitamin C or use tobacco for at least 4 to 6 hours before the study (table 1).

FACTORS	COMMENTS
Hours	The examination should be performed at the same time of day
Temperature	Ultrasonographic evaluation should be performed at constant temperature, in an environment equipped with air conditioning
Drugs	All vasoactive drugs should be discontinued the night before the exam
Coffee and The	The day of the examination, the patient should refrain from taking coffee or tea
Smoking	Patients should abstain from smoking
Influence of food	Patients should not take copious meals or high in fat
Brachial artery diameter	It must be between 2.5 and 5 mm

Table 1. Prerequisites and factors that influence the flow-mediated dilation

The 7,5 MHz electronic probe is positioned 4–5 cm above ante-cubital fossa to obtain longitudinal B-mode vascular scanning of the brachial artery with clear anterior and posterior intimal-lumen interfaces, and once the optimal artery image is achieved, the probe can be maintained in the right position using a mechanical arm. A pulsed wave Doppler recording is obtained from the midartery.

The procedure lasts 9 minutes: the first minute evaluate baseline diameter, measured at the onset of the R-wave on the electrocardiogram.

At the end of the first minute, the cuff is inflated 200-250 mmHg in order to close arterial inflow of the forearm (42). This causes ischemia and, consequentially, dilation of downstream resistance vessels by autoregulatory mechanisms.

After the sixth minute, the cuff is rapidly deflated: a brief high-flow state through the brachial artery to accommodate the dilated resistance vessels happens, and this reactive hyperemia produces a shear stress stimulus that induces the endothelium to release nitric oxide with subsequent vasodilation of the brachial artery between the 6th and 9th minute.

The software calculates FMD value as percentage of increasing of diameter value from baseline:

FMD = [(postiperemia diameter - baseline diameter) / baseline diameter] x 100

The maximal increase in diameter occurs approximately 60 to 90 seconds after cuff release. FMD values greater than 5-10% are considered "normal" (21). A schematic overview of this imaging technique could be observed in figure 1a.

This reactive hyperemia phase is confirmed by measuring the arterial blood flow using pulse-wave Doppler. The peak blood flow in the brachial artery is obtained with the sample volume in the centre of the artery and a correction angle of 70°. It is estimated at rest and during the first 15 s after cuff deflation, taking the average of the pulsed Doppler velocity signal of 3 measurements. The maximum speeds considered normal is 50–70 cm/s. Reactive hyperemia is calculated as the ratio of the maximal velocity divided by the maximal velocity at baseline.

Because of its low reproducibility and accuracy (43,44), the technique requires very high methodology accuracy and a mechanical support for the probe with micrometer adjustment to prevent movement of the vascular probe, and specific software ("FMD Studio") to measure second to second changes in artery caliber (21). The variations in caliber measured are small (from 0 to 15%), so the FMD represents a stimulus-type "on / off" poorly modulated.

Therefore, in order to obtain results that have a clinical validity, it is necessary to study a large number of patients. In support of the role of endothelial function as marker of cardiovascular risk and of the validity of the FMD method, there is also correlation with the invasive test data of coronary endothelial function (45) and with the severity and extent of atherosclerosis coronary (46).

Moreover, the noninvasive nature of the technique allows repeated measurements over time to study the effectiveness of various interventions that may affect vascular health.

4. APAO

Up to now the infrarenal anteroposterior diameter of abdominal aorta (APAO) has been always related to the abdominal aortic aneurysms (AAAs), as a measurement to be used in the diagnostic and follow-up phase of this disease and for surgical intervention planning.

An abdominal aortic aneurysm is defined by some authors as an infrarenal aortic diameter ≥ 3.0 cm, or a ratio between infrarenal and suprarenal aorta diameters greater than 1.2, all measured by ultrasound B-mode (47). As coronary heart disease and stroke continue to be the leading causes of death and disability among adults in developed countries, an early detection of vascular damage and, consequently, adequate cardiovascular risk stratification has received an intense attention in the last years in order to decrease the impact of cardiovascular disease.

To detect the "primum movens" of atherosclerotic disease, several studies have been conducted in the last years for identify new ultrasonographic markers (48).

Intima-media thickness of abdominal aorta has been firstly suggested as cardiovascular risk marker in patients stratification risk profile (49).

Recently, in addition to arterial wall thickening, attention has been paid on APAO as a possible early marker of atherosclerosis (before clinical manifestations have become evident). Indeed, arterial dilatation is a well-known age-related manifestation, and some of the molecular events causing this alterations are involved in the pathogenesis of cardiovascular disease (50,51).

There is a relationship between APAO in the non-aneurysmal range (<30 mm in diameter) and all-cause mortality: in a cohort of 12203 men aged 65 years and older infrarenal aortic diameter is turned out to be an independent predictor of all-cause mortality, particularly cardiovascular mortality (52). In another study on 4734 participants > 65 years old underwent to abdominal aortic ultrasound evaluation, has been demonstrated that for those with an infrarenal aortic diameters >2.0 cm, there was a significantly higher risk of future cardiovascular events and total mortality, suggesting a value of infrarenal aortic diameters between 2.0 and 3.0 cm as another manifestation of subclinical atherosclerosis (53).

Furtheremore, Allison et al (54) showed that age, gender, body mass index, and the presence and extent of calcified atherosclerosis in both the abdominal aorta and iliac arteries are significantly associated with increasing aortic diameter independently of other cardiovascular risk factors. A study by Ciccone et al. involving women with polycystic ovary syndrome PCOS (55) showed that the increase in APAO is the earliest arterial alteration in women with PCOS, thus preceding the IMT of other arteries such as common carotid arteries and common femoral arteries. This identifies APAO as an early marker of atherosclerosis.

However, this alteration seems to be due to body weight secondary to PCOS and not to PCOS *per se*. In fact, Gorter PM et al (56) showed that intra-abdominal fat accumulation and metabolic syndrome are associated with larger infrarenal aortic diameter in patients with clinically evident arterial disease, indicating a role for intra-abdominal fat in the development of larger aortic diameters.

To explain these findings it can be hypothesized that APAO may represent a measure of cumulative exposure to genetic and environmental risk factors implicated in atherosclerosis development. For these reasons, APAO can be considered as an early marker of cardiovascular risk, and because of its noninvasive measurement and feasibility might be used to investigate determinants of atherosclerosis at an early stage of the process and to assess modifiers of atherosclerosis disease progression, such as lifestyle and pharmacological interventions.

5. Procedure description

Wilmink and colleagues (57,58) showed that the use of ultrasounds to measure the infrarenal aortic diameter is attractive as it is rapid, cheap, and noninvasive. The good accuracy of infrarenal aortic diameter measurements by ultrasound makes this method acceptable for clinical decision-making.

With the patient in supine position, the examination is carried out with a 3.5 MHz electronic probe placed one centimetre left of the umbilicus. The longitudinal ultrasound scans allow the

study of the aorta and the best image in long axis projection of the abdominal aorta is used for the measurement. To improve the image acquisition, subjects are asked to keep fasting for at least 6-8 hours and follow a fiber diet for the two days prior to the examination to reduce intestinal bloating (diet preparation). To reduce the bias and interobserver variability the study of infrarenal abdominal aorta should be performed by same physician (59,60).

In the study of Ciccone et al.(55) the anteroposterior diameter of the aorta was defined as the maximal external cross-sectional measurement. It was calculated as the distance between the near and the far walls of the abdominal aorta on images that were frozen in systole. All the measurements were performed at 0.5, 1, and 2 cm above the umbilicus and were expressed in centimetres (see also Figure 1c and 1d).

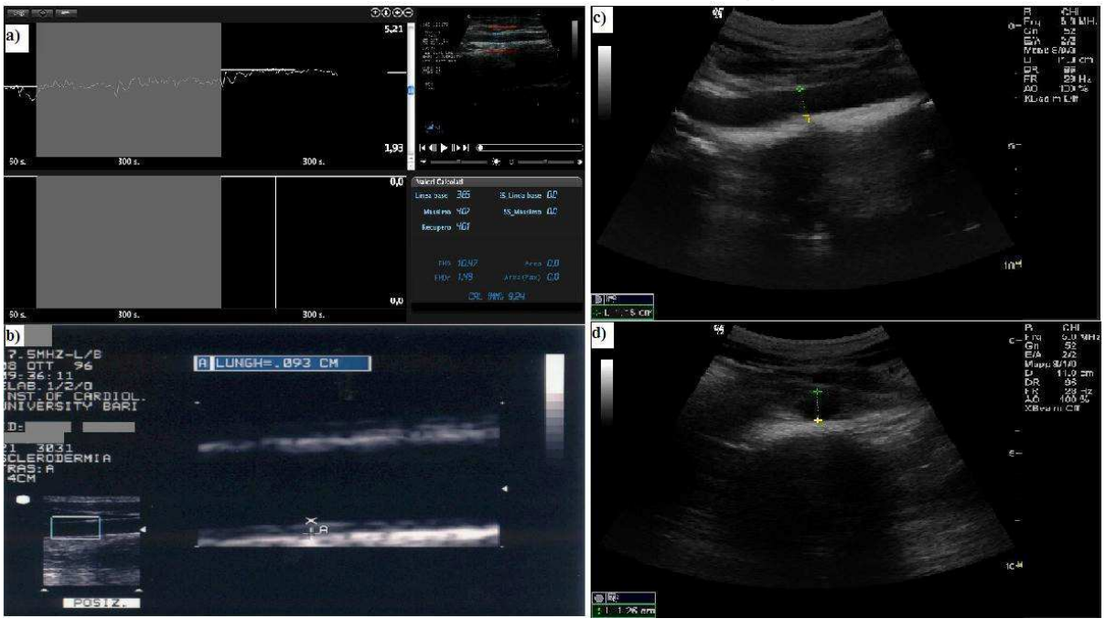

Fig. 1. a) Flow-mediated vasodilation (FMD) technique image. **b)** Ultrasound evaluation of common carotid artery intima-media thickness. **c)** Antero-posterior abdominal aorta diameter in long axis views. **d)** Antero-posterior abdominal aorta diameter in short axis views

However, in several studies the position of the probe and the part of abdominal aorta evaluated may be different.

van den Bosch et al. (61) studied distal aortic diameter to assess the relationship between abdominal aortic diameter and peripheral arterial occlusive disease. They demonstrated that both patients with an aortic diameter too large and patients with an aortic diameter too small are prone to peripheral arterial occlusive disease.

The study of Norman P. et al. (52) was carried out using a 3.75 mol/L Hz probe to measure the maximum transverse and antero-posterior diameter of the infrarenal aorta. The largest measurement was recorded as the aortic diameter.

Pleumeekers et al. (62) evaluated the observer variability of ultrasound measurements of proximal and distal part of the abdominal aorta. Their results were that ultrasound

measurements are more accurate for the distal than for the proximal aorta measurement and the definition of the aortic diameter based on a combination of both distal and proximal measurement may be more accurate.

6. IMT

Atherosclerosis is a disease with a slowly progressive course and a long asymptomatic period. The clinical manifestations generally appear in middle age (63), and the first event triggered by atherosclerosis can be fatal.

Since the atherosclerotic disease is a multidistrict and multifocal process, identifying the changes of the vascular wall at subclinical stages of atherosclerosis is essential in assessing global cardiovascular risk (64) and in promoting the use of preventive strategies, as well as optimization of preventive and protective care.

Among imaging techniques for detection of early preclinical stages of atherosclerosis, the best is the measurement of the carotid intima-media thickness (CCA-IMT) using ultrasound high-resolution B-mode; the evaluation of this parameter is a noninvasive and reproducible method for identifying and quantifying subclinical vascular disease.

It is a well-validated research tool that has been translated increasingly into clinical practice as a cardiovascular risk marker (65,66).

Many studies demonstrated the role of CCA-IMT in the early evaluation of atherosclerosis disease. In fact, this parameter was found to be associated with the presence of cardiovascular risk factors (67,68,69) and with atherosclerotic lesions in other vascular districts, such as coronary and lower extremity arteries (70,71,72). Gasparyan (73) already put on evidence the importance of carotid ultrasound assessment in the clinical practice. Apart from CCA-IMT evaluation, the ultrasound evaluation should consider all the characteristics of carotid wall: it is necessary to evaluate IMT and, at the same time, morphological aspects of carotid wall.

Prospective epidemiological studies showed that individuals with elevated carotid IMT are more likely to suffer from cardiovascular or cerebrovascular events, suggesting that thickened carotid IMT is a powerful and independent indicator of the likelihood of general arteriosclerosis (74,75). The predictive power of carotid IMT is maintained even after adjustment for major cardiovascular risk factors. Thus, measurement of IMT may provide informations in addition to traditional risk factors during assessment of global cardiovascular risk profile in asymptomatic subjects (76).

SSeveral works in the last decade confirmed the role of this parameter in the early detection of atherosclerosis and in measure of its severity (77,78).

Moreover, changes in carotid IMT may be used as a measure of efficacy of pharmacologic intervention.

7. Procedure description

Carotid ultrasound can be performed using vascular echographic apparatus equipped with high-frequency transducers (usually 3-10 MHz and linear array) and appropriate software.

The patient should be positioned supine with slight (45°) hyperextension and rotation of the neck in the direction opposite the probe.

CCA-IMT is defined as the distance between the lumen-intima interface and the media-adventitia interface, which corresponds to the inner and outer echogenic lines seen on the B-mode ultrasound image [see figure 1b] (24,79).

Measurement of carotid IMT (c-IMT) is traditionally performed with the image of the carotid artery in the longitudinal axis, revealing the common carotid artery, the carotid bifurcation, and the internal and external carotid arteries.

Although these measurements have been performed for years, significant variability exists when measuring the near wall due to technical and acoustic difficulties encountered when imaging the c-IMT of the near wall (80). Due to these technical limitations, clinical measurement of c-IMT using B-mode ultrasound is often applied to the far (posterior) wall of the common carotid artery.

IMT is measured at about 2 cm proximal to the dilation of the bulb of the common carotid artery.

Three measurements coming from three different sites [according to the method described by Pignoli et al. (79): about 2 cm above the flow-divider, about ½ cm above the flow-divider and in middle zone] are considered for IMT evaluation. An average of all these values would be calculated at the end of the measures.

Mean IMT (m-IMT) and maximum IMT (M-IMT) are measured. m-IMT represents the mean value of all measurements at each common carotid artery, averaging the left and right sides. M-IMT represents the mean value of the single highest IMT measurements at each common carotid artery, averaging the left and right sides. Carotid plaque is defined as the presence of a greater than 1.5 mm c-IMT measurement or an area within the carotid artery that is at least 50% greater than the size of the surrounding vessel wall.

The same physician should perform the evaluation in order to reduce bias and improve the results.

A problem associated with the ultrasonographic IMT measurement is the variation in the readings, which leads to different results of repeated measurements from the same observer. In general, the inter- and intra-observer errors are acceptable and the technique has a good reproducibility (81,82).

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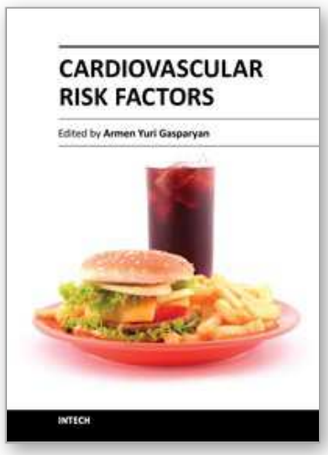

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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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