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Review article

Comprehensive assessment of vascular health in patients; towards endothelium-guided therapy

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ABSTRACT

Endothelial function has diagnostic, prognostic and therapeutic significance. A number of non-invasive techniques were introduced for its assessment, including flow-mediated dilation (FMD), finger plethysmography (RH-PAT) and digital thermal monitoring (DTM). All these methods can be performed simultaneously. In addition, various methods for measuring arterial wall stiffness are available such as: pulse wave analysis (PWA), pulse wave velocity (PWV), pulse contour analysis (PCA) and carotid wall distensibility coefficient (DC). Finally, carotid intima-media thickness (cIMT) and ankle brachial index (ABI) are used as surrogate read-outs of atherosclerosis. Here, we briefly describe the advantages, limitations and interrelationships of various methods used for the assessment of endothelial function, arterial stiffness, and present the concept of an integrated evaluation of vascular health based on multiple methods. This strategy may be useful to stratify cardiovascular risk and represents a step towards multiparametric assessment of endothelium for effective endothelium-guided therapy in patients with cardiovascular diseases.
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Introduction

Healthy endothelium is essential for undisturbed functioning of the cardiovascular system, while endothelial dysfunction – characterized by impaired production of vasoprotective endothelial mediators, excessive production of pro-oxidant, pro-thrombotic and pro-inflammatory mediators – leads to various pathologies [1,2]. For example, endothelial dysfunction plays a central role in the initiation and propagation of inflammatory and pro-thrombotic mechanisms of atherothrombosis and predicts poor long-term outcomes in coronary artery disease, hypertension [3], as well as in healthy subjects [4]. Accordingly, endothelial dysfunction may be regarded as a barometer of cardiovascular risk [5], having additional predictive value as compared with traditional risk factors [6]. Indeed, many individuals with coronary artery disease have only one or none of the traditional risk factors, suggesting that non-traditional or unknown risk factors could play an important role in atherogenesis. Therefore, endothelial function representing an integrated index of atherogenic and atheroprotective factors may be useful in stratifying cardiovascular risk and identifying individuals at higher risk [2,7]. Furthermore, since the therapeutic effects of cardiovascular drugs, such as statins and inhibitors of renin-angiotensin system on endothelium, including anti-inflammatory, anti-thrombotic and vasoprotective actions, contribute significantly to their therapeutic efficacy, endothelium-guided therapy may represent an efficient way for individuals to tailor cardiovascular therapy [2,7].

Given the overwhelming clinical evidence of the diagnostic, prognostic and therapeutic significance of endothelial function, it is not surprising that a number of methods have been introduced to assess endothelial function: from the quantitative angiography with intracoronary acetylcholine, the first direct method of endothelium-dependent vasodilation assessment of human coronary arteries [8], through to various techniques of non-invasive testing of endothelial function in peripheral arteries including flow-mediated dilation (FMD) or peripheral arterial tonometry (RH-PAT).

This review provides a brief overview of commonly used non-invasive methods of endothelial function evaluation and vascular health assessment in humans, summarizing their principles, advantages and disadvantages with the aim of discussing clinical perspectives of their use for cardiovascular risk assessment and endothelium-guided pharmacotherapy.

Non-invasive assessment of endothelial function

Flow-mediated dilation (FMD)

FMD, introduced by David Celermajer et al. [9,10], is the gold standard method for a non-invasive endothelial function assessment. This method is based on monitoring the brachial artery diameter with a two-dimensional ultrasound, before and after artery occlusion [9], achieved with the cuff pressure inflated slightly above the systolic blood pressure for 5 min. Sudden release of the cuff results in the hyperemic increase of the blood flow and an increase of the laminar shear stress that activates the release of nitric oxide (NO), mediating subsequent artery vasodilation–flow-mediated dilation (FMD) (Fig. 1c'and c–d). According to the guidelines [11], the brachial artery should be imaged above the antecubital fossa in the longitudinal plane, while the occlusion cuff should be placed on the forearm, as placing the cuff on the upper arm may generate some confounding factors [12–14] and artery dilation is less NO-dependent [15]. The best reproducibility of FMD is offered by a wall-tracking software, but manual measurements of vessel diameter are more popular [16]. We developed our own wall-tracking system that offers some advantages over commercially available solutions [17].

FMD value has been found to be dependent on the baseline artery diameter [18,19]. Atkinson and Batterham [20] even suggested that the predictive value of FMD is actually explained by the predictive value of the baseline artery diameter, negatively related to FMD. That is why some authors recommend normalizing the dilation to the initial artery diameter [20,21]. Various other parameters, such as shear rate, arterial pressure, body mass, muscle mass or height have been proposed to modulate FMD measurements [22]. Interestingly, shear stress itself, a stimulus for the arterial dilation [23], as well as a time delay to maximum dilation [24] may be important indicators of vascular FMD response. Indeed, Pyke et al. [25] advocate for shear-rate normalization, when groups with different baseline arteries are examined. Furthermore, Padilla et al. [26] found that the ratio of FMD to shear stress, but not FMD alone, discriminated a population with moderate cardiovascular risk from a low-risk population. Anderson et al. [27] demonstrated that hyperemic velocity, but not FMD itself, possesses the prognostic value additive to traditional risk factors and carotid IMT (cIMT). There is an ongoing discussion regarding FMD methodology, yet FMD standardization has still not been finalized [21,22,25].

Interestingly, while FMD is a measure of the vasodilation, recently introduced low-flow-mediated constriction (L-FMC) is a measure of vasoconstriction occurring at a low-shear stress [28,29]. Flow mediated-dilation is mediated by NO, while L-FMC seems to be mediated by endothelin-1 (ET-1). The FMD and L-FMC appear to be complementary and in combination provide a better way to assess vascular function than FMD alone [28,30,31].

It is worth adding that the FMD technique has a number of limitations, among them inter- and intra-observer variability, as well as attenuation of ultrasound signal in obese patients [32]. Also, due to operator-dependency it requires highly qualified staff, and small differences between groups can only be found while examining large numbers of subjects. Furthermore, reproducibility is relatively low [33] unless real time and continuous brachial artery imaging is performed along with automatic wall-tracking algorithms that increase the accuracy of measurements. Nevertheless, FMD is considered as a gold-standard test of endothelial function and is widely used in clinical studies as a surrogate endpoint to assess cardiovascular risk [3], both among subjects without heart disease [4] and in large community-based studies [34]. It has been confirmed in many clinical trials that brachial artery FMD is an independent predictor of cardiovascular events [35]. It is also considered as an indicator of endovascular procedure failure. In a group of patients with single-vessel coronary artery disease, undergoing coronary stent implantation, impaired FMD was an independent predictor of in-stent restenosis [36]. Patients with peripheral arterial disease (PAD) had significantly lower FMD than healthy subjects [37] as well as lower coronary flow reserve, and its impairment correlated with the degree of peripheral endothelial dysfunction [38]. The FMD was also used to assess treatment efficacy [39,40] and in studies on the vascular safety of drugs [41].

Finger plethysmography

Peripheral arterial tonometry (PAT) has been recently introduced as an alternative method to FMD in evaluating endothelial function based on volume changes during reactive hyperemia–RH-PAT measured by EndoPAT (Fig. 1a' and 1a) [23,42]. In this method, reactive hyperemia index (RHI) is calculated as the ratio of the average amplitude of the PAT signal over a 1 min time interval starting 1 min after cuff deflation divided by the average amplitude of the PAT signal of a 3.5 min time period before cuff inflation

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