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How to assess endothelial function in (secondary) prevention

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Patients who suffered cardiovascular events should be referred to a cardiac rehabilitation / secondary prevention program with the objective to improve lifestyle and clinical outcome. (1) Endothelial dysfunction, defined as an abnormal vasomotor response to physical and chemical stimuli which is related to structural and/or functional abnormalities of the endothelium, is present in the majority of them and may not respond to traditional medications. The assessment of endothelial reactivity should be recommended before and after cardiac rehabilitation to determine the degree of endothelial dysfunction, which may be present despite medications, and the response to exercise training and nutrition. From our experience, two/thirds of patients after myocardial revascularization procedures have persistent endothelial dysfunction, and 80% of them improve endothelial function after cardiac rehabilitation. Endothelial dysfunction is an indicator of atherosclerotic artery disease progression and predicts future cardiovascular events. The long-term maintenance of a normal endothelial function after a cardiovascular event is a prerequisite for a better prognosis.

However, there is no consensus on the most appropriate technique for assessing endothelial function. We summarize here the most common methods employed in clinical practice.

Topic(s): Rehabilitation

NONINVASIVE TECHNIQUES

The most popular noninvasive techniques are:

- A: flow mediated dilation of the brachial artery (FMDBA)
- B: peripheral arterial tonometry (PAT)
- C: venous occlusion pletismography (VOP)

A – FMD is an ultrasound-based technique using a standard equipment based on high-frequency vascular linear array transducer ranging 8-12 MHz with B-mode bidimensional imaging and spectral Doppler display to monitor BA internal diameter and blood flow, respectively. Blood pressure drop after BA occlusion by a sphygmomanometer for 5 minutes and release generates a shear stress able to induce flow-mediated dilation. The amount of post-occlusion dilation is proportional to endothelium ability to produce mediators such as nitric oxide (NO), prostanoids and

hyperpolarizing factor (EDHF).(2-4) Nitric oxide seems to play a major role in BA, since flow-mediated vasodilation is abolished by the NO synthase inhibitor l-NMMA.

Cuff may be positioned at upper arm or at the wrist. In the first case shear stress stimulus is greater than wrist occlusion, but it evokes release of other vasodilators besides nitric oxide (NO). (2-4)

Changes in BA internal diameter and flow are measured after cuff release compared to baseline, as follows :

FMD (% change) = post-occlusion BA diameter (POBAD) – baseline diameter (BABAD) / BABAD x 100 (normal values >7%).

Baseline and post-occlusion blood flows are calculated from the time-averaged pulsed Doppler time velocity integral (TVI) as follows :

BATVI x vessel diameter (πr^2) x heart rate = blood flow.

FMD represents a measure of endothelial dysfunction which predicts clinical outcome in patients with coronary artery disease and heart failure,(5,6) and may quantify the effect of medications or cardiac rehabilitation. (7-9)

FMD is a complex technique which requires expertise and technical accuracy in order to give reproducible results. It may be useful in secondary prevention to stimulate patients to adhere to prescribed medications and maintain lifestyle changes lifelong to prevent cardiovascular events.

B – PAT is a simple operator independent technique based on a pneumatic plethysmograph providing uniform pressure at the distal finger (EndoPAT, Itamar Medical).(10) Beat to beat plethysmographic recordings of the arterial wave amplitude at the finger are obtained and analyzed by a computerised automated algorithm that provide the average pulse amplitude for each 30-second interval after forearm cuff deflation up to 3 minutes. Similar to FMD, a pressure cuff is placed on the arm and inflated above systolic pressure for 5 minutes, and then deflated to induce reactive hyperemia, while contralateral arm serves as control. An index between the two arms is automatically calculated to adjust for possible systemic drift in vascular tone during the test. This index has been validated in many independent controlled studies as a marker of endothelial function of microvessels partly dependent on NO.(10,11) PAT index is correlated with coronary microvascular function in patients with early atherosclerosis and predicts cardiovascular events. (12) In two large studies involving 6,900 patients PAT index was only modestly correlated FMD, suggesting that they measure different aspects of vascular biology in different districts, the former microvessels, the latter conduit vessels.(10) Endothelial dysfunction in peripheral arteries is a marker of cardiovascular risk and contributes to coronary artery disease progression and cardiovascular events. (12,13)

C – VOP is one of the most used and old technique based on the concept that forearm volume increase after venous occlusion is proportional to arterial blood inflow until venous pressure rises towards the occluding pressure. Volume changes are obtained by reactive hyperemia after forearm occlusion. In the first case, a catheter should be placed into the brachial artery, with the advantage to quantify endothelium-dependent and independent vasodilation in a dose-dependent manner. Typically, an inflation pressure of around 40 mmHg allowing arterial inflow is used for intervals of 10 seconds, followed by 10 seconds deflation. Plethysmographic assessment of forearm blood flow can be useful in clinical setting for measuring the effects of various drugs on the peripheral resistance vessels in vivo and may predict clinical outcome. (14)

INVASIVE TECHNIQUES

Invasive evaluation of endothelial function is based on the response in diameter and flow to intraarterial infusion of vasoactive substances such as acetylcholine or nitroglycerin which can differentiate between endothelium-dependent and endothelium-independent responses. Vascular

responses are determined not only by the functional status of the vasculature but also by the structural condition of the resistance arteries in the microvasculature. Changes in diameter and flow are quantified by intravascular ultrasound (coronary arteries) or strain gauge plethysmograph (peripheral arteries).

VOP may be also considered an invasive technique when volume changes are obtained in response to intraarterial infusion of substances. In this case, a mercury strain gauge detects blood volume changes after injection of vasoactive substances such as acetylcholine or nitroglycerin to assess endothelium-dependent or endothelium-independent vasodilation, respectively, in a dose-dependent manner. However, the interpretation of the results may be not comparable in different populations or in the same patient at different times due to variability in initial blood pressure, heart rate and vessel size. (15)

Coronary endothelial functional test is performed to measure epicardial and resistance vessel endothelial function. After acetylcholine infusion, vessels and segments with an intact endothelium vasodilate, whereas vessels and segments with dysfunctional endothelium will respond with vasoconstriction as a result of direct activation of muscarinic receptors on vascular smooth muscle cells.(16) After cardiac rehabilitation, endothelium-dependent relaxation improves in patients with coronary artery disease. (17) Coronary microvascular function can be assessed by calculating coronary flow reserve, i.e. the ratio between maximal coronary blood flow during maximal coronary hyperemia with provocative stimuli (such as adenosine infusion, pacing, or exercise) and the resting coronary blood flow. It reflects both endothelium-dependent and endothelium-independent vasomotor response, while endothelium-dependent reactivity is analysed after acetylcholine.(18)

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