Available online at www.sciencedirect.com

ScienceDirect

www.onlinepcd.com

Assessment and Prognosis of Peripheral Artery Measures of Vascular Function

Todd J. Anderson[a,*], *Shane A. Phillips*[b]

[a]*Libin Cardiovascular Institute of Alberta, Cumming School of Medicine, University of Calgary, Calgary AB Canada*
[b]*Department of Physical Therapy, Integrative Physiology Laboratory, College of Applied Health Sciences, University of Illinois at Chicago, Chicago, IL, USA*

ARTICLE INFO

Keywords:
Atherosclerosis
Endothelium
Vascular function
Doppler
Ultrasound
Laser
Plethysmography

ABSTRACT

The endothelium plays a crucial role in the regulation of vascular homeostasis. Our understanding of its role in health and disease has increased dramatically since the pivotal discovery of nitric oxide more than 30 years ago. Clinical researchers utilized emerging technologies to study the vasodilator properties of the endothelium in both the coronary and peripheral circulation. Early studies established the methodologies and were able to demonstrate attenuated endothelium-dependent vasodilation in response to atherosclerosis and its risk factors. A variety of interventions can modulate endothelial function. More recent studies have established that some of these measures are independent predictors of cardiovascular outcomes. As such, peripheral measures of endothelial function are now established surrogate markers of vascular risk and have become important markers for clinical research. In this review, we will discuss a variety of measures of peripheral artery function to assess both conduit and resistance vessel function in humans.

The field of vascular biology has evolved remarkably since the pivotal discovery of nitric oxide (NO) by Furchgott.[1] It quickly moved from the basic science laboratory to the clinical arena where much has been learned about the vascular endothelium in health and disease.[2] The endothelium plays a key role in vascular homeostasis through the release of paracrine factors such as NO, with favourable effects on vasodilation, inflammation and platelet aggregation. In a dynamic fashion, the state of endothelial health reflects a balance between vasodilators such as NO, prostacyclin and endothelium-derived hyperpolarizing factor (EDHF) and vasoconstrictors including endothelin-1, oxygen free radicals, angiotensin-II and thromboxane.[3] In this review, we will focus on the myriad of methods that have evolved to measure peripheral artery vasodilator function in patients over the past 20 years.

Rationale for measuring peripheral arterial function

The endothelium occupies a unique position in that it is able to secrete a variety of vasoactive molecules and is also exposed to direct vascular injury. It is thus an important mediator of atherosclerosis formation and is widely perceived to be a metric of vascular risk. Previous studies have demonstrated a correlation between measures of coronary vasodilator function and

Statement of Conflict of Interest: see page 10.

Supported in part by the National Institutes of Health grant numbers HL85614 and HL095701.

* Address reprint requests to Todd J. Anderson, MD, Libin Cardiovascular Institute of Alberta, University of Calgary, 1403-29th St NW Calgary, Alberta, T2N 2T9.

E-mail address: todd.anderson@albertahealthservices.ca (T.J. Anderson).

http://dx.doi.org/10.1016/j.pcad.2014.11.005
0033-0620/

Abbreviations and Acronyms

Ach = Acetylcholine

Aix = Augmentation index

BP = Blood pressure

CAD = Coronary artery disease

CV = Cardiovascular

EDHF = Endothelial derived hyperpolarizing factor

FATE = Firefighters and their endothelium

FMC = Flow-mediated constriction

FMD = Flow-mediated dilation

HR = Heart rate

LDF = Laser Doppler flowmetry

LDPI = Laser Doppler perfusion imaging

LSCI = Laser speckle contrast imaging

NO = Nitric oxide

PAT = Peripheral arterial tonometry

PWA = Pulse wave amplitude

PWV = Pulse wave velocity

flow-mediated dilation (FMD).[4] The systemic nature of endothelial dysfunction thus allows the peripheral circulation to be evaluated non-invasively as a metric of vascular risk in the coronary and cerebrovascular circulation. Early studies established that attenuated vascular responses occur prior to the development of atherosclerosis in response to a milieu of risk factors, thus making measurements attractive as a screening tool for cardiovascular (CV) risk.[5] Endothelial function is dynamic and can be attenuated rapidly in response to acute oxidative stress (cigarette smoking, high fat load). In addition, interventions that are associated with a decrease in vascular risk will improve vasodilation within a period of months allowing one to determine the impact of novel interventions in a timely fashion.[6] And finally, as will be discussed in detail below, several large studies have determined the prognostic implications of endothelial dysfunction in a clinical setting (see summary in Table 1). All of these have established several vascular measures as surrogate markers of atherosclerotic activity. The development of reliable, non-invasive measures of vascular function, thus have important implications for the conduct of clinical research and ultimately clinical decision tools for global risk assessment.[7]

Conduit vessel endothelial function

The first study to evaluate endothelial function in humans was reported by Ludmer and colleagues in 1986.[8] They infused acetylcholine (Ach), an endothelium-dependent agonist in the coronary arteries of healthy controls and atherosclerotic patients. The key observation was that normal arteries dilate as a result of NO release, whereas subjects with atherosclerosis demonstrate vasoconstriction. This pivotal observation led to a large number of coronary studies that evaluated conduit vessel endothelial function by quantitative coronary angiography or coronary resistance function with a Doppler flow-wire.[9] While this has been established as a "gold standard", the invasive nature and cost has limited use for large studies.

FMD

Based on earlier work[10] Celermajer and Deanfield published the first report of the measurement of peripheral artery FMD in 1992.[5] Not only were they able to describe a novel method, but also demonstrated that children with familial hypercholesterolemia had impaired function at an early age. Since this first report literally thousands of studies have been reported using this methodology.

a) *Protocol:* The guidelines for measuring Brachial artery FMD are summarized in Table 2. Briefly a high resolution (>10 MHz) linear array ultrasound probe is used to longitudinally image the brachial (or radial) artery at rest. A thin blood pressure (BP) cuff is inflated to supra-systolic pressure for 5 minutes on either the forearm or less often the upper arm. After the cuff is released, the artery dilates in response to shear stress mediated NO release and maximum dilation occurs between 45 and 120 seconds. After a further 5 minute recovery period, sublingual nitroglycerine may be given to assess endothelium-independent dilation. Adverse effects from cuff inflation or nitroglycerine administration include pain or hypotension which very rarely results in incomplete studies (about 1/500). There are no lasting complications of this test.

b) *Evidence:* There are many reasons that this methodology has become widely used. The testing is non-invasive, safe and relatively inexpensive. It is done with commonly available echocardiography equipment or vascular ultrasound. The FMD response has been shown to be mediated mainly by NO, thus it reflects endothelium-dependent vasodilation.[11] Early studies were difficult to interpret because of the lack of a standardized procedure and these were addressed by several guideline recommendations.[7,12,13] Highly standardized labs will now employ rigorous protocols that may include a) an arm fixation device, b) B mode edge detection tracking, c) off-line analysis, d) determination of peak dilation as opposed to dilation at 60 seconds, and e) discontinuation of vasoactive drugs. With these measures in place test-test co-efficient of variation should be in the 10-15% range. Baseline responses in healthy population with a lower arm cuff position will generally be 5-8% depending on the baseline brachial artery diameter, which is an important determinant of response. Some groups have suggested that instead of representing FMD as simply the % change in diameter with hyperaemia compared with baseline, there needs to be normalization to the shear stress stimulus.[14] However, there is some controversy around this point. The relative improvement in FMD with an intervention study would not be expected to be more than an absolute change of 1.0 to 1.5%. Thus, the sample size for these types of studies has increased compared to earlier reports, with studies now requiring more than 100 patients to be meaningful.[15]