Review

Flow-Mediated Vasodilation as a Diagnostic Modality for Vascular Failure

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Vascular endothelial dysfunction represents an initial step of "vascular failure," which we have recently proposed as a comprehensive syndrome of failed vascular functions that extends from risk factors to established atherosclerotic disease. The early detection of vascular failure is essential in order to appropriately intervene and prevent its progression. Many efforts have been made to assess vascular endothelial function, and one of the most promising methods is the measurement of endothelium-dependent flow-mediated vasodilation (FMD) using high-frequency ultrasonographic imaging and transient occlusion of the brachial artery. The reactive hyperemia caused by the transient brachial arterial occlusion induces the release of local nitric oxide, resulting in vasodilation that can be quantified as an index of vasomotor function. The noninvasive nature of this technique allows repeated measurements over time to study the effectiveness of various interventions that may affect vascular health. Although there are technical and interpretive limitations of this technique, FMD-guided therapeutic approaches for vascular failure should contribute to the improvement of cardiovascular mortality and morbidity. (*Hypertens Res* 2008; 31: 2105–2113)

***Key Words*: flow-mediated vasodilation, vascular endothelial function, vascular failure, atherosclerosis**

Introduction

Vascular endothelial dysfunction represents an initial stage of atherosclerosis. In addition to endothelial dysfunction, smooth muscle dysfunction, metabolic abnormalities of the vessel wall including inflammation, oxidative stress, and breakdown of the neurohormonal balance occur in the early stages of atherosclerosis. We recently proposed a new clinical entity, "vascular failure," characterized as the integration of these vascular abnormalities (*1*, *2*). Vascular failure is not an anatomical disease entity but a comprehensive syndrome of vascular dysfunctions that extends from risk factors to advanced atherosclerotic disease with arterial stenosis, and further to calcification of the vessel wall or serious vascular events that may be caused by plaque rupture and thromboembolic occlusion (Fig. 1). Patients who have atherogenic risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking are known to have impaired endothelial function, smooth muscle function, and vessel-wall metabolism. The early clinical detection of vascular failure even in the absence of anatomical vascular abnormalities is important in order to appropriately intervene and prevent its progression. Thus, there is an urgent need to establish the diagnostic crite-

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ria in order to diagnose vascular failure. In this review, we propose a standardized method to assess vascular endothelial function for the purpose of detecting the early stages of vascular failure.

Vascular Endothelial Function

The endothelium is a flat monolayer of cells that covers the vascular lumen throughout the body. The optimally placed healthy endothelial cells are not merely constituents of the vessel wall but are able to respond to physical and chemical signals by producing a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation (*3*). The importance of the endothelium was recognized by its effect on vascular tone. This is characterized by the production and release of several vasoactive substances that relax or constrict the vessel, as well as by the response to and modification of circulating vasoactive mediators. These substances are divided into two classes: endothelium-derived relaxing factors (EDRFs) and endothelium-derived constricting factors (EDCFs). Furchgott and Zawadzki first demonstrated an EDRF that was subsequently shown to be nitric oxide (NO) (*4*). NO is generated from L-arginine by the action of endothelial NO synthase (eNOS) in the presence of cofactors such as tetrahydrobiopterin (*5*). NO diffuses to the vascular smooth muscle cells and activates guanylate cyclase, which leads to cyclic guanosine monophosphate (cGMP)–mediated vasodilation. The endothelium also mediates the hyperpolarization of vascular smooth muscle cells *via* a NO-dependent pathway, which increases potassium conductance and subsequently propagates the depolarization of vascular smooth muscle cells, maintaining vasodilator tone. In this context, endothelium-derived hyperpolarization factors (EDHFs) were found (*6*). The EDHFs involved in this process are only partially understood and may differ between vascular beds. However, it is well recognized that EDHF can compensate for the loss of NO-mediated vasomotor tone, partially in the microcirculation, and this appears important when NO bioavailability is reduced. The endothelium modulates vasomotion, not only by the release of vasodilator substances (EDRFs) but also by an increase in constrictor tone *via* the generation of EDCFs such as endothelin. Endothelial dysfunction is characterized by a reduction of the bioavailability of EDRFs, particularly NO, with an increase in EDCFs (*7*). This imbalance leads to an impairment of endothelium-dependent vasodilation, which represents the functional characteristic of endothelial dysfunction. Moreover, endothelial dysfunction, aside from denoting impaired endothelium-dependent vasodilation, also comprises a specific state of "endothelial activation" that is characterized by a pro-inflammatory, proliferative, and pro-coagulatory milieu that favors all stages of atherogenesis (*8*). Given the relationship between endothelial dysfunction and atherosclerosis, it is likely that the status of the endothelial function may reflect the propensity of an individual to develop atherosclerotic disease, and thus, the presence of endothelial dysfunction may serve as an indicator of the initial stages of vascular failure. Strong evidence of a role for endothelial dysfunction as an independent predictor of cardiovascular event stems from several studies investigating the presence and prognosis of endothelial dysfunction in both the coronary and systemic circulations (*9*–*14*).

Assessment of Vascular Endothelial Function in Humans

Biomarkers

To clinically assess endothelial function, the easiest and the most convenient methods involve blood testing, namely, measurement of endothelium-derived vasoactive substances or markers of endothelial damage. Circulating levels of nitrites and nitrosylated proteins in part reflect endothelial generation of NO. However, these levels are difficult to measure and may not always represent endothelial NO production (*15*). Specifically, the values are confounded by the formation of adducts from other nitrogen-containing species and other sources of NO, including a wide variety of dietary NO. Asymmetric dimethylarginine (ADMA) is an endogeneously derived competitive antagonist of NO synthase. Increased levels of ADMA are associated with a reduction of NO bioavailability and are linked to preclinical atherosclerotic disease burden and adverse outcomes, so the ADMA may prove to be a useful measure of endothelial status and a potential marker of risk in clinical practice (*16*, *17*). At present, however, the measurement of ADMA remains challenging and expensive. Endothelial cell activation leads to an increased expression of adhesion molecules that is essential for leukocyte adhesion to and migration into the vessel wall, which is the fundamental process in atherosclerotic lesion initiation, progression, and destabilization. Well-characterized cell adhesion molecules that can be measured at their circulating levels with commercial immunoassay methods include E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) (*18*, *19*). Similarly, the platelet-endothelial cell interaction or procoagulant consequences of endothelial activation can be assessed by measurement of von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1), or thrombomodulin (*20*, *21*). Endothelium-derived microparticles (EMPs) are vesicles formed by the cell membrane when the endothelial cells are activated. The circulating EMPs are elevated in association with endothelial activation or apoptosis (*22*. *23*). Although their function is not well understood, they may not merely be endothelial activation markers but also have functions as diffusible mediators in proinflammatory cell signaling. Also, the measurement of circulating endothelial progenitor cells (EPCs) provides a novel and exciting means to follow the determinants of endothelial injury and repair,

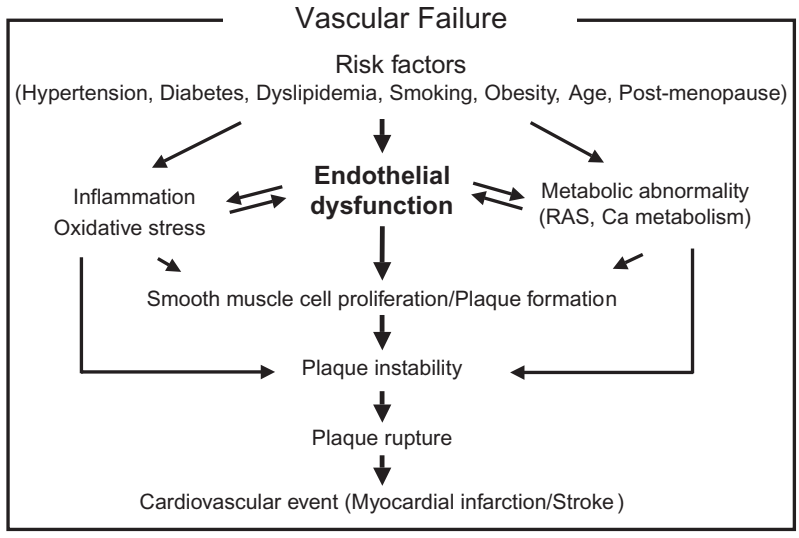

Fig. 1. *Vascular failure. "Vascular failure" is a concept that integrates endothelial dysfunction, smooth muscle dysfunction, and metabolic abnormalities of the vessel wall including inflammation, oxidative stress, and breakdown of the neurohormonal balance. Vascular failure is a comprehensive syndrome of failed vascular functions that extends from risk factors to established atherosclerotic disease with arterial stenosis, and further to serious vascular events that may be caused by plaque rupture. RAS, renin-angiotensin system.*

and it has been shown to be associated with future cardiovascular events (*24*). However, EMPs and EPCs require very complex and expensive technology, such as the flow cytometry, to be detected, so both measures remain far from clinical use.

Although the measurement of biomarkers can provide important information regarding the mechanisms and severity of endothelial dysfunction in various populations, many of these markers not only are difficult and expensive to measure but are also often affected by various confounding factors. Therefore, these markers currently have only a limited significance in the clinical assessment of endothelial function and are therefore used only in the clinical research setting.

Assessment of the Endothelium-Dependent Vasomotor Response

Endothelium-dependent vasomotion has been the most widely used clinical endpoint for the assessment of endothelial function. Its assessment involves the pharmacological and/or physiological stimulation of endothelial release of NO and other vasoactive compounds, and often a comparison of vascular response to endothelium-independent dilators such as nitroglycerin.

Since the first description of endothelial dysfunction in atherosclerotic epicardial coronary arteries, in 1986 by Ludmer *et al*. (*25*), the invasive assessment of coronary endothelial function by quantitative coronary angiography, along with graded intracoronary infusions of endothelium-dependent vasodilators such as acetylcholine (ACh), has been considered the "gold standard" for endothelial function testing. ACh causes both vasodilation by promoting endothelial NO release and vasoconstriction by a direct action on the vascular smooth muscle. ACh dilates normal blood vessels that have an intact endothelium, but, paradoxically, it constricts vessels if their endothelium is damaged (*25–29*). Thus, the effect of ACh on vasomotion is a very sound method for evaluating vascular endothelial function. In addition, coronary Doppler flow measurements with intracoronary injection of ACh provide information regarding the endothelial function of coronary resistance vessels, because blood flow is regulated by the vasomotion of the resistance vessels (*30*, *31*).

During the last decade, minimally invasive or noninvasive techniques have been developed to assess the endothelium-dependent vascular function of the forearm arteries, namely peripheral vascular endothelial function. These techniques include forearm blood flow measurement by strain gauge plethysmography using the venous occlusion technique and flow-mediated vasodilation (FMD) by high-resolution ultrasonography. Forearm blood flow is influenced mainly by the endothelial function of the resistance vessels, whereas FMD reflects mainly the endothelial function of the conduit arteries (*32*). Using strain gauge plethysmography, the endothelial function of the resistance vessels can be evaluated by an ACh-induced blood flow increase or postischemic reactive hyperemia (*33*). However, ACh must be administrated by direct intra-arterial infusion, which is invasive. Postischemic reactive hyperemia is also mediated by endothelial NO (*34*) but is less invasive. An occlusion of blood flow to the upper extremity produced by the inflation of a blood pressure cuff,

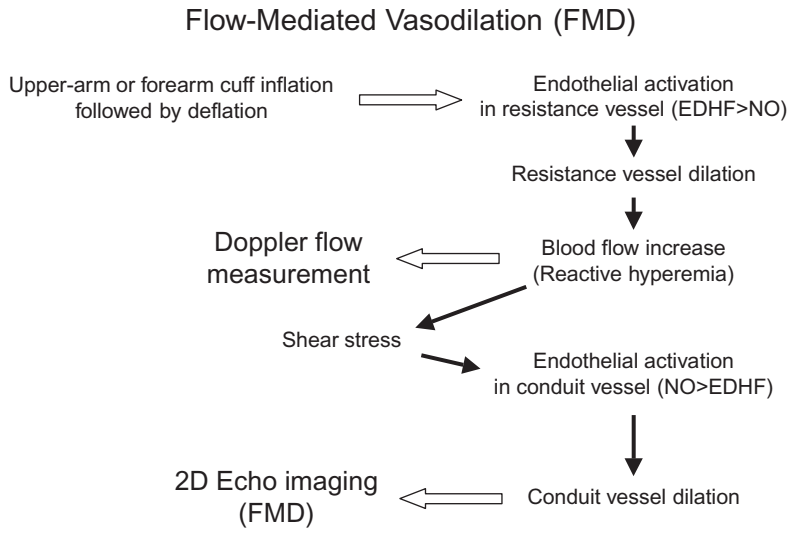

Fig. 2. *Mechanism of flow-mediated vasodilation (FMD). An occlusion of blood flow to the upper extremity produced by the inflation of a blood pressure cuff, followed by the release of the occlusion, results in an immediate increase in blood flow (reactive hyperemia). Reactive hyperemia increases the vessel wall shear stress in the proximal artery with subsequent flow-dependent vasodilation. FMD can also occur in response to a change in the shear stress produced by a hyperemic stimulus. In addition, FMD of the conduit artery may be related to any change in flow, indirectly mediated by changes in the microcirculation (i.e., vasomotion of the resistance vessels) rather than an improvement of the endothelial function of the conduit vessel per se. The endothelium-derived relaxing factors control vascular endothelial function. Although endothelium-derived NO is the most important vasodilatory substance in the conduit arteries, endothelium-derived hyperpolarizing factor (EDHF) predominantly acts in the resistance vessels.*

followed by the release of the occlusion, results in an immediate increase in blood flow, namely, reactive hyperemia. However, the technique of venous occlusion plethysmography with reactive hyperemia is somewhat complex. Since reactive hyperemia increases the vessel wall shear stress in the proximal artery with subsequent flow-dependent vasodilation, FMD of the brachial artery is currently the most frequently used noninvasive surrogate of endothelial function (Fig. 2). The noninvasive nature of this technique allows repeated measurements over time to study the effectiveness of various interventions that may affect vascular health. Noninvasive assessment of FMD of the brachial artery was shown to be strongly correlated with the coronary endothelial function assessed by a change in conduit vessel diameter in response to ACh during coronary angiography (*35*). Recently, guidelines for FMD measurement were released to provide state-of-the-art information on this attractive, evolving technique (*36*).

Alternative noninvasive methodologies have been developed to assess endothelial function. A β2 adrenergic agonist, salbutamol, reduces arterial stiffness in an NO-dependent manner. Therefore, changes in the stiffness that occurs with a salbutamol inhaler at standard clinical use, measured with pulse wave analysis by radial artery tonometry or pulse contour analysis by digital photoplethysmography, can be used as a measure of endothelial function. Changes in an augmentation index, calculated from the effects of arterial stiffness and arterial wave reflection on a central aortic waveform, have been also validated (*37*). Similarly, reactive hyperemia has been used to elicit changes in conduit artery pulse wave velocity and digital pulse volume that can be measured by oscillometry to identify limb arterial pulse pressure, wave form, timing, and also digital pulse amplitude tonometry (*38*, *39*). However, the relative contribution of structural alterations in the vessel wall and endothelium-dependent biology remains uncertain, so these measurements may merely complement FMD testing.

Although FMD has several issues that still need resolution, it appears to be the most practical method for assessing the vascular endothelial function of conduit arteries. The methods used to measure FMD require standardization before this technique can achieve widespread use among practitioners who are not specialists in cardiovascular medicine.

Practice of FMD Measurement

Conditions for FMD Measurement

There are several confounding factors, including circadian variations, diet, tobacco use, physical activity, posture, time of day, and use of vasoactive medications, that can affect the magnitude of FMD and the reproducibility of the data. There-

fore, we should unify the conditions for the measurement to control these factors.

The measurement should be performed in a dark, quiet, and temperature-controlled (23–26°C) room and generally in the morning after at least 12 h of fasting. If the measurements are necessarily performed in the afternoon, the subjects should eat only a light meal and should fast for at least 4 h before the study. The subjects should not exercise and should not ingest substances that might affect FMD, such as caffeine, high-fat foods, and vitamin C, or use tobacco for at least 6 h. In addition, all vasoactive medications should be withheld for at least 4–5 half-lives. If the subjects are premenopausal women, the phase of the menstrual cycle should be recorded (*40*). The subjects should be asked to rest in a supine position for at least 10 min prior to the FMD measurement. The investigators should measure blood pressure and heart rate and should confirm that the subjects are free from hypotension or bradycardia.

Equipment for Measurement

High-resolution ultrasound systems must be equipped with vascular software for two-dimensional (2D) imaging with the pulsed Doppler flow velocimeter. A linear array transducer probe with a frequency of 7–12 MHz should be used, attached to a high-quality mainframe ultrasound system. For multicenter comparisons, the same frequency should be used. A stereotactic probe-holding device and a system with a support arm should be used to minimize movements during the measurement.

Image Acquisition

In general, the brachial artery is used for FMD measurement. The measurements are performed with the subject in a supine position, with the arm kept in a comfortable position for imaging. The brachial artery is imaged just above the antecubital fossa in the longitudinal axis. A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall is selected for continuous 2D grayscale imaging. During image acquisition, anatomic landmarks such as veins and fascial planes are recorded to help image the same segment of artery throughout the study.

Endothelium-Dependent FMD

A blood pressure cuff is placed on either the upper arm, proximal to the probe, or the forearm, distal to the probe. A baseline resting image is acquired, and blood flow is estimated by time-averaging the pulsed Doppler velocity signal obtained from a mid-artery sample volume. Then, the cuff is inflated to 30 mmHg above systolic pressure to occlude arterial inflow for 4.5 min. This causes ischemia and consequent dilation of downstream resistance vessels *via* autoregulatory mechanisms. Subsequent cuff deflation induces a brief high-flow state through the brachial artery (*i.e.*, reactive hyperemia) to accommodate the dilated resistance vessels. The resulting increase in shear stress causes the brachial artery to dilate. The longitudinal image of the artery is recorded continuously from baseline to the complete return to baseline after cuff deflation. A mid-artery pulsed Doppler signal is simultaneously obtained immediately upon cuff release and no later than 15 s after cuff deflation to assess maximum hyperemic velocity.

Traditional approaches to the FMD calculation express that the maximal increase in diameter occurs approximately 60 s after the release of the occlusive cuff, or 45–60 s after the peak reactive hyperemic blood flow (*41*, *42*). However, recent evidence demonstrated that the time to maximum diameter was significantly different between young and older subjects and that in some older sedentary subjects it reached more than 120 s (*43*). Thus, more sophisticated validations for the time course of FMD may be required.

Studies have variably used either upper-arm or forearm cuff occlusion, and there is no consensus as to which technique provides more accurate or precise information. The dilatory response at both the brachial and the radial artery levels after the release of forearm cuff occlusion can be blocked by the infusion of a specific NO antagonist, N^G-monomethyl-L-arginine (L-NMMA), and therefore the FMD obtained using the forearm cuff occlusion technique is dominantly NO-dependent (*44*). The forearm cuff technique yields highly reproducible data, but it provides less hyperemic vessel dilation and often produces complications such as petechiae. In contrast, the vasodilation after the release of upper-arm occlusion consists of both NO-dependent and NO-independent factors due to tissue ischemia at the point of measurement, although the upper-arm technique elicits a greater change in brachial arterial diameter due to more reactive hyperemia (*41*, *45*, *46*). Recently, Guthikonda *et al*. demonstrated that the upper-arm technique could not accurately detect either endothelial dysfunction or its improvement with xanthine oxidase inhibition (*47*). In addition, the upper-arm occlusion is technically more challenging for accurate data acquisition, as the image is distorted by the collapse of the brachial artery and the shift in soft tissue. Thus, for the upper-arm technique, a narrow cuff for a child should be used, and the cuff should be positioned as far from the probe as possible to avoid the image shift.

Endothelium-Independent Vasodilation with Nitroglycerin

To determine whether the decreased FMD specifically depends on endothelial dysfunction or whether it is derived from vascular smooth muscle dysfunction or the changes in vascular structure, endothelium-independent vasodilation should be assessed simultaneously, using a direct smooth muscle relaxant such as nitroglycerin (Table 1).

After at least 15 min of rest following completion of the FMD measurement, another image is acquired to document the recovery of baseline conditions. In most studies to date, a

Table 1. Flow-Mediated Vasodilation (FMD) *vs.* Nitroglycerine Vasodilation (NTGD)

FMD	NTGD	Vascular function
→	→	Normal
↓↑→	↓	Smooth muscle dysfunction, change in vascular structure
↓	→	Endothelial dysfunction

single 0.4 mg dose of a sublingual nitroglycerin spray or a sublingual nitroglycerin tablet has been given to determine the maximum obtainable vasodilator response, and to serve as a measure of endothelium-independent vasodilation that reflects vascular smooth muscle function (*48*). However, the maximum vasodilatory response to this dose reaches 120%, which is greater than the FMD response, and it is therefore not suitable for an internal control. In contrast, the European Society of Hypertension guideline states that 25 μg of sublingual nitroglycerin produces a maximum vasodilator response equivalent to the FMD response. Actually, however, 25 μg of sublingual administration is difficult to obtain in practice. Our group previously demonstrated that the maximum vasodilator response to a quarter tablet (75 μg) of sublingual nitroglycerin was 110%, which is equivalent to the FMD response (unpublished data). Since a quarter tablet can be easily made using a tablet cutter, we currently propose 75 μg as a practical dose for the clinical assessment of vascular smooth muscle function. Peak vasodilation occurs 3–5 min after nitroglycerin administration, and the images should be continuously recorded during this time period. The blood flow velocity obtained by the pulsed Doppler signal is also recorded at baseline and at the time of maximum flow velocity.

Measurement of the Arterial Diameter

Using electrocardiographic gating, the brachial artery diameter is measured in the image at the end-diastolic phase identified by the onset of R-wave. The "m-line"—the diameter between the media-adventitia interfaces of anterior and posterior walls—is measured as the artery diameter. For manual tracing, the diameter is measured at 3 points in a single frame using a caliper and averaged at baseline. The FMD is assessed at the point where maximum dilation is obtained in the continuous recording, generally 45–60 s after cuff release (*42*). Recently developed automated computerized analysis systems of the brachial artery ultrasound scan with a wall tracking algorithm provide for the continuous evaluation of the time course of the total dilation response during reactive hyperemia testing (*49*). If such an auto edge tracking system is used, it is necessary to confirm that the noise in the recording is not used as the boundaries of the vessel wall. The FMD is typically expressed as the maximum change in diameter after cuff release normalized to the baseline diameter (% of baseline diameter).

Reproducibility

Despite its deceptively simple appearance, ultrasonographic assessment of brachial artery reactivity requires high reproducibility. It is technically challenging and has a significant learning curve, typically requiring at least 6 months of training and at least 100 supervised scans. In addition, a minimum of 100 scans per year should be performed to maintain competency. Periodic participation in training courses or workshops may also be useful to maintain competency. Intraobserver and interobserver variability in image acquisition and analysis should be established and periodically reassessed for each condition, including baseline, reactive hyperemia, and nitroglycerin administration. Longitudinal studies, in which interventions are tested over weeks to months, require that reproducibility measurements be performed at longer intervals. Because FMD is a percentage-ratio measure, small differences between observers appear very large. There is no single ideal measurement for assessing the reproducibility of this technique. The automated edge detection systems for measuring artery diameter are mandatory to reduce the variability of the measurement. Acceptable reproducibility is a variation of FMD over time of less than 5% (*50*).

A novel vascular ultrasound system that installs 2D imaging with an edge-tracking system and the pulsed Doppler flow velocimeter for automatic measurement has also been developed (UNEXEF; Unex Corporation, Nagoya, Japan). The system is unified with a probe-holding device and an arm-supporting unit. The automatic measurement function of this system displays serial changes in both vessel diameter and blood flow velocity, and it calculates not only maximum vasodilatory and blood flow responses but also potential novel endothelial function indices, such as time to maximum responses (Fig. 3) or area under the curves. These novel indices should be evaluated in various pathophysiologic states.

Limitations

FMD is a simple and widely available tool for assessing endothelial function, but it has several limitations as there are confounding factors that might potentially affect the result. FMD can be affected by a change in the shear stress produced by a hyperemic stimulus. Therefore, the flow stimulus should be consistent. Otherwise, any change in FMD of the conduit artery may be related to changes in flow, indirectly mediated by changes in the microcirculation (*i.e.*, vasomotion of resistance vessels) rather than an improvement of the endothelial function of the conduit vessel *per se* (Fig. 2). Another potential factor that might confound interpretation of FMD is the baseline diameter. If the baseline diameter changes, the resulting percent change in diameter might be affected. For any given absolute change in the postflow stimulus diameter, a larger baseline diameter yields a smaller measure of percent change. In contrast, smaller arteries appear to dilate more than

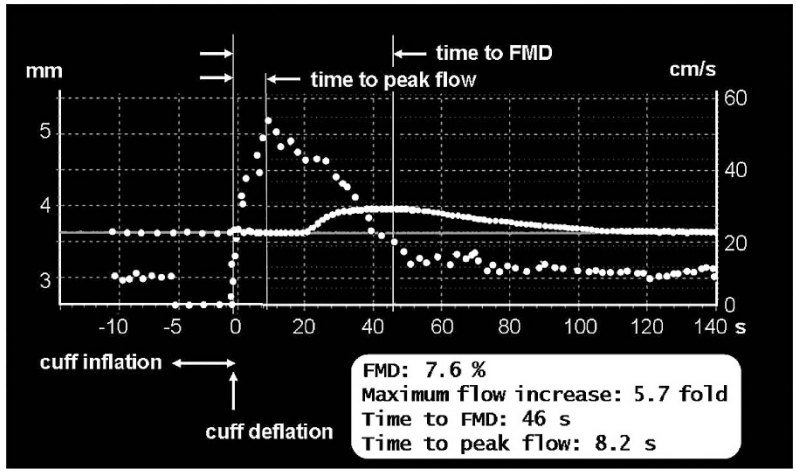

Fig. 3. *A continuous recording of brachial artery diameter and blood flow velocity during cuff inflation and after cuff deflation. The FMD indicates the endothelial function of the conduit artery, while the maximum blood flow response indicates that of the resistance vessels, although FMD is also indirectly affected by the endothelial function of the resistance vessels. In addition to FMD and the maximum blood flow increase, the time to maximum response for FMD or blood flow may also be used as indices of endothelial function.*

larger arteries do (*51*), because postischemic systolic flow depends on the squared radius of the vessel, and therefore hyperemic shear stress is greater in small arteries (*52*). FMD values have gender differences that might in part be a result of differences in baseline artery diameters (*53*). In addition, sympathetic activation, at a clinically relevant range, has a profound effect on the FMD response through an α adrenergic mechanism (*54*). Thus, data acquisition should include baseline vessel diameter, rheological parameters such as hematocrit that provide shear stress, blood pressure, and heart rate at the time of the measurements, maximum vessel diameter at FMD, percent increase in maximum diameter at FMD per baseline diameter, maximum vessel diameter after nitroglycerin administration, percent increase in maximum diameter after nitroglycerin administration per baseline diameter, and percent increase in the Doppler blood flow velocity at the peak per baseline blood flow velocity.

In the assessment of conduit artery endothelial function using serial measurements of FMD in longitudinal studies, the baseline arterial diameter and blood flow increase attributable to reactive hyperemia should remain constant over time. If FMD is used to evaluate the risk of a cardiovascular event or disease progression, multivariate analysis should be used to assess whether FMD is independent of other conventional risk factors. In longitudinal interventional studies designed to improve FMD, conventional risk factors should remain constant during the observational period. In multicenter studies, methods of the measurement should be unified as much as possible, and a core laboratory should be used to analyze FMD data to minimize measurement variability among different centers.

Clinical Perspectives

FMD has been used to identify novel cardiovascular risk factors or to investigate the process of atherosclerosis as a translational research tool. Endothelial function assessed by FMD may serve as an integrating index of risk factor burden and genetic susceptibility and a preclinical marker of cardiovascular disease (*36*). Ongoing studies should determine whether the early measurement of FMD stratifies patients at risk for developing coronary artery disease, cerebral vascular disease, and/or peripheral vascular disease. FMD is particularly well suited for study of the earliest stages of vascular failure and thus may provide an important opportunity to prevent it. Various studies have demonstrated that brachial artery reactivity improves with risk factor modification and treatment with drugs known to reduce cardiovascular risk. Because there are no studies that have shown a correlation between improvement in FMD and improvement of outcome, it remains unknown whether an improvement in endothelial function directly translates into a reduction of cardiovascular events. In the future, however, even practitioners who are not specialists in cardiovascular medicine may use FMD to assess the response to drug therapy and to modify patient risk factors. We believe that the FMD-guided therapeutic approaches for vascular failure would contribute to improvement of cardiovascular mortality and morbidity.

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