Flow-Mediated Vasodilation*

A Diagnostic Instrument, or an Experimental Tool?

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Brachial arterial flow-mediated dilation (FMD), assessed by high-resolution ultrasonography, reflects endothelium-dependent vasodilator function. FMD is diminished in patients with atherosclerosis and with coronary risk factors, and improves with risk-reduction therapy. Therefore, the measurement of FMD can be a good prognostic instrument in preventive cardiology, is useful to predict short-term postoperative cardiovascular events in a high-risk population and to assess long-term cardiovascular risk in a lower risk population, and is an excellent experimental tool to detect changes in endothelial function after new therapeutic interventions. In this review article, the pathophysiology of FMD, based on reactive hyperemia, is extensively discussed. Furthermore, an overview is given of the actual clinical indications of FMD measurement.

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Key words: coronary artery disease; endothelial dysfunction; flow-mediated vasodilation; review

Abbreviations: CAD = coronary artery disease; eNOS = endothelial nitric oxide synthase; FMD = flow-mediated dilation; IMT = intima-media thickness; NO = nitric oxide; PWV = pulsewave velocity

Coronary angiography has been the cornerstone in the diagnosis of coronary artery disease (CAD) for decades and is used to quantify significant prognostic information about epicardial coronary arteries. However, this technique is restricted to analyzing the lumen and does not assess the functional reactivity of the coronary arteries (ie, endothelial function). Furthermore, angiography is invasive and may miss significant atherosclerosis that is present in the vessel wall before eventual encroachment on the lumen occurs. Therefore, the assessment of vessel function may yield additive prognostic information to that derived from standard coronary angiography only.

Normal vascular endothelial cells support cardiovascular function by promoting vasodilatation, and by inhibiting platelet aggregation, WBC adhesion, and smooth muscle cell proliferation. In contrast, a dysfunctional endothelium is characterized by an impaired endothelium-dependent vasodilation response, which favors platelet aggregation and WBC adhesion, and promotes smooth muscle cell proliferation. Endothelial dysfunction is characterized by a decreased production and/or local bioavailability of nitric oxide (NO). It plays a pivotal role in the development, progression, and clinical manifestations of atherosclerosis, as well as in the development of ischemia and thrombosis in the late stages of the disease, by promoting coronary vasoconstriction and thrombosis.

Impaired endothelium-dependent dilation in the coronary circulation is associated with coronary atherosclerosis and coronary risk factors, and improves with risk-reduction therapy. Consequently, endothelial function has been defined as an “excellent barometer” of vascular health and can be used to gauge cardiovascular risk. A pathogenic link between coronary endothelial dysfunction and cardiovascular events was almost simultaneously demonstrated by Suwaidi et al and Schächinger et al.

Endothelial function can be evaluated by the following different approaches: (1) measurement of morphologic and mechanical characteristics of the vascular wall (eg, intima media thickness, compliance, distensibility, and remodeling indexes); (2) determination of soluble endothelial markers (eg, von Willebrandt factor, plasminogen activator, inhibitor complex thrombomodulin adhesion molecules, and N-oxides); and (3) measurement of the endothelium-dependent regulation of vascular tone at focal sites of the circulation.
Invasive vasomotor techniques (eg, quantitative coronary angiography and strain gauge plethysmography) are considered to be the diagnostic standard for the evaluation of endothelium-dependent vasodilation. However, patients cannot be frequently subjected to these invasive techniques as is needed in clinical applications and population-based studies. Therefore, brachial artery flow-mediated dilation (FMD) measurement by high-resolution ultrasonography is a broadly applicable method that is used for the examination of endothelial function.11–14

Both peripheral and coronary endothelial dysfunction may be induced by several risk factors, as in familial hypercholesterolemia,15,16 smoking,17,18 diabetes mellitus,19,20 and hyperhomocysteinemia.21,22 Coronary endothelial function has been found to correlate with endothelial function in accessible peripheral arteries, such as the brachial artery.23 A close relation has been demonstrated between FMD in the brachial artery and the coronary circulation, both in terms of morphologic lesions24 and the functional responses to acetylcholine.23,25

**Physiology of FMD**

FMD is designated as an endothelium-dependent process that reflects the relaxation of a conduit artery when exposed to increased flow and, thereby, increased shear stress. When blood flow increases through a vessel, the vessel dilates. This physiologic response was first described by Schretzenmayer26 and was subsequently demonstrated in a number of conduit arteries. An impaired (ie, diminished) FMD response reflects endothelial dysfunction.

**Reactive Hyperemia**

In peripheral arteries, a temporary increase in shear stress can be induced by increasing the local blood flow, the so-called reactive hyperemia. Reactive hyperemia can be achieved by inflating a pneumatic sleeve around the forearm to 220 mm Hg for 4 min and then deflating it. This results in an abrupt decrease in vascular resistance. After deflation, the arterial diameter is measured at 60 and 90 s to determine the maximum posthyperemia diameter. FMD is expressed as the absolute or relative change in diameter from the baseline measurements.

**Shear Stress**

Shear stress is mainly determined by blood flow and its attractive force exerted at a vector perpendicular to the long axis of the vessel (Fig 1). The endothelium acts as a mechanotransducer that senses changes in shear stress and subsequently modifies the output of dilator factors. The endothelial signaling cascade, which is responsible for converting mechanical stimuli into the release of vaso-dilatory molecules, has not been fully clarified.

FMD has been shown to be predominantly dependent on endothelium-derived NO.27,28 The endothelial cell membrane contains specialized ion channels, such as calcium-activated potassium channels, that open in response to shear stress.29–31 The effect of potassium channel opening is to hyperpolarize the endothelial cell, increasing the driving force for calcium entry. Calcium activates endothelial NO synthase (eNOS), and the subsequent generation of NO appears to account for FMD.28,32

Several mechanisms are responsible for the increase in NO in response to changes in shear stress. Very short-term changes may be mediated by the increase in intracellular calcium that occurs when ion channels open. Slightly longer time periods of shear stress are responsible for the phosphorylation of eNOS via serine/threonine protein kinase and Akt/protein kinase B, even at low calcium concentrations. In addition, other posttranslational modifications of the enzyme (myristilation or palmitoylation) or interaction with caveolin can affect intracellular localization of the enzyme and thereby alter its function. Longer time periods (many minutes or hours) of

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**Figure 1.** The genesis of FMD, in response to different changes in shear stress. * = very short-term changes; ** = changes taking place over slightly longer periods (minutes); *** = changes taking place over a longer time (many minutes or hours). PGI₂ = prostacycline; EDHF = endothelium-derived hyperpolarizing factor; Kc = calcium-activated potassium channel.
shear stress activate eNOS gene transcription, which may result in continued increases in NO generation if shear stress is maintained at high levels.35

FMD depends not only on NO formation, but also on NO inactivation and the sensitivity of the underlying vascular smooth muscle for NO. Regular exercise simultaneously induces the up-regulation not only of eNOS but also of superoxide dismutase expression.34 This feed-forward mechanism could prevent superoxide-mediated inactivation of NO and thus increase shear stress-dependent FMD.

Very recently, Mitchell et al35 demonstrated that impaired FMD of the brachial artery may not be due to the impaired release of NO from the vascular endothelium, but from a lesser stimulus to NO release as a consequence of decreased flow velocity and shear stress during reactive hyperemia caused by impaired microvascular response.

The reduced NO bioavailability that characterizes endothelial dysfunction may induce important steps in the appearance and progression of the atherosclerotic lesions, including monocyte and leukocyte adhesion and platelet-vessel wall interaction. NO also reduces vascular tone, decreases endothelial permeability, and inhibits vascular smooth muscle cell migration and proliferation.

The principal mediator, but not the only mediator, of FMD is NO. In the eNOS knockout mice, FMD appears to be mediated by endothelium-derived prostanoids since it is blocked by indomethacin.36 It is unknown whether mediators, such as the unidentified endothelium-derived hyperpolarizing factor, can cause FMD if both the NO and prostanoid pathways are blocked.

In human forearm circulation, endothelial responses to blood flow depend on the characteristics of the flow stimulus. FMD after brief episodes of hyperemia is often almost exclusively mediated by NO, whereas dilatation during sustained hyperemia is unaffected by the inhibition of NO synthesis.37 Additionally, FMD is diminished by reductions in extracellular calcium and sodium,38 and is improved by magnesium.39

Endothelium-Independent Vasodilation With Nitroglycerin

An exogenous NO donor (e.g., a single high dose of nitroglycerin [0.4 mg]) is used to determine the maximum obtainable vasodilator response, and to serve as a measure of endothelium-independent vasodilation, reflecting vascular smooth muscle function.40 As cardiovascular risk factors increase in number, smooth muscle dysfunction becomes apparent, and thus the nitroglycerin response is progressively impaired independently of endothelial dysfunction.41 This should be taken into account when studying patients with either coronary or systemic atherosclerosis. In hypertensive subjects, for example, nitroglycerin-mediated vasodilation is also impaired, suggesting an impairment of overall vascular function but not necessarily a single impairment of endothelial function.42

Rather than increasing doses, a single bolus of nitrates is preferable, because nitrates may further bring changes in smooth muscle function or arterial compliance. Peak vasodilation occurs 3 to 4 min after nitrate administration. This measurement can only take place at least 10 min after reactive hyperemia, since baseline conditions are not yet reestablished prior to this moment.

Indication for FMD Measurement

Risk Stratification for Cardiovascular Events

Two major invasive studies8,9 have disclosed the relation between coronary endothelial dysfunction and cardiovascular events. Several studies have addressed the question of whether endothelial function in a peripheral artery as such also provides prognostic information about cardiac events. Heitzer et al43 demonstrated that patients with CAD with impaired forearm microvessel responses to acetylcholine developed more cardiovascular events over a 4.5-year follow-up period. Perticone et al44 examined endothelial function in response to intraarterial acetycholine infusion in 225 patients with newly diagnosed hypertension. Patients with lower vasodilator responses had a significantly higher risk of experiencing a cardiac or vascular event (relative risk, 2.084). Very recently, Fathi et al45 examined the value of the measurement of brachial artery reactivity in predicting cardiovascular events in a group of 444 patients with a significant risk of cardiovascular events. They demonstrated that patients with FMD of < 2% had significantly more cardiovascular events than those with normal FMD (> 6.3%) or mildly abnormal FMD (2.1 to 6.3%). However, in this study, the mean intima-media thickness (IMT), rather than FMD, was the vascular factor independently associated with mortality.

Risk Stratification in Patients With Chest Pain

Neunteufl et al44 demonstrated in patients with angina pectoris (n = 74) that those with lesions who were undergoing standard coronary angiography had reduced FMD. Angiography revealed CAD (≥ 30% diameter stenosis) in 44 patients (age range, 32 to 67 years) and smooth coronary arteries in 30 patients
(age range, 22 to 73 years). Patients with CAD showed markedly impaired mean (± SD) FMD compared to the group without CAD (5.7 ± 4.8% vs 12.6 ± 6.7%, respectively; p < 0.0001). The authors further demonstrated a relation between FMD and the extent of CAD (ie, one-vessel, two-vessel, or three-vessel disease).

In another study, Neunteufl et al described the 5-year prognostic value of FMD in patients with chest pain. The evaluated end points in this study were death, myocardial infarction, percutaneous transluminal angioplasty, and coronary artery bypass surgery. These cardiovascular events occurred more often in patients with impaired FMD compared with patients with preserved FMD (ie, FMD < 10% vs FMD > 10%, and FMD 50% vs FMD 15%, respectively; p = 0.002). Events after the first month were observed only in patients with FMD of < 10%, and in this group hospitalization also was necessary more often.

Shroeder et al examined 122 consecutive patients with a clinical suspicion of CAD. Of these patients, 101 were found to have any angiographically detectable disease of any severity. FMD of the brachial artery was significantly better in the group with no CAD (mean FMD, 7.0 ± 3.5%) as opposed to the group with CAD (mean FMD, 3.8 ± 4.1%). FMD showed a 71% sensitivity and a 81% specificity in predicting any CAD. These researchers found that the optimal cutoff point for FMD in terms of sensitivity and specificity in predicting CAD was ≤ 4.5%. These studies suggest that FMD is a parameter worth measuring in patients with clinical suspicion of CAD before coronary angiography, especially if the results of one of the screening tests is negative.

Risk Stratification for Postoperative Cardiovascular Events

Gokce et al demonstrated that impaired FMD of the brachial artery independently predicts short-term cardiovascular events in patients undergoing vascular surgery. No relation was observed between nitroglycerin-mediated dilation and events, and between the extent of reactive hyperemia and events. The predictive value of FMD was independent of vessel size. These observations imply that the results cannot be explained by the altered function of vascular smooth muscle variation in the stimulus for vasodilation, or by larger vessel size in patients who have experienced cardiovascular events. Therefore, FMD measurement can be used as an independent factor in risk stratification in patients undergoing vascular surgery, with high short-term postoperative cardiovascular risk. A potential approach would be to combine the results of endothelial function testing with other test or clinical scoring systems of surgical risk.

Evaluation of New Therapies on Endothelial Function

The assessment of FMD of the brachial artery in clinical trials is increasingly used because of its user-friendly, efficient, and noninvasive nature. Both parallel-group and crossover designs for short-term and longer term intervention trials have successfully used FMD measurement as a reliable technique. A significant improvement in FMD can be seen with 20 to 30 patients in a crossover design study, and with 40 to 60 patients in a parallel-group design study. In studies of this size, the minimal statistically significant improvement that can be detected with intervention is an absolute change in FMD of 1.5 to 2%. An important parameter in such trials is the time-dependent reproducibility of FMD. An acceptable reproducibility is a mean difference of 2 to 3% in FMD over time (on a baseline vasodilation of about 10%). An important factor for the interpretation of the results is the change in baseline diameter. For example, a decrease in baseline diameter will result in an increase in FMD. This increase in FMD is a result of the change in resting tone and not of the beneficial effect of the intervention on endothelial function. Follow-up studies assessing the effects of therapeutic interventions on endothelial function need to have highly standardized study protocols regarding all variable factors.

Investigation of Neurally Mediated Syncope

Takase et al demonstrated that patients with neurally mediated syncope have significantly higher endothelium-dependent and endothelium-independent vasodilation of the brachial artery compared with control subjects. Paradoxical peripheral vasodilation is one of the suspected mechanisms of neurally mediated syncope. Parasympathetic peripheral vasodilation contributes to this vasodilation. Due to increased vagal activity, there is an augmented presence of the postsynaptic transmitter acetylcholine. The increased level of acetylcholine can cause vasodilation through NO.

In the past, head-up tilt table testing was the diagnostic technique of choice for clinically assessing a patient’s susceptibility to neurally mediated syncope, particularly of the vasovagal type. However, tilt testing is a sensitive, but nonspecific, method for confirming neurocardiogenic syncope. Most studies have suggested that such testing discriminates relatively well between symptomatic patients and asymptomatic control subjects, of whom 10 to 15% have
false-positive test results. The sensitivity of tilt table testing is more difficult to evaluate because there is no accepted diagnostic “gold standard.” However, sensitivity (measured against a classic presentation) has been estimated to range from 32 to 85%, with most reports favoring the higher end of this range.51 Therefore, the measurement of FMD might contribute to the diagnostic accuracy of neurally mediated syncope.

**Variable Factors in FMD Measurement**

Changes in FMD have been described not only in the presence of classic risk factors, but also in a variety of other factors such as endogenous, exogenous, environmental, and familial factors (Table 1). This observation is very interesting but makes a correct serial evaluation of FMD in the same subject or a comparison of FMD between subjects very difficult because of the special attention that should be paid to all factors that can influence FMD.

Age and gender are well-known classic risk factors. Diminished endothelial function with advancing age already has been described.52,53 The mechanisms remain uncertain but may relate to age-associated increases in reactive oxygen species production.54 In women, there is even an age-related decline in FMD.

Sustained arterial hypertension blunts FMD in conduit arteries in the peripheral55 and coronary circulation.56–58 The degree of coronary endothelial dysfunction depends on the severity and duration of arterial hypertension as indexed by the degree of left ventricular hypertrophy.59,60 The pathogenesis of the association between endothelial dysfunction and hypertension is not fully understood. There is evidence that endothelial dysfunction may antedate and possibly contribute to the development of essential hypertension.61 However, the larger recent Framingham Heart study62 failed to determine whether endothelial dysfunction is a cause or a consequence of hypertension, or, alternatively, whether FMD and systolic BP are associated with a third factor, such as arterial stiffness.

Diabetic patients demonstrate a glucose-mediated endothelial dysfunction. Potential mechanisms for this include reduced NO bioavailability caused by the increased formation of reactive oxygen intermediates,63,64 glucose autooxidation,65 activation of protein kinase C,66,67 formation of advanced glycosylation end products,68 decreased NO synthase expression,69 and direct chemical inactivation of NO by glucose.70 Short-term antioxidant stress possibly plays a role in glucose-mediated endothelial dysfunction, because pretreatment with antioxidant vitamins may reverse hyperglycemia-induced impairment in endothelial function.71,72

FMD is also impaired by elevated levels of cholesterol, whereas the plasma level of triglycerides does not affect FMD.73,74 In hypercholesterolemia, the impaired vasodilator response may result from increased NO inactivation by oxygen free radicals generated by the presence of oxidized low-density lipoprotein cholesterol and/or lipoprotein (a) particles in the subendothelial space,75 or, in some circumstances, by substrate-limited NO production.

FMD has been shown to be blunted in obese individuals. FMD is significantly lower in healthy obese subjects, compared with healthy nonobese volunteers.76 The mechanisms of obesity-induced endothelial dysfunction are multifactorial, including dyslipidemia, elevated BP, increased inflammation, oxidative stress, and changes in glucose metabolism.

Additionally, weight reduction with a very-low-calorie diet improves FMD in obese individuals. This improvement is related to the reduction in plasma glucose concentration, suggesting that changes in glucose metabolism may determine endothelial vasodilatory function in obese persons.77

Patients with even mild hyperhomocysteinemia have an impaired endothelium-dependent vasodilation. The underlying pathobiological mechanisms are multiple. Hyperhomocysteinemia leads to the increased oxidative inactivation of NO by oxygen-derived free radicals that are formed during the autooxidation of homocysteine, and/or accumulate as a consequence of the homocysteine-mediated inhibition of antioxidant enzymes or of increased endothelial synthesis of the endogenous NO synthase inhibitor asymmetric dimethylarginine. Additionally, elevated homocysteine levels induce the expression of several chemokines and adhesion molecules. Folic acid is well-accepted as the therapeutic strategy for hyperhomocysteinemia. In healthy adults without conventional atherosclerotic risk factors but with mildly elevated homocysteine levels (ie, > 13 μmol/L).

**Table 1—Factors That May Impede FMD**

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**Table 2—Factors That May Impede FMD**

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L), folic acid not only lowers the plasma level of homocysteinemia, it also improves FMD.

It has been shown that a high percentage of patients with unstable angina pectoris have concurrent diminished FMD. Interestingly, the disturbance of endothelial function was reversible after the treatment of acute coronary syndromes. In patients with stable CAD, plasma levels of C-reactive protein were associated with FMD, confirming the relationship between inflammation and the integrity of the endothelium.

FMD is also influenced by hormonal factors, such as circulating levels of estrogen, progesterone, and catecholamines. The investigator should be cognizant of professional sleep deprivation, mental stress (catecholamines), and the phase of the subject's menstrual cycle (estrogen), as these factors may also affect FMD.

Etsuda et al and Otto et al showed a significant diurnal variation in FMD within healthy young men (FMD: 8:00 AM, 4.0%; 12:00 PM, 5.3%; 5:00 PM, 9.7%; 9:00 PM, 6.9%), demonstrating the importance of standardizing the time of day for assessment. Additionally, Title et al and Plotnick et al demonstrated an attenuated response in FMD after a glucose or fat load. These transient reductions lasted up to 3 and 4 h, respectively. Clearly, this indicates the importance of the timing of meals before testing. Therefore, it is recommended that the time of day for testing (between 7:00 and 10:00 AM) be standardized and that a fast of at least 8 h be required.

To limit the factors that can affect FMD vascular reactivity (Table 2), the patients should fast, including caffeine, for at least 8 h before the study and should not have exercised before the test. Preferably FMD measuring should take place in the morning, in a quiet, temperature-controlled room. In addition, patients should not smoke, and all vasoactive medications should be withheld for at least four half-lives, if possible. There are no racial differences in conduit vessel FMD.

Low birth weight is associated with impaired endothelial function in childhood, which is a key early event in atherogenesis. Growth in utero may be associated with long-term changes in vascular function that are manifested by the first decade of life and that may influence the long-term risk of cardiovascular disease. FMD correlates positively and significantly with birth weight.

Healthy young adults with a family history of premature CAD have impaired FMD, even in the absence of other risk factors. This impaired brachial artery FMD not only coincides but also correlates with a greater IMT of the common carotid artery, indicating early functional and structural changes in the vascular endothelium in the offspring of patients with premature CAD. Similar results were obtained in first-degree relatives of patients with type 2 diabetes. Endogenous factors as well as environmental factors, like passive smoking, may impair brachial artery FMD.

### Table 2—Practical Setup

| Quiet, temperature-controlled examination room |
| Examination between 7:00 AM |
| Starvation (including caffeine) ≥ 8 h |
| No smoking (active and passive) |
| No exercise, no night work |
| No mental stress |
| Stop vasoactive medication ≥ 4 × half-life |
| In case of long-term follow-up: cave changes in BP, cholesterol level, and weight; be aware of stage of menstrual cycle |

In healthy people, FMD is 7 to 10% of the baseline diameter, but in patients with cardiovascular disease FMD is impaired or absent, with FMD values of 0 to 5%. Recently, in the Framingham Heart Study (n = 2,883; age range, 33 to 88 years), the mean FMD in women was 3.3% (interquartile range, 1.1 to 4.9%), and 2.4% in men (interquartile range, 0.7 to 3.7%).

Numerous factors may contribute to the variability of FMD, mainly equipment-related, surgery-related, and physiologic influences. Hijmering et al analyzed the reproducibility in healthy volunteers (n = 112). The intrasession variability was 1.1% (extremes, 0.06 to 2.0%), and the intersession variability was 3.6% for observer 1 and 3.8% for observer 2.

Sorensen et al calculated that in clinical trials a mean improvement in FMD of ≥ 2% is necessary to detect a treatment benefit and that for any individual a difference of 4 to 8% is necessary to account for natural variability. Welsch et al studied the clinical trial design and calculated that in a study with a cross-sectional design (ie, smokers vs nonsmokers) 23 subjects would be required to detect an FMD difference of 60% (two-tailed) (eg, 5% vs 8%, respectively, at 90% power). To achieve an FMD difference of 40% (eg, 5% vs 7%, respectively, at 90% power), 46 subjects have to be included.

To achieve a power of 90% in a study with an interventional design (ie, pre-posttreatment), 10 and 19 subjects are required to detect FMD differences of 60% and 40%, respectively (two-tailed). To achieve a power of 80%, 46 subjects are needed to detect an FMD difference of 20% (two-tailed).

FMD measurement can be considered to be a
stable and reproducible technique when performed under strictly controlled conditions. Importantly, to ensure high reproducibility, it is recommended that study designs incorporate a single tester to ensure that subjects are scanned by the same individual each visit.

**INTERRELATIONSHIP AMONG FMD, IMT, AND PWV**

FMD of the brachial artery, pulsewave velocity (PWV), and carotid IMT are all noninvasive techniques that are used for the assessment of cardiovascular risks, and are all used as surrogate markers for atherosclerosis. IMT detects morphologic changes of the carotid artery, consisting of both an intimal atherosclerotic process and medial hypertrophy. IMT is measured by B-mode ultrasonography. PWV reflects arterial distensibility and is measured by pressure or volume pulsewave analysis using a transducer.

There is a significant correlation between aortic PWV and carotid IMT, and there is a negative correlation between FMD and IMT. Recently, Kobayashi et al demonstrated that decreased FMD in the brachial artery was related to increased brachial-ankle and heart-carotid PWV, as well as to increased carotid IMT. The combination of these three methods is very useful in predicting the burden of atherosclerosis, since it was found that subjects with the worst tertiles of all three measurements had a markedly higher prevalence of atherosclerotic disease and carotid plaques. The combination of FMD, IMT, and PWV serves as a more accurate indicator of clinical atherosclerosis than any single measurement.

**Caveats in FMD Measurement**

First, it should be noted that the FMD value is influenced by changes in baseline diameter. Baseline diameter is an important determinant of measures of the percent of change and must be considered when comparing vasodilator responses between different groups of subjects. Aging appears to result in progressive dilation of the brachial arteries at rest and in progressive diminution of the vasodilator response to a flow stimulus.

Most studies published so far have found a negative relationship between baseline diameter and FMD. Many studies have recognized this possible confounder and have matched for baseline diameters. However, drugs that produce increases in baseline diameter, such as angiotensin-converting enzyme inhibitors, angiotensin 1-receptor inhibitors, or calcium antagonists, will lead to smaller estimates of FMD without correction.

Second, there is no consensus about upper vs lower cuff placement. In addition, FMD can be studied in the radial, axillary, and superficial femoral arteries. However, arteries < 2.5 mm in diameter are difficult to measure, and vasodilation is generally less difficult to perceive in vessels > 5.0 mm in diameter.

Third, and perhaps most important, is the specification of the ultrasound system used. Most authors use regular B-mode imaging, which is capable of discerning two adjacent points at least 0.2 to 0.3 mm apart. To show a 5% increase in vasodilation in a brachial artery with 5 mm diameter, a diameter of 0.25 mm must be visualized. Clearly, without the use of modified B-mode systems or M-mode systems with radiofrequency signal processing, it is impossible to reliably detect small changes in FMD. Additionally, there are no long-term prognostic data that link FMD to really hard end points, such as overt atherosclerosis, myocardial infarction, stroke, and death.

**Conclusion**

It has been shown that peripherally measured endothelial function in the brachial artery predicts future cardiovascular disease and the postoperative occurrence of cardiovascular events. It is also an excellent tool in the risk stratification of patients with chest pain, especially before they undergo angiography and when the first test results are negative. Additionally, FMD measurement can be useful in the difficult diagnosis of neurally mediated syncope and in judging the potential utility of new interventions for cardiovascular disease.

The noninvasive evaluation of FMD is very attractive, and in this way it provides a minimal burden to the study population. Therefore, it is the preferred tool with which to study endothelial function in children and pregnant women. The following equipment needed is generally present in each clinical setting: a pneumatic cuff to create reactive hyperemia; and high-resolution ultrasonography to quantify diameter changes. The whole procedure is finished in < 30 min. However, because of the large variation in intersession FMD responses, often exceeding half of the baseline FMD value, the use of FMD as a “therapeutic target” for an individual patient is limited, particularly since the variation seems to be largely due to physiologic fluctuations. However, the measurement of FMD is an attractive tool for serial measurements and long-term studies.
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