

## Technique Report

# Guidelines for the Ultrasound Assessment of Endothelial-Dependent Flow-Mediated Vasodilation of the Brachial Artery

## A Report of the International Brachial Artery Reactivity Task Force

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Endothelial function is thought to be an important factor in the pathogenesis of atherosclerosis, hypertension and heart failure. In the 1990s, high-frequency ultrasonographic imaging of the brachial artery to assess endothelium-dependent flow-mediated vasodilation (FMD) was developed. The technique provokes the release of nitric oxide, resulting in vasodilation that can be quantitated as an index of vasomotor function. The noninvasive nature of the technique allows repeated measurements over time to study the effectiveness of various interventions that may affect vascular health. However, despite its widespread use, there are technical and interpretive limitations of this technique. State-of-the-art information is presented and insights are provided into the strengths and limitations of high-resolution ultrasonography of the brachial artery to evaluate vasomotor function, with guidelines for its research application in the study of endothelial physiology. (J Am Coll Cardiol 2002;39:257-65) © 2002 by the American College of Cardiology

The vascular endothelium is a large paracrine organ that secretes numerous factors regulating vascular tone, cell growth, platelet and leukocyte interactions and thrombogenicity. The endothelium senses and responds to a myriad of internal and external stimuli through complex cell membrane receptors and signal transduction mechanisms, leading to the synthesis and release of various vasoactive, thromboregulatory and growth factor substances. Endothelial dysfunction is thought to be an important factor in the development of atherosclerosis, hypertension, and heart failure. Over the past decade, a noninvasive technique has evolved to evaluate flow-mediated vasodilation (FMD), an endothelium-dependent function, in the brachial artery (1-4). This stimulus provokes the endothelium to release nitric oxide (NO) with subsequent vasodilation that can be imaged and quantitated as an index of vasomotor function. This technique is attractive because it is noninvasive and

allows repeated measurements. However, despite its widespread use, there are technical and interpretive limitations. This report presents state-of-the-art information in this area of research and provides insights into the strengths and limitations of this attractive and evolving technique.

### PHYSIOLOGY OF FMD

The capacity of blood vessels to respond to physical and chemical stimuli in the lumen confers the ability to self-regulate tone and to adjust blood flow and distribution in response to changes in the local environment. Many blood vessels respond to an increase in flow, or more precisely shear stress, by dilating. This phenomenon is designated *FMD*. A principal mediator of FMD is endothelium-derived NO.

The precise mechanisms for the acute detection of shear forces and subsequent signal transduction to modulate vasomotor tone are not fully understood. The endothelial cell membrane contains specialized ion channels, such as calcium-activated potassium channels, that open in response to shear stress (5-7). The effect of potassium channel opening is to hyperpolarize the endothelial cell, increasing the driving force for calcium entry (there are no voltage-gated calcium channels in endothelial cells). Calcium activates an enzyme, endothelial nitric oxide synthase (eNOS), and the subsequent generation of NO appears to account for FMD (8,9). Indeed, endothelial denudation or treatment

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**Abbreviations and Acronyms**

ECG	= electrocardiogram/electrocardiographic
eNOS	= endothelial nitric oxide synthase
FMD	= flow-mediated vasodilation
NO	= nitric oxide
NOS	= nitric oxide synthase
NTG	= nitroglycerin
2D	= two-dimensional

with a nitric oxide synthase (NOS) inhibitor abolishes FMD in a variety of arterial vessels. However, it was recently shown that blood vessels from mice genetically engineered to lack the eNOS enzyme (eNOS knockout mice) still respond to shear stress by dilating (10). In the eNOS knockout mice, FMD seems to be mediated by endothelium-derived prostanoids, as it is blocked by indomethacin (10). Thus, there is some redundancy in the system, and more than one endothelial mediator is capable of acting as the signal between endothelium and smooth muscle. It is unknown whether other mediators, such as the putative endothelium-derived hyperpolarizing factor, can cause FMD if both NO and prostanoids are deficient.

Several mechanisms may underlie the increase in NO in response to changes in shear stress. Very acute changes may be mediated by the increase in intracellular calcium that occurs when ion channels open (see the previous text). Over slightly longer time periods (minutes), shear-stress-induced phosphorylation of eNOS via a serine/threonine protein kinase, Akt/PKB, increases eNOS activity, even at low calcium concentrations, and this may be important to allow continued output of NO (11,12). In addition, other post-translational modifications of the enzyme (myristylation or palmitoylation) or interaction with caveolin can affect intracellular localization of the enzyme and thereby alter its function. Over longer time periods (many minutes or hours), eNOS gene transcription is activated, and this can result in continued increases in NO generation if shear stress is maintained at high levels.

**TECHNIQUE**

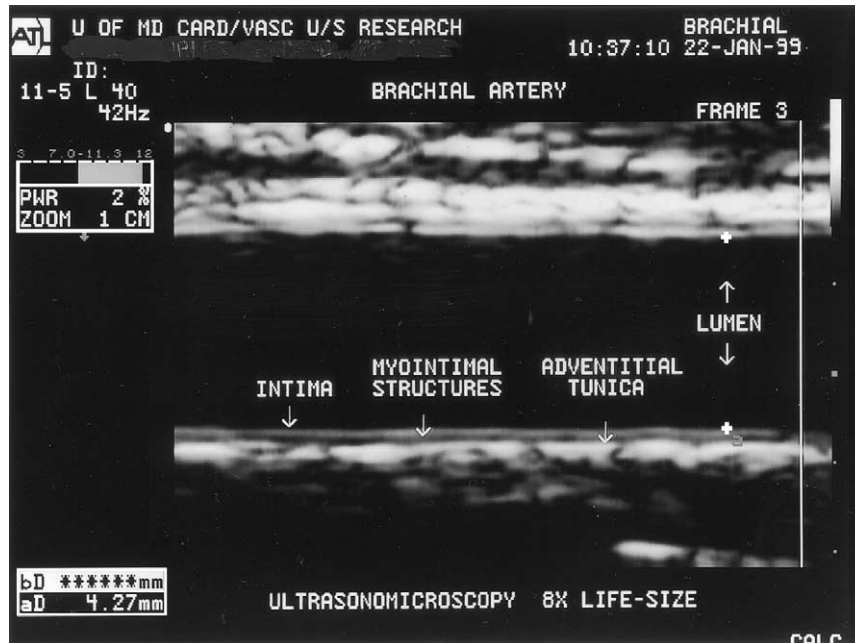
**Subject preparation.** Numerous factors affect flow-mediated vascular reactivity, including temperature, food, drugs and sympathetic stimuli, among others. Therefore, subjects should fast for at least 8 to 12 h before the study, and they should be studied in a quiet, temperature-controlled room. All vasoactive medications should be withheld for at least four half-lives, if possible. In addition, subjects should not exercise, should not ingest substances that might affect FMD such as caffeine, high-fat foods and vitamin C or use tobacco for at least 4 to 6 h before the study. The investigator should be cognizant of the phase of the subject's menstrual cycle, as it too may affect FMD (13). All of these confounding factors must be considered in preparing a subject in studies that seek to determine the impact of a single intervention. For observational cohort

studies, data must be collected on those factors known to affect the measurement of FMD, and analysis should address their impact (14-16).

**Equipment.** Ultrasound systems must be equipped with vascular software for two-dimensional (2D) imaging, color and spectral Doppler, an internal electrocardiogram (ECG) monitor and a high-frequency vascular transducer. A linear array transducer with a minimum frequency of 7 MHz, attached to a high-quality mainframe ultrasound system, is used to acquire images with sufficient resolution for subsequent analysis. Image resolution is enhanced with broadband (multiple-frequency: 7 to 12 MHz) linear array transducers. Timing of each image frame with respect to the cardiac cycle is determined with simultaneous ECG recording on the ultrasound system video monitor.

**Image acquisition.** The subject is positioned supine with the arm in a comfortable position for imaging the brachial artery. The brachial artery is imaged above the antecubital fossa in the longitudinal plane (Fig. 1). A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall is selected for continuous 2D grayscale imaging. Currently, cross-sectional imaging of the brachial artery cannot be used to determine maximum diameter or area of the lumen because of inadequate image definition of the lateral walls. Also, skew artifacts from cross-sectional imaging limit accurate diameter determination. In addition to 2D grayscale imaging, both M mode and A mode (wall tracking) can be used to continuously measure the diameter (17,18), yet these techniques may be more subject to error owing to tracking drift. No direct comparison has been made of diameter determinations from continuous recording using grayscale images versus wall tracking. During image acquisition, anatomic landmarks such as veins and fascial planes are noted to help maintain the same image of the artery throughout the study. A stereotactic probe-holding device can be helpful.

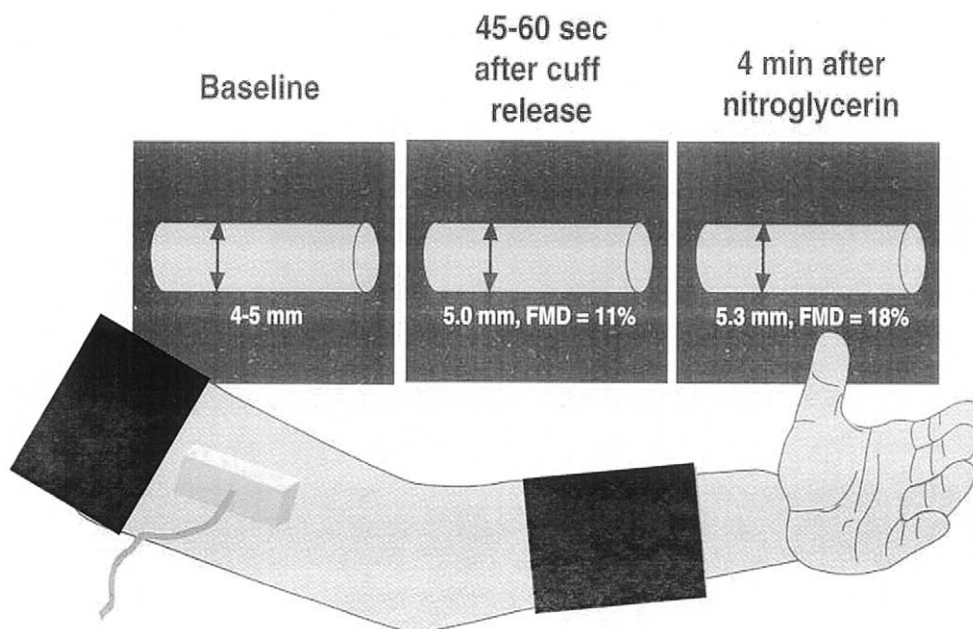
**Endothelium-dependent FMD.** To create a flow stimulus in the brachial artery, a sphygmomanometric (blood pressure) cuff is first placed either above the antecubital fossa or on the forearm. A baseline rest image is acquired, and blood flow is estimated by time-averaging the pulsed Doppler velocity signal obtained from a midartery sample volume. Thereafter, arterial occlusion is created by cuff inflation to suprasystolic pressure. Typically, the cuff is inflated to at least 50 mm Hg above systolic pressure to occlude arterial inflow for a standardized length of time. 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 (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 30 s before to 2 min after cuff deflation. A midartery pulsed Doppler signal is obtained upon immediate cuff release and no later than 15 s after cuff deflation to assess hyperemic velocity.



**Figure 1.** Ultrasound image of the brachial artery (longitudinally) at 8× magnification, 11-MHz transducer frequency annotated for anatomic landmarks.

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 (Fig. 2, schematic drawing). When the cuff is placed on the upper part of the arm, reactive hyperemia typically elicits a greater percent change in diameter compared with that produced by the placement of the cuff on the forearm (19–21). This may be due to a greater flow stimulus resulting from recruitment of more resistance vessels or possibly to direct effects of ischemia on the brachial artery.

However, upper-arm occlusion is technically more challenging for accurate data acquisition as the image is distorted by collapse of the brachial artery and shift in soft tissue. The change in brachial artery diameter after cuff release increases as the duration of cuff inflation increases from 30 s to 5 min. The change in diameter is similar after 5 and 10 min of occlusion; therefore, the more easily tolerated 5-min occlusion is typically used. Also, FMD may be studied in the radial, axillary and superficial femoral arteries. Notable caveats are that arteries smaller than 2.5 mm in diameter are



**Figure 2.** Schematic drawing of ultrasound imaging of the brachial artery with **upper** versus **lower cuff** placement and transducer position above the antecubital fossa. BP = blood pressure; FMD = flow-mediated vasodilation.

difficult to measure, and vasodilation is generally less difficult to perceive in vessels larger than 5.0 mm in diameter (4,17,22).

**Endothelium-independent vasodilation with nitroglycerin.** At least 10 min of rest is needed after reactive hyperemia (i.e., FMD) before another image is acquired to reflect the reestablished baseline conditions. In most studies to date, an exogenous NO donor, such as a single high dose (0.4 mg) of nitroglycerin (NTG) spray or sublingual tablet has been given to determine the maximum obtainable vasodilator response, and to serve as a measure of endothelium-independent vasodilation reflecting vascular smooth muscle function (23). Peak vasodilation occurs 3 to 4 min after NTG administration; images should be continuously recorded during this time, and NTG should not be administered to individuals with clinically significant bradycardia or hypotension. Determining the vasodilator responses to increasing doses of NTG, rather than a single dose, may further elucidate changes in smooth muscle function or arterial compliance that might be playing a role in any observed changes in FMD.

## ANALYSIS

Accurate analysis of brachial artery reactivity is highly dependent on the quality of ultrasound images.

**Anatomic landmarks.** The diameter of the brachial artery should be measured from longitudinal images in which the lumen-intima interface is visualized on the near (anterior) and far (posterior) walls (Fig. 1). These boundaries are best visualized when the angle of insonation is perpendicular. Thus, clear visualization of both the near and far wall lumen-intima boundaries indicates that the imaging plane is bisecting the vessel in the longitudinal direction, and diameters measured from these images likely reflect the true diameter. Once the image for analysis is chosen, the boundaries for diameter measurements (the lumen-intima or the media-adventitia interfaces) are identified manually with electronic calipers or automatically using edge-detection software. The variability of the diameter measurement is greatest when it is determined from a point-to-point measurement of a single frame, and least when there is an average derived from multiple diameter measurements determined along a segment of the vessel (Fig. 3).

Similarly, cross-sectional images are less reliable, for only a single point in the vessel's length is used to determine maximal diameter. The diameter measurement along a longitudinal segment of vessel is dependent upon the alignment of the image. Skew occurs when the artery is not completely bisected by the plane of the ultrasound beam. With slight skew, the maximal diameter measured is constant, and thus yields a more accurate measurement. Some edge-detection programs can account for skew from transducer angulation (17,18).

**Timing of FMD.** Flow-mediated vasodilation is an endothelium-dependent process that reflects the relaxation

of a conduit artery when exposed to increased shear stress. Increased flow, and thereby increased shear stress, through the brachial artery occurs during postocclusive reactive hyperemia. Several studies have suggested that the maximal increase in diameter occurs approximately 60 s after release of the occlusive cuff, or 45 to 60 s after peak reactive hyperemic blood flow (20,22). The increase in diameter at this time is prevented by the NOS inhibitor N<sup>G</sup>-monomethyl-L-arginine, indicating that it is an endothelium-dependent process mediated by NO (24,25). Other measures of vasodilator response include time to maximum response (26), duration of the vasodilator response (27) and the area under the dilation curve (28).

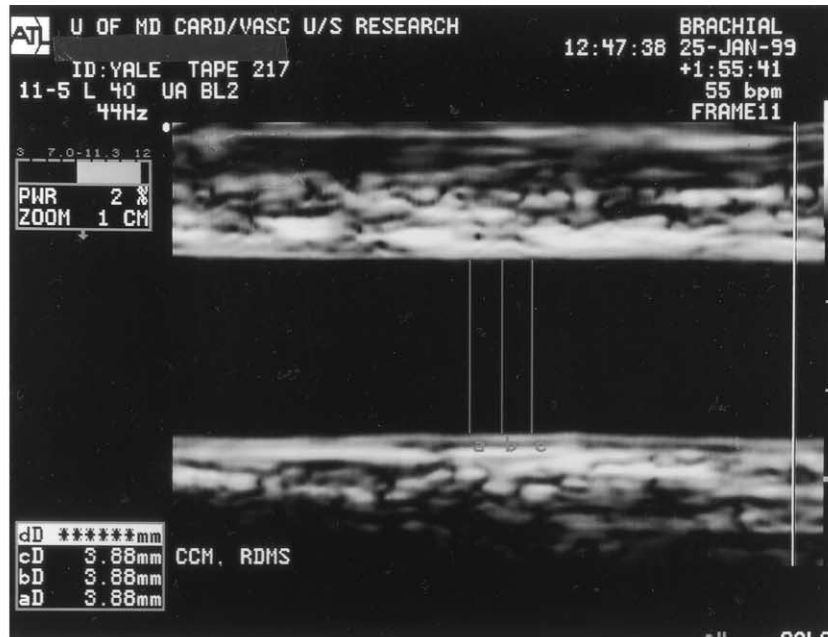
### Timing of the measurement during the cardiac cycle.

Brachial artery diameter should be measured at the same time in the cardiac cycle, optimally achieved using ECG gating during image acquisition. The onset of the R-wave is used to identify end diastole, and the peak of the T-wave reproducibly identifies end systole. Peak systolic diameter is larger than end systolic diameter, because the vessel expands during systole to accommodate the increase in pressure and volume generated by left ventricular contraction. The magnitude of systolic expansion is affected by the vessel compliance, and it may be reduced by factors such as aging and hypertension (possibly by reduced bioavailability of NO). Thus, functional characteristics of the brachial artery may obfuscate the measurement of FMD if diameter is measured during end systole; however, this concern has not been tested in a rigorous trial.

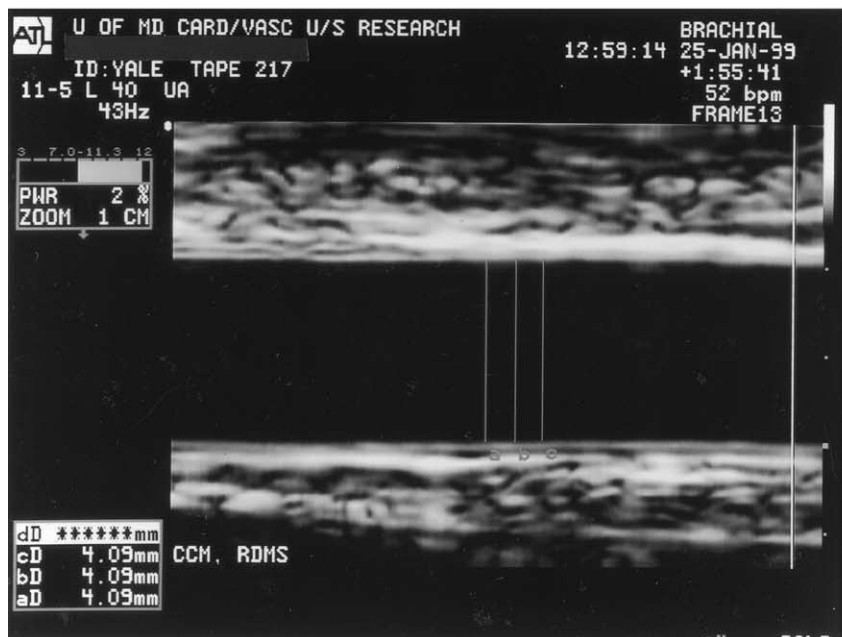
**Characterizing FMD.** Flow-mediated vasodilation is typically expressed as the change in post-stimulus diameter as a percentage of the baseline diameter (3). Baseline diameter influences percent change in two ways. First, for any given absolute change in the postflow stimulus diameter, a larger baseline diameter yields a smaller measure of percent change. Reporting absolute change in diameter will minimize this problem. Second, smaller arteries appear to dilate relatively more than do larger arteries (3). Both factors merit consideration when comparing vasodilator responses between individuals and groups with different baseline diameters. For studies in which comparisons are made before and after an intervention in the same individuals, percent change might be the easiest method to use if baseline diameter remains stable over time. However, the best policy may be to measure and report baseline diameter, absolute change and percent change in diameter.

## TRAINING AND QUALITY IMPROVEMENT

Despite its deceptively simple appearance, ultrasonographic assessment of brachial artery reactivity is technically challenging and has a significant learning curve. The elements necessary to ensure optimal implementation of the technique are outlined in Table 1. Ideally, an individual trained in the principles and technical aspects of 2D and Doppler ultrasonography would perform the technique. The learning



A



B

**Figure 3.** Ultrasound image of the brachial artery at (A) baseline and (B) 1 min after hyperemic stimulus.

curve typically requires several months and depends both on the technical skill of the individual and the frequency with which the technique is performed. Optimal training in the technique requires hands-on training by an experienced individual who can demonstrate the pitfalls and ultrasound artifacts and who can delineate manual techniques and optimal ultrasonography system parameters.

Thorough training in the technique helps to establish high quality and consistency in the method and data. An important component of training and protocol development is attention to ergonomic issues. The operator should sit in

a comfortable position and support the arm holding the probe. Both the quality of the images and the measurements rely on steady transducer imaging of the brachial artery while minimizing stress-related fatigue and injuries. It is recommended that at least 100 supervised scans and measurements be performed before independent scanning and reading is attempted; 100 scans per year should be performed to maintain competency. This recommendation is based in part on criteria for ultrasound proficiency established by the Intersocietal Commission for the Accreditation of Vascular Laboratories. Ongoing feedback from the

**Table 1.** Training and Quality Improvement Protocol

Elements	Scanning	Measurement
Manuals	Subjects: written procedure description Sonographers: Succinct protocol flow sheet at station Longer protocol documentation manual	Explicit written measurement protocol documentation to enhance consistency Manual and automated measurements: Frame and segment selection Criteria for unmeasurable studies
Worksheets	Record subject factors: If ineligible, why Potential FMD modifiers (e.g., food) Blood pressure and cuff inflation pressure Record-scan factors	Log book to track status of studies Worksheet to record technical quality of study
Training	Scientific Rationale and Physiology of FMD	
	Basic knowledge of ultrasound equipment, two-dimensional and Doppler analysis Demonstrate technical tips and pitfalls Ergonomic issues Qualification criteria Training period with close supervision Periodic review of scan performance Minimum number of studies: At least 100 supervised scans prior to scanning independently At least 100 scans per year to maintain competency	Qualification criteria Training period with close supervision and feedback Formal observer-specific reproducibility assessment Minimum number of studies: At least 100 supervised scans prior to scanning independently All observers from a given study measure 100 studies together prior to reading independently At least 100 scans per year to maintain competency
Reproducibility	Image variability In single-site study, each sonographer scans the same participants to assess for systematic differences	Multisite studies should have core reading laboratory, intra- and interobserver variability, temporal variability
	Statistics	
	Correlations, mean and absolute differences, components of variability (systematic vs. random differences) Assess on baseline and peak deflation diameters and FMD. Doppler, if assessed.	
Descriptive Statistics	Assess for systematic differences by sonographer and by site	Assess for systematic differences by observer and by site
	Routine Studies	
	Mean baseline and peak deflation diameters and FMD. Doppler data, if reported. Per time period and over time to assess for secular drifts in measurements	
Data Cleaning	Missing worksheet or measurement data Criteria to re-evaluate study: range checks, consistency checks	
Laboratory Meetings	Periodic laboratory meetings Review work flow, compliance with scan and measurement protocols Measure random and difficult studies together Review results of data cleaning and reproducibility analyses	
Education	Initial training is most efficiently gained by visiting experienced laboratories The field would benefit from the availability of more formal course opportunities	
Certification	Although noninvasive measurement of endothelial function is a research tool, certification will remain study-specific Prior to becoming a clinical tool, formal certification requirements, courses and ongoing continuing medical education will be necessary	

FMD = flow-mediated vasodilation.

trainer and review of videotapes showing recorded brachial artery vasoactivity testing provide valuable education. Criteria for acceptable image quality for optimal FMD measurements set a useful standard to qualify brachial artery studies for research protocols.

**Evaluating precision of the technique.** Intraobserver and interobserver variability in image acquisition and analysis should be established and periodically reassessed for each condition, including baseline, reactive hyperemia and NTG administration. Image variability is best judged by having two sonographers independently scan the same series of subjects at different times. The highest reproducibility is likely to be shown over a short interval, during which the individual vasodilator response is unlikely to have changed

owing to environmental or other influences. This can be accomplished by taking two measurements on the same day within a 10- to 15-min interval, or on separate days in otherwise identical circumstances. Longitudinal studies in which interventions over weeks to months are tested require that reproducibility measurements be performed at longer intervals. The image analysis and measurement of the vasodilator response from repeated studies should be performed by an individual who is blinded as to sequence. Measurement variability is assessed, typically, by a designated core laboratory for multicenter trials, prior to site certification and periodically thereafter to analyze for temporal drifts.

Several approaches exist to describe the differences in any

two sets of measurement results. One is the *correlation coefficient*, which is derived from data that represent the entire range of measurements anticipated in the setting in which the technique will be employed. A second metric is simply the *mean and range of differences between the measures*, which gives an intuitive understanding of the lower limits of differences that can meaningfully be ascribed to variation between subjects or secondary to intervention. The third metric, the *coefficient of variation*, is intended to communicate the size of the variance of a measure relative to the mean value of what is being measured. Because FMD is a percentage-ratio measure, small differences between observers appear very large.

There is no single ideal measurement to assess reproducibility of this technique. A scatterplot showing results obtained at time one and time two along with the line of identity, accompanied by the results of the three metrics described in the previous text, is likely the most complete way to describe reproducibility of FMD of the brachial artery. Rigorous attention to protocol standardization, training and ongoing quality improvement is critical to generating valid, reproducible data.

## APPLICATION IN CLINICAL TRIALS

Assessment of FMD of the brachial artery in clinical trials has increased because of its seeming ease of use, efficiency and noninvasive nature. Owing to the biological and technical variability of the measurement, several caveats should be considered when planning a clinical trial where FMD is the end point of interest. These include study design, sample size and uniform technique.

**Study design.** Recent studies have reported on the effect of pharmacologic or physiologic interventions on FMD of the brachial artery. These include both acute (16,29,30) and longer-term intervention trials (31–33). Both parallel-group and crossover designs have been successfully employed. Implications of approach for sample size determinations have been reported (4). The majority of studies to date have been from single institutions, but multicenter studies are now being reported (34). Multicenter studies require one site serving as the core laboratory to ensure uniform methodology, as previously discussed.

**Sample size.** Typically, significant improvement in FMD can be seen with 20 to 30 patients in a crossover design study and 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%. The sample size depends greatly on the variance of repeated measurement in the control group in a particular vascular laboratory; the power of the study should be based on the group's control data. This is particularly important in order to exclude type II error in negative studies.

With intervention trials, an important parameter to report is the time-dependent reproducibility of FMD. For

example, in the placebo group, the pretreatment and postintervention FMD measures are usually reported, and often are very similar. However, if the mean difference between the two measurements for each patient is quite high, it indicates that the variance of the technique might limit interpretation of the study results. An acceptable reproducibility is a mean difference of 2% to 3% in FMD over time (on a baseline vasodilation of about 10%) (4). This value has not been readily available in published trials.

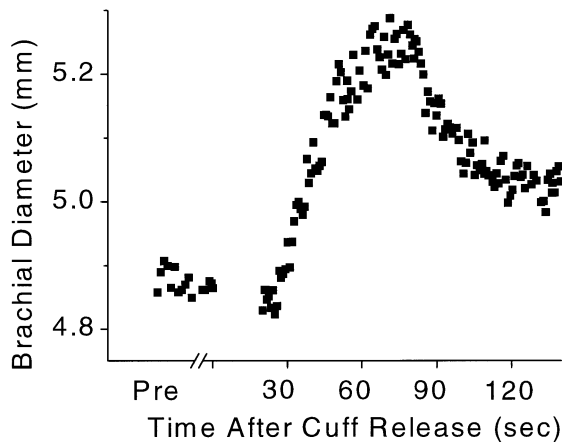
**Methodology.** As discussed above, several techniques have been employed to measure FMD (35,36). Laboratories should select the method that gives them the most reproducible results, and for multicenter studies, the same scanning protocol should be employed at all sites.

For studies employing repeated measurements following intervention, FMD might change as a result of the intervention. However, FMD could also be affected by a change in the 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) rather than improvement of endothelial function of the conduit vessel per se. As such, peak hyperemic flows, as reflected by the Doppler velocity measurement, should be reported. 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 example, a large increase (>10%) in baseline diameter might result in a decrease in FMD that is a result of the change in resting tone, not the effect of the intervention on endothelial function.

## FUTURE DIRECTIONS

Ultrasound assessment of brachial artery FMD has yielded important information about vascular function in health and disease, yet several new approaches and technological advances have emerged. Most prior studies examined FMD at a single time point, typically 1 min after cuff release. This practice evolved from the observations that the maximal dilator response occurs at approximately 1 min in healthy subjects (22) and that the necessity for manual acquisition and measurement placed a practical limit on the number of image frames that could be analyzed.

Commercially available technology now makes it possible to acquire multiple images of the brachial artery automatically using the ECG signal as a trigger and to measure arterial diameter automatically using computer-based edge-detection techniques. This approach allows investigators to examine the entire time course of brachial dilation in response to reactive hyperemia (Fig. 4), the true peak response, the time to peak and the overall duration of FMD as discussed in the previous text. The time course and extent of brachial expansion within a single cardiac cycle, possibly reflecting vessel compliance, can be examined. In the carotid artery, compliance has been shown to correlate with cardio-



**Figure 4.** Time course of brachial artery flow-mediated vasodilation (FMD) in a healthy individual. The FMD was determined with the occlusion cuff on the upper arm as previously described (17). Images of the brachial artery were digitized (one image/cardiac cycle on the R-wave) at baseline (Pre) and continuously for 2 min beginning 20 s after cuff release using a commercially available image acquisition system (CVI Acquisition, Information Integrity, Stow, Massachusetts). Brachial artery diameters were measured using an automated edge-detection system (Brachial Tools, Medical Imaging Applications, Iowa City, Iowa).

vascular risk (37). About 70% of the dilation observed 1 min after cuff release is attributable to NO synthesis (24). Further studies are needed to evaluate other vasoactive mechanisms and to determine whether various disease states influence the kinetics and/or extent of FMD.

Careful examination of the vasodilator response to NTG provides another potential avenue for investigation. Although most studies have detected little effect of disease states on this response, there is evidence that cardiovascular risk factors might impair the vasodilator response to NTG (38), especially when a dose-response curve is measured (39). These findings are consistent with experimental studies demonstrating that inactivation of NO by reactive oxygen species is an important mechanism of vascular dysfunction (40). Further information about the causes of vascular dysfunction and the response to interventions may be gained by examining the response to a submaximal dose of NTG or a series of NTG doses.

The effect of disease states and/or interventions on the blood flow response to cuff occlusion (reactive hyperemia) is underexplored. Current technology limits the utility of spectral Doppler to reproducibly assess changes in flow, which might provide useful information about endothelial function of the microvasculature.

Tremendous interest exists in determining the clinical utility of brachial artery FMD. Investigators have hypothesized that endothelial function may serve as an integrating index of risk factor burden and genetic susceptibility, and that endothelial dysfunction will prove to be a preclinical marker of cardiovascular disease (41). Several studies suggest that the presence of endothelial dysfunction in the coronary circulation is an independent predictor of cardiovascular disease events (42,43). Ongoing studies in several large populations, including the Framingham Heart Study

and the Cardiovascular Health Study, shall determine whether endothelial dysfunction in the brachial artery will identify patients at risk for developing coronary artery disease, cerebral vascular disease and/or peripheral vascular disease. The technique is particularly well suited for study of the earliest stages of atherosclerosis in children and young adults, thus providing maximal opportunity for prevention.

Numerous studies have demonstrated that brachial artery reactivity improves with risk factor modification and treatment with drugs known to reduce cardiovascular risk. It remains unknown whether an improvement in endothelial function directly translates into improved outcome. In the future, however, practitioners may use brachial artery FMD to assess response to drug therapy and to individualize patient risk factor modification programs. Further studies are needed to determine whether the methodology is sufficiently reproducible and whether biological variability is sufficiently low to make assessment of FMD a clinically useful measure of cardiovascular risk on an individual or group basis. To that end, the methodology will need to mature, with formal opportunities for training, certification and continuing medical education, as currently exist for other cardiovascular testing modalities.

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