Shear stress and flow-mediated dilation: all shear responses are not created equally

Michael E. Widlansky

Department of Medicine, Cardiovascular Medicine Division and Department of Pharmacology, Medical College of Wisconsin, Milwaukee, Wisconsin

Since the introduction of brachial artery reactivity testing in 1992 by Celermajer et al. (1), the measurement of endothelial function with the use of high-frequency ultrasonography of the brachial artery has proven to be an effective research tool for the assessment of cardiovascular risk (16). To date, 12 publications have demonstrated that endothelial dysfunction as measured by impaired flow-mediated dilation (FMD) in the brachial artery predicts an increase future cardiovascular risk (14, 17, 19).

While measurement of FMD in the brachial artery shows promise as a surrogate marker of cardiovascular risk, the specificity of FMD in the prediction of future risk remains low. A portion of the lack of specificity is very likely attributable to current technical limitations of both the hardware and software required for these measurements; the heterogeneity of the techniques used to elicit, measure, and report FMD; and an incomplete correlation of responses measured in the brachial artery to vascular homeostasis in the conduit vessels of clinical interest (e.g., coronary and cerebral circulations). However, our current, incomplete understanding of the mechanisms, interactions, and confounding factors that influence brachial FMD remains a significant contributor to the variability of FMD.

A central influence on brachial FMD is the laminar shear stress applied to the endothelium. Shear stress activates signaling cascades in the vascular endothelium that lead to a vasodilator response. Brachial FMD is performed by creating a temporary occlusion of blood flow to the forearm and hand, usually with a simple blood pressure cuff inflated to significantly above the individual’s systolic blood pressure. Ischemia secondary to this occlusion leads to compensatory vasodilation of the distal resistance microvessels under the influence of multiple actors, including adenosine, potassium and hydrogen ions, hydrogen peroxide (18), and nitric oxide (NO) (7). Upon cuff release, this reduction in local vascular resistance leads to an acute, reactive hyperemic flow response to the ischemic tissues. Using appropriate testing parameters (2), acute, reactive hyperemia leads to an increased laminar shear stress on the conduit brachial artery endothelium, inducing vasodilation that is primarily dependent on NO production from the local endothelium (6). Shear stress is directly dependent on flow velocity and blood viscosity and inversely dependent on diameter (shear stress = \( \gamma v/D \)). Shear rate (\( v/D \)) is often measured as an adequate surrogate for shear stress in settings where blood viscosity is not directly measured. Recent studies suggest that reporting shear as the area under the shear rate curve from cuff deflation to peak vasodilation (SS\textsubscript{AUC}) supplies the reactive hyperemia data most closely associated with FMD measurements (13).

Although shear stress appears to relate to risk factors and reactive hyperemia is emerging as an independent predictor of cardiovascular risk (4, 8), variability in reactive hyperemia responses may introduce error into the FMD measurements, reducing the ability of FMD to reflect true endothelial function. Well-designed studies in healthy subjects employing repeated-measure designs have demonstrated that an individual’s brachial FMD is highly dependent on shear stress and that normalizing FMD measurements for shear eliminates this dependence under their study conditions (9, 12, 13). These recent studies have led some investigators to advocate for the normalization of all FMD measurements to their shear stimuli, suggesting that this normalization will increase the validity of relating FMD measurements to the true conduit vessel endothelial function.

Thijssen and colleagues (15) investigated the relationship between FMD and shear in unmatched healthy populations of 51 children, 57 young adults, and 27 older adults. For young adults, the authors found a modest but statistically significant correlation between brachial FMD and SS\textsubscript{AUC} (\( r^2 = 0.14 \)), whereas for children and older adults, no significant correlation between FMD and SS\textsubscript{AUC} was identified. The modest association between FMD and SS\textsubscript{AUC} in young adults is consistent with the finding that hyperemic shear stress accounted for ~15% of the variability of FMD in a recently reported multivariable-adjusted model in a large cohort (8). These data seem to significantly contrast with the findings of Pyke and Tschakovsky (13), who found that 56% of the FMD response was accounted for by SS\textsubscript{AUC}.

A small amount of the discrepant findings might be due to minor differences in technique or subject populations. If we consider the differences in study design, the findings do not appear to be in conflict. The study by Pyke and Tschakovsky (13) employed repeated measurements of the same subjects with graded increases in the applied shear stimulus and found a large association between FMD and SS\textsubscript{AUC}. Their study design significantly reduces the between-subject variation we would expect to influence FMD responses to shear. Between-subject factors that are likely to increase the variability of an FMD response to a given magnitude of shear stimulus include differences in structural characteristics of the conduit and microvessels (5), differences in the contour of the shear stimulus (8), differences in baseline traditional and novel cardiovascular risk factor profiles that might influence endothelial NO synthase bioavailability (17), differences in individual genetic susceptibility that might influence response to a given shear stimulus (11), differences in the NO dependence of reactive hyperemia under the influence of different risk factors and disease states (3), differences in sympathetic nervous...
system activity and metabolic influences (10), and very likely other as-yet unrecognized factors.

Given this multitude of factors that create intersubject variability, a shear stimulus of identical magnitude in two different individuals will very likely elicit different amounts of absolute vasodilation. In a study population where FMD measurements are not related, in order for normalization of FMD measurements by dividing SS_{AUC} into FMD to increase the validity of FMD measurements, a given amount of shear stress must 1) always elicit the same or near identical amount of absolute vasodilation regardless of the individual in which it occurs and 2) have a strong linear relationship between FMD and SS_{AUC} over the physiologically relevant range of these measurements in the population being studied. Based on the data presented by Thijssen and colleagues (15), the first assumption does not appear to be true, and the validity of the second assumption is, at best, a question that would need to be answered for the population undergoing testing before applying any normalization technique. A greater degree of intersubject variability of the FMD/shear relationship combined with small subject populations likely explains the lack of any significant association between FMD and SS_{AUC} in children (in different stages of growth and development) and older adults (with likely a wider range of risk factor exposure) in the study by Thijssen et al. The modest correlation in the young adult group between FMD and SS_{AUC} likely reflects less intersubject heterogeneity in the FMD and shear stress relationship compared with children and older adults, but the marked attenuation of the association in comparisons to the findings by Pyke et al. (15) suggests a significant complication of the FMD/shear relationship with the introduction of intersubject variability.

These data have important implications for researchers who use FMD as a research tool. As suggested by Thijssen and colleagues (15), these data suggest that a normalization of FMD to SS_{AUC} is not appropriate for studies that measure FMD but do not involve repeated measures and may introduce greater error into the measurement. Furthermore, normalizing FMD to SS_{AUC} in studies that employ repeated FMD measurements pre- and postinterventions also are unlikely to benefit from this normalization since an intervention may alter the FMD/shear relationship.

However, these data do not reduce the importance of shear and its relationship to the FMD response, and, as the authors suggest, should not be taken as evidence that shear stress is not relevant to the FMD response. Rather, these data enhance our appreciation that the relationship between shear stress and FMD is not simple and linear but rather the result of complex interactions between multiple competing influences. Reporting the characteristics of reactive hyperemic responses alongside corresponding FMD data remains important to allow researchers to determine whether the differences in the stimulus for FMD between groups may be contributing the observed between-group differences. Shear stress data give important complementary information about microvascular function and perhaps further insight into future cardiovascular risk (3, 4, 8). Thus, while “all shear is not created equally,” we should not ignore the important influence of shear and microvascular function when interpreting studies that employ FMD.

REFERENCES