Pick your Poiseuille: normalizing the shear stimulus in studies of flow-mediated dilation

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FLOW-MEDIATED DILATION (FMD; the shear-evoked conduit artery dilatory response to a period of tissue ischemia) has emerged as one of the standard noninvasive techniques for assessing endothelial function and predicting the existence and extent of pathological and physiological states (8, 30). For example, FMD provides independent prognostic value to cardiovascular risk assessment in postmenopausal women (23) and has been strongly correlated with coronary artery function (1). Although the mechanisms underlying endothelial function and dysfunction as represented by FMD remain poorly understood [i.e., what combination of oxidative stress, heightened sympathetic outflow, diminished smooth muscle dilation, altered release of vasoactive substances, etc., contribute to observed population differences (29)], many efforts have been made to refine the technique for reliability and accuracy. Recent findings support normalization of the dilatory response to the shear stimulus as the most effective and appropriate way to express FMD (21). In addition to reducing the day-to-day variability associated with peripheral artery reactivity, this method is thought to account for the magnitude of the stimulus evoking FMD (24, 26). Thus equating each individual’s response to the underlying stimulus increases the probability that between-population or treatment differences in the measurement of FMD truly represent variations in conduit artery dilatory responsiveness, rather than the effect of a discrepant ischemic stimulus.

The technique of normalizing to the shear stimulus has evolved significantly in the past 5 yr. First reports normalizing FMD to the shear stimulus used the peak shear response to occlusion (6, 11, 16); further evidence suggested that the appropriate normalization was the area under the curve (AUC) shear response in the first minute postocclusion (19) since the peak diameter was generally observed at this timepoint. Most recent evidence suggests that the most accurate normalization may be the AUC shear response from postocclusion to the time at which peak diameter is observed (3). Future calculations involving the kinetics of the shear response will no doubt arise as more sophisticated approaches take into account the effect that time course and magnitude of the shear rate response have on the FMD response (5, 20).

Interestingly, the shear response to occlusion, occurring due to the increase in blood moving along the conduit endothelium as evoked by ischemically mediated vasoactivity and/or changes in pressure and mechanosensation in the resistance vasculature (10), appears to also yield important information about vascular health. For example, in the Framingham Study, risk factors such as age, sex, mean arterial pressure, pulse pressure, heart rate, body mass index, lipid medication use, and hormone replacement therapy were related to occlusion-evoked hyperemic shear stress in multivariable analyses (14). Similarly, brachial artery hyperemic shear stress appears to differentiate effectively between men with and without metabolic syndrome and even between the number of metabolic syndrome criteria present in an individual (28). Recent evidence also suggests that the shear response to a standard 5-min period of distal occlusion is limb specific (15) and may be influenced by acute sympathetic activation (7, 17). Differences in the shear response to occlusion are also observed between healthy controls and subjects with spinal-cord injuries (6), diabetics (25), and older subjects (17, 25). Indeed, it is becoming common practice to report the shear response to occlusion independently rather than simply as a denominator in the normalized FMD calculation.

In light of the importance of FMD and the role of the shear stimulus, then, it is important that the calculation of the shear stimulus with respect to Poiseuille’s Law also be fairly uniform. Briefly, Poiseuille’s Law states that shear stress is equal to $4\eta q/\pi r^3$ or $4^* \eta q/\pi r^3$ the product of the viscosity of blood and measured flow divided by the product of pi and the lumen radius to the third power. Common practice favors the estimate of shear rate rather than shear stress due to the more invasive nature of measuring blood viscosity. Accordingly, Poiseuille’s Law states then that shear rate equals $8^* \text{measured mean blood flow velocity/} \text{internal artery diameter}$. Alternatively, if only
center line (or peak) flow velocity is determined, in conjunction with the assumption of a parabolic velocity profile, the numerator in the equation becomes $4\theta$ measured peak blood flow velocity $(9, 22)$. Despite the standards set forth by Poiseuille’s Law, however, there is significant variation in the literature with respect to calculating shear rate: estimates of velocity/diameter alone $(12, 20)$, $8\theta V/D$ with mean blood velocity $(2, 7)$ and $4\theta V/D$ with peak and mean blood velocity $(4, 15, 27)$ accompany recent FMD publications. While incorporating different constants into the shear rate calculation will change neither the nature of the data nor the normalization of FMD, it is difficult to compare between studies when there is no standard calculation of shear rate with respect to Poiseuille’s Law. It should be noted that estimating shear rate with uniform respect to Poiseuille’s Law still involves considerable and unavoidable error, as Poiseuille’s Law is inherent to stiff and straight arteries, with Newtonian fluid, steady laminar flow, and a parabolic velocity profile. Clearly in vivo blood flow does not meet these conditions; for example, computer modeling suggests that introducing distensibility into the carotid artery wall decreases wall shear rate by $\sim 30\%$ compared with a rigid artery $(18)$. Variations in the velocity profile across blood vessels and between subject populations $(24)$ and even differences between ultrasound machines used to measure velocity are other examples of the additional difficulties associated with estimating shear rate accurately. Thus using Poiseuille’s Law to calculate in vivo shear rate still represents only a “best estimate” of the true shear rate; however, it can be argued that at minimum, applying Poiseuille’s Law uniformly eliminates a source of controllable variability in the calculation of shear rate. Indeed, if the purpose of the shear rate calculation is to 1) improve the accuracy and reduce the variability of FMD and 2) provide independent information regarding the vasculature, then it is of utmost importance that researchers who use this measure use standardized methodology with which to derive the actual estimation of shear rate (Fig. 1). Otherwise, the use of both shear rate and FMD to facilitate between-study comparisons of arterial dilatory responsiveness is diminished and investigators continue to be limited to the data generated from their own work. Recently, Minson and Green $(13)$ stated the following postulate regarding a good measure of vascular reactivity aimed at improving cardiovascular risk assessment: The measure should be reproducible, observer independent, and easily standardized. The shear response to a period of occlusion could fit that bill (in addition to the role it plays in properly assessing endothelial function via data normalization); however, standardization of estimates regarding shear rate as defined by Poiseuille’s Law are necessary before we can move closer to understanding the true utility of this measure. (Fig. 1)


