

Letter to the Editor

Flow-Mediated Dilatation: Just a Marker of Local Shear Stress?

To the Editor:

We read with interest the article by Mitchell et al¹ and agree that flow-mediated dilatation (FMD%) response may be partially explained by shear stress (diastolic shear stress [DSS]) or flow changes.² However, this does not necessarily mean that risk factors do not influence the vascular response. Indeed, Megnien et al³ showed that shear stress reduction provokes different diameter changes in hypercholesterolemic compared with normal subjects. Moreover, experiments performed by our group (M. Laclaustra et al, unpublished data, 2003) on healthy male subjects showed that HDL-cholesterol level was the strongest predictor of FMD% among all lipid variables considered in the study. This finding was actually apparent after controlling by average flow velocity during the first minute of hyperemia (model's $R^2=0.173$). Thus FMD% may have a greater sensitivity to detect the effects of risk factor modification than shear stress, as shown in previous articles, including the one incorporating the very first description of the flow-mediated dilatation technique.⁴ Indeed, in those reports, significant differences among groups were found for FMD% values but not for hyperemic flow values.

Mitchell et al¹ rightly point out that the fact that brachial artery diameter was included in the equations used for calculations of FMD% and DSS could have induced a spurious mathematical relationship between these 2 variables that does not necessarily reflect a physiological one. Indeed, both the modeled variable (FMD%) and the explanatory variable (DSS) are multiplied by the same factor (1/basal diameter). Pure mathematical experiments (Monte Carlo) indicate that 2 independent random variables become linked with an R^2 value that tends to 0.184 when multiplied by a common third independent random variable. It is, therefore, possible that shear stress becomes the most explanatory variable for FMD%, forcing risk factors, more weakly linked to FMD%, out the statistical model.

To disprove the hypothesis, Mitchell et al¹ eliminated basal diameter from both FMD% and DSS, thus actually modeling absolute diameter change (ADC) (in millimeters). Unlike FMD%, ADC is only weakly associated to risk factors according to data in the literature and to our unpublished observations. In fact, ADC is virtually never reported in the literature despite that current guidelines for the use of FMD⁵ encourage authors to do so. Moreover, Mitchell et al¹ express this model in terms of R^2 change and, in doing so, do not allow the reader to compare the coefficients (SD) with those given in their Table 3, where no R^2 changes are shown. Incidentally, a discrepancy exists between the model's R^2 value cited in text versus that on Table 3, probably a typo, which further confuses the issue.

In summary, FMD% is likely to represent a more sensitive measurement than hyperemic flow and could be a reflection of the effects of risk factors on both hyperemic flow and the vascular response to flow changes. In view of the potential clinical use of brachial artery responses, studies are necessary to specifically assess the mechanisms whereby different pathological conditions affect FMD%.

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Response: Flow-Mediated Dilatation: Just a Marker of Local Shear Stress?

We thank Drs. Laclaustra et al, for their careful reading and thoughtful critique of our study.¹ They suggest that attenuation of the association between cardiovascular disease risk factors and flow-mediated dilatation (FMD), after adjusting for hyperemic shear response, does not necessarily mean that risk factors do not influence the vascular response. They propose that FMD may have a greater sensitivity to detect the effects of risk factor modification than shear stress. We agree with this point, in principle. However, the issue is not whether FMD or flow is better at detecting abnormalities in regional vascular function. The 2 components of the test (FMD and flow or shear response) evaluate 2 related but distinct aspects of regional vascular function (macrovascular and microvascular). Furthermore, the FMD (macrovascular) component is critically dependent on the flow (microvascular) response, which serves as the stimulus to evoke FMD. Therefore a full understanding of FMD requires consideration of variability in the flow response.

Laclaustra et al also raise the issue, discussed in our paper, that relations between FMD and shear may be attributable to their common dependence on diameter. This was the reason for including a model that evaluated absolute diameter change (FMDmm) and adjusted for hyperemic flow velocity. Laclaustra et al indicate that in their unpublished data, FMDmm is only weakly associated with risk factors and that FMDmm is virtually never reported in the literature. Additionally, they note that Table 3 in our article does not present partial R^2 values, making it difficult to compare the FMDmm and FMD% models. We are not in a position to comment on their unpublished FMD data; however, we have shown similar (although not identical) relations between risk factors and FMD whether expressed in absolute (FMDmm) or relative (FMD%) terms.² The partial R^2 values for shear when included in the FMD% model (partial $R^2=0.195$, model $R^2=0.335$) were comparable to those for flow when included in the FMDmm model (partial $R^2=0.165$, model $R^2=0.269$). Therefore, most of the association between FMD% and hyperemic shear is attributable to the relations between diameter change and flow rather than the common effects of diameter in the denominators of the FMD% and shear stress equations.

The authors have correctly noted that the R^2 values in the footnote for our Table 3, which are incorrect, differ from those in the text, which are correct. The R^2 values in the footnote for Table 4 were erroneously duplicated in the footnote for Table 3 during typesetting. We appreciate this important feedback and apologize for the confusion.

We enthusiastically concur with Laclaustra et al that additional studies are needed. We reiterate our recommendation that in future studies, the hyperemic flow stimulus should be carefully assessed in

a reproducible manner and formally included in statistical analyses of the associated FMD response. Furthermore, correlates of the absolute systolic, diastolic, or mean hyperemic flow response should be considered separately from the brachial FMD response. Approaches that consider both flow and FMD responses should allow for important and novel insights into factors that differentially affect large and small vessel function.

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