
To the Editor: We applaud the contributors to the flow-mediated dilation (FMD) Point:Counterpoint series. As researchers using FMD as defined by Green (1), we add a corollary point to the issue highlighted by Parker and Proctor (2) regarding sex as a potential variable influencing nitric oxide and FMD. We believe that characterizing hormone profiles is essential when considering nitric oxide contributions to vascular responsiveness. The contribution of nitric oxide to FMD in females may differ across a menstrual cycle, contraceptive use, or menopause. Adding to this complexity, evidence suggests that exogenous hormones modulate vascular responsiveness of the endothelium differently based on dose, formulation, and combination. This brings to light an important consideration in assessing variability in FMD studies in women, because hormonally induced vascular changes may alter factors such as baseline diameter. For instance, the initiation of contraceptive hormone use could lead to vascular remodeling and/or changes in sympathetic activity affecting basal tone, shear stress-induced dilation, and responsiveness to exogenous nitric oxide donors. Therefore, calculations of variance estimates (4) could be more reflective of vascular changes than ultrasonographer repeatability in some studies of women. We note that in some previous studies of FMD, only mean data are reported to explain study outcomes. Reporting calculations of variability in addition to individual subject’s baseline diameters and FMD and responses to nitric oxide donors may have greater utility in evaluating pre- to posttreatment affects on vascular changes. This may assist readers in drawing conclusions regarding the data and findings.

REFERENCES


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To the Editor: NO flow-mediated vasodilation? No, flow-mediated vasoconstriction? We agree that nitric oxide (NO) is importantly involved in vasomodulation, whether or not flow mediated (1). However, its role is highly dependent on the vessel size and the degree of shear stress, and NO is not the sole vasoregulatory factor.

Indeed, if NO is an important mediator of flow-mediated dilation in large vessels (as investigated by the FMD approach proposed here), bradykinin and endothelium-derived hyperpolarizing factor (EDHF) might participate. Furthermore, in human microvessels, most of the relaxation can be achieved by EDHF (4).

Exercise, important physiological stimulus, is interesting to consider. Exercise studies support a major implication of NO in flow-mediated vasodilation. Thus NO plasmatic concentration—increased in response to a high level of shear stress—strongly relates to exercise capacity in healthy humans (3). However, this is not true in patients (3), likely because of an enhanced sympathetic activity blunting the flow-mediated dilation. Moreover, still during exercise, a lower degree of shear stress increases endothelin-potent vasoconstrictor, arising mainly from not working muscles and visceral organs (2). Thus, at the same time, blood flow changes stimulate both the NO and the endothelin pathways (between others), allowing the elevated cardiac output to be preferentially directed to the working muscles.

Therefore, flow mediates either vasodilation and/or vasoconstriction. The resulting vascular tone depends on the precise interplay of agonist and antagonist systems, which largely relies on vessel size. These arguments, in addition to those previously presented with spirit (and good spirits) (1) support that flow-mediated changes do not necessarily reflect NO endothelial function.

REFERENCES


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