De Motu Arteriarum
Hemodynamics and Arterial Function in Humans
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In reductionist times, it is refreshing to appreciate the creativity of apparently “simple” technical approaches coupled with clever experimental design. The study of Jiang et al1 evokes Harvey2 in its manipulation of human vascular behavior using a “ligature,” coupled with careful visual appraisal, to examine the impact of pressure on artery diameter responses. They modified a technique introduced by Celermajer et al3 involving inflation of a pneumatic cuff placed around the forearm to high pressure (for ≈5 minutes) to induce distal limb ischemia. Cuff deflation is associated with a large increase in blood flow through the upstream radial or brachial artery,4 which, in turn, induces a “flow-mediated” dilation (FMD).3 This, in turn, has been attributed to the release of vasodilator paracines such as NO from the endothelium, as a consequence of shear stress–mediated signal transduction.5 The FMD test has become a popular noninvasive test of endothelial function, in part because it predicts future cardiovascular events.6,7

The kinetics of the vasodilator response after cuff deflation in the FMD test have always been quizzical in that the peak blood flow (and shear stress) response occurs and resiles rapidly after cuff deflation (Figure), whereas the peak dilator response is delayed.8 Jiang et al1 hypothesized that vasodilator responses may be affected by changes in pressure, as well as those in shear, after cuff deflation. They cleverly manipulated the FMD test by re-interrupting flow via distal cuff inflation. They also examined the role of NO in dilator responses may be affected by changes in pressure, radial or brachial artery,4 which, in turn, induces a “flow-mediated” dilation (FMD).3 This, in turn, has been attributed to the release of vasodilator paracines such as NO from the endothelium, as a consequence of shear stress–mediated signal transduction.5 The FMD test has become a popular noninvasive test of endothelial function, in part because it predicts future cardiovascular events.6,7

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Like all good studies, the work of Jiang et al1 leaves some questions unanswered. The study was performed in healthy young subjects, and the interaction between shear stress and pressure may be influenced by the aging process and/or exposure to cardiovascular diseases or risk factors. It is unclear whether the results would be similar in those with decrease in transmural pressure, which they tested by inflating a cuff to 20 mm Hg while imaging the underlying radial artery. This alternate method of decreasing transmural pressure resulted in a 7.6% decrease in artery diameter. The authors therefore concluded that, in response to the FMD test, NO-mediated vasodilation occurring as a result of increased shear stress is offset by a vasoconstriction resulting from direct impact of hydrostatic pressure drop. Monomethyl-arginine significantly and similarly affected artery diameter, regardless of whether cuff re-inflation occurred, suggesting that any vasoconstrictor response may be NO mediated.

There are several implications of these findings. First, Jiang et al1 reinforce most, but not all, previous studies which suggest that conduit artery FMD responses are largely NO mediated.5 This study also reveals the importance of considering differences in response “kinetics” within9 and between subjects.10 Second, the assumption that FMD is simply the consequence of shear stress is brought into question. This is relevant because it has been proposed that FMD dilator (percentage) responses should be normalized via division by the shear stress, although this method of normalization and its relevance have been questioned previously.11,12 Although the FMD test is largely NO and endothelium mediated and associated with cardiovascular outcomes,6,7 its use as a method of uniquely shear-mediated vasodilator function can no longer be assumed. We think that the novel findings of Jiang et al1 have broader implications than providing insight into the physiological mechanisms of the FMD response. The involvement of both shear and pressure in acute vasodilator responses raises the question of chronic effects of these variables in humans. The proposal that transmural pressure is involved in arterial wall remodeling is not new: Folkow et al13 proposed a link between hypertension and increased wall:lumen ratio in the 1950s and 1960s, although the effects of interventions such as exercise have only recently received attention.14 As summarized recently,15 changes in transmural pressure and cyclic strain have significant proatherogenic and antiatherogenic effects, although it remains difficult to dissociate pressure from shear in the in vivo setting. The approach of Jiang et al1 may open doors to better understand the effects of these hemodynamic variables on vascular function and structure in humans.
increased cardiovascular risk (especially hypertension). Moreover, recent reports have demonstrated heterogeneity between arteries regarding arterial structure and function, which suggests that caution must be exercised when extrapolating the results from Jiang et al to other conduit arteries.

In summary, Jiang et al have highlighted, using a simple and elegant approach, the potential interactive effects of hemodynamic stimuli on vascular function in humans. Nearly 4 centuries after De Motu Cordis, much can still be achieved with a ligature and some ingenuity.

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None.

References

Figure. Graphic representation of the change (increase: ↑, decrease: □) in conduit artery shear stress (black solid line), transmural pressure (gray solid line), and diameter (black dotted line) during the first 120 seconds after the occluding cuff release. The region between the observed and hypothesized diameter change (shaded gray) represents the dilation that is “masked” by a putative flow-induced vasoconstrictor.
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