Low-Flow Motion in the Vascular Ocean

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Much like the ebb and tide of the seas, most physiologic functions are observed to operate in balance; a constant yin and yang of biology operates to maintain the body in careful equilibrium, yet the realm of vascular biology has focused mostly on the ability of vessels to dilate in an effort to improve the supply of flow to demanding tissues. It is only fitting and appropriately balanced that new data now support the concept of the endothelium and vascular wall directing constriction to low-flow territories. Moreover, we just might be able to harness the ability of vessels to appropriately constrict as a measure of endothelial health. Despite the fact that the notion of low-flow mediated constriction (L-FMC) has been intermittently studied over the past decades,\(^1,2\) and recently been reprised in the cardiac literature,\(^3\) relatively little is known regarding the mechanisms behind this phenomenon, let alone their potential clinical implications. In this issue of *Circulation: Cardiovascular Interventions*, Dawson et al\(^4\) present new data showing that vascular injury—potentially secondary to denudation of the endothelium or smooth-muscle cell injury—following a radial access approach impairs both endothelial-dependent dilation and L-FMC, and moreover, that this can be ameliorated with subsequent isometric handgrip exercise training. This complex study design and provocative set of results not only implicates a potential mechanism for L-FMC, but also provides a relatively safe and easy treatment for an increasingly common complication seen in interventional practice.

**Article see p 713**

The present study by Dawson et al essentially combines 2 separate experiments to effectively underscore the importance of the endothelium in L-FMC. The first experiment follows 32 patients immediately before a radial approach to percutaneous coronary intervention and then 1 day after, to measure vascular reactivity to reactive hyperemia in both the catheterized arm and contralateral arm. Investigators measured radial artery diameter and blood velocity before, during, and after suprasystolic inflation of an upstream blood pressure cuff. This observational study shows a significant impairment in L-FMC as well as in the combination of L-FMC and flow-mediated dilation (FMD) in the limbs subjected to a radial procedure.

Although there are no successive confirmatory mechanistic studies using other endothelial antagonists in the contralateral limb or even smooth-muscle agonists such as nitrates in the study limb (especially after the 7-week training period), the powerful combination of the study model supports the relatively convincing conclusions that the endothelium may be involved in the mechanism behind L-FMC.

In the second set of experiments, a separate cohort of 18 similar patients was randomized to undergo postprocedure regional exercise training versus regular care. All these patients underwent a precatheterization reactive hyperemia protocol, repeated postprocedure at 7 weeks. Although L-FMC was reduced as far out as 7 weeks postprocedure in both groups, this reduction was significantly attenuated in the exercise group. Taken together, not only does this study highlight the importance of the endothelium in the relatively evolving notion of L-FMC, but it also makes evident that the simple intervention of a 30-minute daily exercise regimen can ameliorate the endothelial dysfunction imposed by radial catheterization. Furthermore, the statistical significance of the results involving such a small study population enriches the convincing nature of these data. This study, therefore, puts forth some interesting data in favor of using exercise to improve vascular health, extending into what is currently quite a controversial topic largely secondary to the diverse testing methods and exercise modalities.\(^5,9\)

A primary strength of the article is the powerful clinical and translational model used in both sets of studies. The ability to recruit patients undergoing radial procedures to show both the concept of L-FMC and the ability of exercise to ameliorate some of the damage caused by radial catheterization allows the authors to draw conclusions directly relevant for clinical care. The current study also has several limitations, including small sample size, inability to completely control the remainder of subjects’ activity level in both limbs, and discrepancy in medications between the latter 2 study groups. Moreover, endothelial-independent vasodilation, such as the response to nitroglycerine, was not assessed. Thus, hypothetically similar phenomena might be observed if the injury is at the level of the smooth-muscle cell. Nevertheless, the authors attempted to reduce the impact of most of these factors, using their resourceful experimental model, and the responses in endothelial function are of such magnitude that sample size was not an issue in terms of statistical significance.

FMD secondary to reactive hyperemia has been for many years the chief surrogate for vascular endothelial health. The increase in arterial diameter and flow seen after a substantial period of relative lack of inward blood flow is largely mediated by a shear-stress–induced release in nitric oxide\(^10,11\) with slight contribution from prostaglandins—both abundantly present and usable in healthy endothelium. Consequently, the ability of a vessel to dilate in response to an increase in shear stress has been a marker for healthy vasculature,\(^12,17\) and those patients

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with an impaired FMD response to shear stress have been found to have a predilection toward atherogenesis and future cardiac events or mortality. The technique is simple, and well explained in the current report earlier in this issue. FMD only becomes problematic with the relative heterogeneity of results and lack of precision in delineating those at greatest risk.

Conversely, and conceivably within the realm of possibility, the ability of peripheral vessels to constrict to low-flow states is now en vogue as another measure of vascular endothelial health and function. The authors show convincing results with an interesting experimental design and model that L-FMC might be a welcome addition to the family of endothelial function tests. Although the ability of a vessel to constrict is relatively confined based on physical principles and potential for disparate local diameter/flow responses, for much the same reasons this test might just expand the dynamic range of vascular function to more precisely delineate endothelial health and fine-tune mechanistic contributions. For example, the changes in L-FMC observed in this study ranged roughly from 1% to 3% in the exercise versus control groups pre- and postprocedure. Subtle statistical differences are difficult to detect in a large patient population to establish clinical significance. However, when combined with the responses in FMD, the dynamic range of possible change nearly tripled (6%–12%). Such a larger range of response might allow us to better detect, quantify, and define abnormal vascular responses.

This publication, although missing comments regarding specific mechanisms for endothelial-mediated L-FMC, generates a springboard for a multitude of future hypotheses and studies. From a pure autoregulatory standpoint, the notion of L-FMC can be justified. Usually a myogenic response overcomes high-pressure states to limit an overabundance of blood flow to tissues in demand. When the demand for blood flow in a certain tissue falls below supply, flow should then be shunted elsewhere by other mechanisms. The resulting low-flow state in the particular low-demand vascular bed could be reversed unless a subsequent and counteractive constriction occurs in that bed as, in response to low pressure, myogenically dilating blood vessels could trigger a pressure gradient that would return unwanted flow back to the tissue bed in question. Thus, a constriction to low flow becomes plausible, and what better regulator than the endothelium to orchestrate such an intricate system? The endothelial contribution to L-FMC should be tested in future studies to explore the involvement of neural or smooth-muscle elements to L-FMC using neural blockade agents and nitric oxide donors in a similar experimental setup. Interestingly, the authors found a strong trend, however, no statistical significance, toward an increase in vessel diameter with a concomitant reduction in shear rate after radial catheterization. This immediate reduction in shear stress as well as flow is the opposite of L-FMC, and even is counterintuitive to the notion that the loss of healthy endothelium induces an overwhelming smooth-muscle-driven vasoconstriction. However, this finding further solidifies the assertion of the authors that arterial intrusion and damage abolishes L-FMC. It is uncertain whether the endothelium is completely denuded, yet the convenient clinical model could easily be modified to use various neural blockade agents, nitric oxide-synthase inhibitors, indomethacin, etc to isolate the immediate contributor to L-FMC.

Next, it is interesting to speculate on the mechanism(s) by which isolated hang-grip exercise ameliorates the reduction in L-FMC after radial procedures. The simple and obvious explanation points to a shear-mediated component to L-FMC, similar to FMD. Some data support shear-mediated constriction, which would juxtapose nicely with mechanisms ascribed to FMD. Thus, increased oxygen and metabolic demand induced by repeated exercise could augment upstream radial artery flow and shear stress subsequently enhancing nitric oxide-mediated vasodilation. Potentially, other means by which downstream demands, and hence upstream flow, produce similar results might include negative pressure chambers, enhanced external counterpulsation, or neural stimulation. The assertion regarding the potential role of endothelial progenitor cells is speculative and still controversial. All the same, the data and conclusions presented here are certainly hypothesis-generating and could quickly shape clinical practice in the face of an increasingly popular interventional procedure.

Thus, Dawson et al boldly wade into uncharted waters using a powerful, clever, and clinically translational model of endovascular damage to show that the balanced notion of L-FMC is not only endothelially mediated, but also can be nearly offset with 7 weeks of contraction/relaxation handgrip exercises. Limitations (although few) aside, this interesting piece of scientific work provides evidence toward an equalized approach to 2 important aspects of scientific and clinical practice. The tide of endothelial function has undoubtedly moved inward and should be used to ride the wave in answering future questions generated by this work.

Disclosures

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