Flow-mediated constriction: further insight into a new measure of vascular function

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This editorial refers to ‘Brachial artery low-flow-mediated constriction is increased early after coronary intervention and reduces during recovery after acute coronary syndrome: characterization of a recently described index of vascular function’†, by J.R. Spiro et al., on page 856

Introduction: why flow-mediated constriction

Abnormalities in the production of numerous endothelial autacoids, a condition termed ‘endothelial dysfunction’, play a critical role in controlling vasomotor tone, in initiating atherogenesis, and in promoting plaque formation and rupture.1 Given its importance in vascular homeostasis, quantitative measures of endothelial function have gained increasing attention and, among these, the most widely employed is flow-mediated vasodilation (FMD).2 FMD is a measure of the capacity of the endothelium, when stimulated by a specific stimulus (a sudden increase in shear stress), to cause smooth muscle cell relaxation and vasodilation. As such, FMD is measured as the vasomotor response (percentage maximal increase in diameter) from a baseline that is assumed to be uniform across every individual undergoing the measurement. FMD has found favour because it is non-invasive, repeatable, predictive of the extent and severity of coronary atherosclerosis,3 and is an independent predictor of prognosis.4 Despite these strengths, it remains unclear whether the assessment of FMD provides information that is additional to that of traditional risk factors, and initial results from the Cardiovascular Health Study suggest that this parameter adds very little to the capacity of the Framingham Risk Score to predict cardiovascular events.5 This highlights the need for further development of techniques that can allow the derivation of additional information from the assessment of endothelial function.

Baseline function vs. ‘recruitability’

A characteristic intrinsic to the concept of FMD is that it provides information about the ‘recruitability’ of endothelial vasomotor function (i.e. its responsiveness to a specific stimulus), but it does not provide information concerning basal endothelial function (i.e. release of endothelial autocoids before FMD measures are initiated). This conceptual limitation is similar to that of coronary flow reserve, which is measured as maximal over baseline coronary blood flow. Coronary flow reserve is thus a function both of maximal vascular reactivity and of the vascular status measured prior to stimulation. A similar reasoning should be applied to FMD: like an increased baseline blood flow will result in a decreased coronary flow reserve, one cannot, in principle, exclude that an impaired responsiveness to an endothelial stimulus (i.e. an impaired FMD) may result from pre-existing vascular (endothelial) activation, rather than from endothelial dysfunction. Such a phenomenon (impaired further recruitability due to pre-existent endothelial activation) might partially explain the classical observation that FMD is inversely related to the baseline diameter of the artery;2 an artery that is already activated (and dilated) would logically show a smaller FMD, independent of the presence of disease. Importantly, when limiting the assessment of vascular function to FMD and pre-FMD arterial diameter, one cannot draw conclusions on baseline vascular tone, and it cannot be excluded that this parameter also might have an important role in vascular homeostasis. As such, the concept of ‘resting conditions’ should not be assumed to be the same for every individual undergoing the measurement, even when guidelines are scrupulously followed.2

Evidence on flow-mediated constriction

The introduction of low-flow-mediated constriction (L-FMC) is an attempt at addressing this limitation. When the pneumatic cuff commonly used in FMD studies is inflated (Figure 1), an immediate reduction in blood flow occurs in the region proximal to the cuff. This low-flow state, and the parallel reduction in shear stress, are associated with a reproducible vasoconstriction, whose magnitude is proportional to the decrease in blood flow.6 Although it did not receive a great deal of attention, the presence of this L-FMC has...
been shown in several reports over the past 20 years: in 1987, Levenson et al. reported that inflation of a wrist cuff caused an \( \approx 4\% \) constriction of the brachial artery.\(^7\) Interestingly, this effect was preserved in older healthy subjects, but appeared to be attenuated in hypertensives. Later, the same authors reported an increased vasoconstriction induced by low flow in patients with hypercholesterolaemia.\(^8\) Similarly, in 1989, Anderson et al. described a 8.2% constriction in healthy volunteers.\(^9\) Mullen et al. reported a 3.9% constriction, and Spieker et al. a 6.8% constriction in healthy young volunteers.\(^9,10\) The mechanism(s) of this vasoconstriction appear to be more complex than that of FMD (Figure 1). Findings to date suggest that L-FMC is determined by release of the vasoconstrictor endothelin-1 and by inhibition of the release of cyclooxygenase-dependent products and

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**Figure 1** The mechanism of L-FMC involves cyclooxygenase-derived mediators (likely prostaglandins, PG) and a cytochrome P450-derived endothelium-derived hyperpolarization factor (EDHF), and endothelin (ET)-1.
endothelium-derived hyperpolarizing factor. Since L-FMC occurs in response to a reduction in shear stress and is determined by endothelial mediators, one can hypothesize that it could complement FMD in two ways: first, because it provides a measure of resting endothelium-dependent vascular tone; and secondly, because, when combined with FMD responses, it may allow the description of an integrated score of basal and stimulated vascular function (Figure 2).

These concepts are very well exemplified in the paper by Spiro et al. The authors demonstrate that L-FMC provides information concerning vascular function that is different from and complementary to that obtained by measures of FMD. They confirm that percutaneous coronary intervention per se leads to impaired FMD, a finding that was previously considered to result from abnormal endothelial function. However, their concurrent observation that L-FMC is increased after a coronary intervention suggests a different mechanism, in which the activation of the peripheral conduit vasculature determines a reduced capacity of the endothelium to respond to a further stimulus (reactive hyperaemia). Thus, an increased baseline release of endothelial autacoids, rather than an endothelial ‘dysfunction’ induced by stenting, might be a sufficient explanation for the reduction in FMD responses. The same concept might indeed apply to acute coronary syndromes, and the question arises of whether the larger L-FMC demonstrated by Spiro et al. in patients with non-ST elevation myocardial infarction reflects a (compensatory?) activation of the endothelium, and a correspondingly increased L-FMC and reduced FMD.

Whatever the explanation for these findings, these observations reinforce our concept that a blunting in FMD should not be taken as indisputable evidence of endothelial dysfunction.

**Relationship between L-FMC and FMD**

Spiro et al. report the existence of a linear correlation between L-FMC and FMD in healthy volunteers but not in patients with an acute coronary syndrome. These data contrast with our own and emphasize again the complexity of the study of ‘endothelial functions’: although both L-FMC and FMD are an expression of the vascular reactivity in response to changes in shear stress, their relationship is neither conceptually simple nor mathematically linear. This is exemplified in Figure 2: the presence of cardiovascular disease, or of traditional risk factors for cardiovascular disease, is associated with a blunting in both parameters. On the other hand, assessment of endothelial function in subjects in whom the endothelium is already stimulated (such as during isometric exercise or after coronary stenting) will result in a blunted FMD and an exaggerated L-FMC response. Speculatively, since FMD, but not L-FMC, is nitric oxide dependent, therapies aimed at this specific pathway will possibly potentiate the former while leaving the latter unaffected. Finally, the impact of genetic factors, environmental factors, and therapies is unknown. Thus, the relationship between ‘resting’ endothelial activity and endothelial ‘recruitability’...
is surely not simple, and it is important to acknowledge that neither measure can allow conclusions to be drawn regarding the other one.

Implications for the past and for the future

These concepts emphasize the complexity of endothelial biology (and of its assessment in clinical practice) and question the interpretation of changes in FMD. The data of Spiro et al. confirm our impression that, when observing a blunted FMD, one should be careful in taking this as definitive evidence of ‘endothelial dysfunction’ (this term invariably implies a negative connotation). While the measurement of nitroglycerine-induced vasodilation serves effectively to exclude endothelium-independent vasodilator dysfunction, the observation of an increased L-FMC in response to stenting opens up alternative explanations for an impaired FMD (independently of the responsiveness to nitroglycerine). The implications of this concept go well beyond this paper. A number of conditions (for instance, mental stress, fat meal, vaccination, therapies, etc.) have been associated with impaired FMD; the understanding of the concepts outlined above, and the study of Spiro et al.,12 challenge in general the previous interpretations of these endothelial dysfunction data, since they may reflect an activation (and subsequent lack of recruitability), rather than dysfunction, of the endothelium.

Finally, the introduction of L-FMC as an additional parameter of shear stress-mediated vascular tone improves our understanding of specific pathophysiology: for instance, we recently found a correlation between L-FMC and coronary slow flow, and proposed that the impaired basal peripheral endothelial vasomotor function (i.e. blunted L-FMC) might reflect the increase in coronary resistances which causes the typical angiographic pattern of slow progression of the contrast medium.15

Taking all this together, while not requiring additional procedures, the introduction of L-FMC provides additional data that might prove to be relevant to the interpretation of FMD. Studies currently ongoing are investigating whether the introduction of L-FMC adds diagnostic and prognostic information to FMD, and whether the combination of the two adds information to the collection of ‘traditional’ risk factors. Until our understanding of ‘endothelial functions’ is completed, data such as those of Spiro et al. confirm our opinion that the complexity of this tissue should not be reduced to a single parameter.

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References