Simultaneous Assessment of Systemic and Coronary Endothelial Function
Can We Kill Two Birds With One Stone?

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Besides lining the inner surface of vessels, endothelium serves other important functions, including keeping blood and platelets in a nonthrombotic status, avoiding intravascular activation of inflammatory cells, and finally what is possibly the most important function—and definitely the most actively investigated—namely regulation of vascular tone and blood flow. To a large extent, these various functions can be traced to the effects of nitric oxide (NO) produced by a healthy endothelium.1,2

A first corollary of the theory, which puts healthy endothelium center stage in vascular homeostasis, is that the opposite condition (ie, endothelial dysfunction) fosters vasoconstriction, thrombosis, and vascular smooth muscle cell proliferation. Accordingly, development of endothelial dysfunction can be viewed as a mechanistic link between cardiovascular risk factors (hypercholesterolemia, hypertension, diabetes mellitus, and smoking) and morbidity.3,4 A second corollary then is that, should we be able to gauge endothelial (dys)function, we would also be able to check vascular health, and consequently to afford better assessment of cardiovascular risk and improved prognostication of vascular events.5

The central question is how to translate a nice theory into clinical practice. How can we reliably measure endothelial function? Because NO-mediated vascular dilatation apparently goes hand-in-glove with the various activities of healthy endothelium, it would seem logical to measure endothelium-mediated dilatation and, through it, assess the degree of vascular (dys)function and possibly correlate it with future cardiovascular events.6 The problem, though, is the choice of the most appropriate methodology.

Since the pivotal study by Ludmer et al,7 which demonstrated the lack of vasodilation in response to intracoronary acetylcholine in patients with atherosclerotic coronary arteries, assessment of response to acetylcholine of coronary artery diameter and flow has been considered the gold standard for endothelial function evaluation.8 However, intracoronary catheterization has obvious limitations, being invasive and restricted to patients with suspected coronary artery disease. As such, it does not lend itself to prevention studies (which typically investigate large cohorts and often low-risk individuals), nor to intervention studies requiring repeat assessment over time. To some extent, similar considerations also apply to coronary positron emission tomography assessment, which makes use of radioactive tracers and complex instrumentation.9

Hence, a major advance was the demonstration that endothelial function can be investigated noninvasively at the level of peripheral vascular beds, typically as postischemia-induced flow-mediated dilation of the brachial artery.10 Several studies indicate that impaired flow-mediated dilation is a hallmark of various clinical conditions associated with increased cardiovascular risk; as for its prognostic capability, this seems to have been established in patients with relatively high cardiovascular risk profile.11–14

All set, then? Well, not quite. For one thing, there is controversy over the prognostic role of endothelial function assessment in subjects at the lower end of cardiovascular risk profile,13,14 in whom refining of classical indicators of cardiovascular risk would be most helpful. In addition, a major issue has to do with an overarching question: is endothelial function of peripheral arteries representative of what occurs at the coronary artery level? Advocates say yes, as atherosclerosis is a systemic disease; critics retort that atherosclerosis at the brachial artery level is virtually unheard of, and that peripheral arteries and coronary arteries are not always simultaneously affected in a given patient: hence, peripheral artery dilation might have little direct bearing on coronary artery function.

Clearly, whether endothelium-mediated dilation of peripheral arteries can be measured as an easier proxy for coronary artery dilation is an issue to be dismissed as a controversy among academicians. Direct, head-to-head comparison between cardiac and peripheral endothelial function assessment has been made only in small studies, and for obvious reasons not in healthy subjects; furthermore, correlation tended to be modest, suggesting that endothelium-dependent vasoreactivity may not be uniform across vascular regions in the same individual.15,16 Also, because of technical constraints, studies comparing endothelial function of peripheral versus coronary vascular beds in the same patients have been performed using different modalities, and at different experimental time points. Overall, a recent meta-analysis points to a modest correlation between the 2 approaches.13 However, meta-analysis findings provide indirect information, gathered
through comparisons of cohorts, and not at individual patient level. Although differences in population characteristics may explain to some extent the underlying heterogeneity between the 2 approaches, it is also conceivable that the observed differences are in fact genuine, reflecting different behavior of different vessels.

In this issue of Circulation: Cardiovascular Imaging, Iantorno et al.17 from Johns Hopkins present an elegant approach to evaluate endothelial function at systemic and coronary circulation level—noninvasively and simultaneously—by use of cardiac magnetic resonance imaging. In this proof of concept study right coronary artery (RCA) and internal mammary artery (IMA) were both visualized simultaneously in 25 patients with coronary artery disease (CAD) and 26 healthy volunteers. Parameters of endothelial function (changes in cross-sectional area [CSA] and blood flow [ie, flow velocity and blood flow per minute]) were measured at rest, and during NO release elicited by isometric handgrip exercise (IHE). In a subset of 8 healthy individuals, the NO-synthase inhibitor monomethyl-l-arginine was infused, and it confirmed that IHE-induced changes were indeed NO-mediated, and hence endothelium dependent.

Consistent with current understanding of endothelial (dys) function in atherosclerosis, IHE elicited different effects on CSA and blood flow parameters depending on whether the protocol was conducted in healthy volunteers, or in patients with CAD. In healthy subjects, both RCA and IMA dilated significantly in response to IHE (P < 0.001). In contrast, in patients with CAD the RCA did not vasodilate in response to IHE, and the IMA showed modest vasodilation with IHE, significantly less than in healthy subjects (%IMA change from baseline: 16.4±2.5% in healthy versus 9.1±1.6% in patients with CAD; P = 0.02). As for flow velocity and blood flow per minute in IMA, both increased significantly with IHE in healthy individuals (P < 0.001). In contrast, in patients with CAD, an attenuated increase was seen in IMA blood flow with IHE. When comparing the 2 vascular beds, the RCA flow response was less than the IMA response in patients with CAD, which did not reach statistical significance.

Thus, the study did achieve its primary goal, as it nicely demonstrates the feasibility of simultaneous and noninvasive investigation of endothelial function in distinct vascular territories, in healthy subjects as well as in patients. It also reinforces the notion that atherosclerotic endothelial dysfunction is a diffuse phenomenon, which can be documented in different vascular territories of the same patient. However, to correctly gauge its relevance and how it may help future investigations in the field, it is also crucial to put in proper perspective some pathophysiological aspects of the study.

A clear finding is the abolished/reduced vasodilator response to IHE (in terms of changes in CSA) of RCA and IMA of patients with CAD, which the authors correctly interpret as evidence of impairment of NO-mediated dilatation. The question, though, is: at what level of vascular tree does NO impairment actually take place? We should be cognizant of the peculiarities of endothelium-mediated dilatation of large conduit vessels (such as IMA and RCA) in vivo, as impaired lumen dilatation at the level of coronary and mammary arteries in patients with CAD may be the product of different mechanisms. In principle, on exposure to an NO-stimulating challenge (such as IHE), 3 different scenarios can occur: (1) NO-mediated dilatation is primitively impaired in the large vessel; (2) NO-mediated dilatation is primitively impaired in the distal microcirculation, which in turn blunts/abolishes dilatation of large vessels. Specifically, if hyperemia after IHE is reduced at the microcirculation level, the lack of flow increase through distal vascular bed will obviously reverberate upstream, blunting flow-induced shear stress in the conduit artery and hence blunting flow-mediated endothelial production of NO at the large artery level.18,19 In other words, lack of dilatation of a large artery does not necessarily imply intrinsic NO dysfunction locally. (3) NO-mediated dilatation is impaired throughout proximal and distal portions of the vessel. Careful evaluation of the data presented provides some hints. Because blood flow increase in response to IHE was blunted in both RCA and IMA of patients with CAD, there is no question that microcirculatory response was impaired, and that this occurred both in systemic and in coronary territories. At the same time, this finding allows us to discard the possibility that lack of dilatation of large vessels was due solely to local impairment of endothelial function of conduit vessels. Whether the primary dysfunction is represented primarily or exclusively by impaired ability of microcirculation to increase blood flow (ie, the stimulus inducing vasodilatation of RCA and IMA), or whether intrinsic impairment of NO-mediated dilatation also occurs upstream in large vessels remains to be elucidated.

Another issue deserving commenting is the choice to investigate the RCA. Authors clearly explain the technical constraints that currently preclude simultaneous acquisition of IMA and left anterior descending coronary artery. Yet, it is important to understand the intrinsic differences between right and left coronary vascular beds. It is well known that phasic changes in blood flow during the cardiac cycle differ between RCA and left anterior descending coronary artery, that is, presence of systodiastolic flow in the RCA versus predominantly diastolic flow in left anterior descending coronary artery. Hence, it is not known whether this physiological difference between RCA and left anterior descending artery phasic flow patterns might influence the changes of vascular parameters in response to IHE to a similar extent in both territories. Future investigations should clarify this issue.

Germane to the above comment about differences in phasic flow between different coronary arteries, is the equally obvious fact that, unlike coronary arteries, flow in the IMA occurs almost entirely during systole. Furthermore, one would expect that under resting conditions (such as during magnetic resonance imaging acquisition) basal perfusion of skeletal muscle is decidedly much lower than that of cardiac muscle: hence, basal tone of distal microcirculation and its gain on a vasodilating stimulus will be different in skeletal versus cardiac muscle. Together, these intrinsic physiological differences might explain why the effects of IHE (although directionally similar) are numerically different when comparing changes in CSA and in flow between IMA and RCA in patients with CAD (see Figs 4 and 5 of Iantorno et al17). Indeed, these inherent differences of perfusion between systemic and coronary arteries might be substantial enough to preclude a perfect matching when comparing the response to vasodilator stimuli in systemic versus coronary...
Disclosures

None.

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