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 intra-vascular 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.\(^1,2\)

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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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 al17 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 dilation. The question, though, is: at what level of vascular tree does NO impairment actually takes place? We should be cognizant of the peculiarities of endothelium-mediated dilation 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 dilation is primitively impaired in the large vessel; (2) NO-mediated dilation is primitively impaired in the distal microcirculation, which in turn blunts/abolishes dilation 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 dilation of a large artery does not necessarily imply intrinsic NO dysfunction locally. (3) NO-mediated dilation 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 dilation 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 dilation 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 systodiatolic 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...
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territories. In fact, although—the average—both CSA and blood flow behaved similarly in RCA and IMA, the correlation actually seen between RCA and IMA for each parameter at the individual patient level was rather weak (see Fig. 6 of Iantorno et al17). However, one may look at this finding not so much as a limitation, but as a sobering (yet important) demonstration that different vessels behave (to some extent) differently; this is something that has always lingered in the mind of vascular physiologists, and that now it has been directly documented.

What lies ahead of this study? In the past decade, many studies have suggested that, in addition to its well-established role in clinical research, noninvasive assessment of endothelial function may provide prognostic information for individual patient risk. Now the time has come to move forward, and to firmly establish whether detection of endothelial function will be useful in the clinical arena. We need to ascertain whether evidence of endothelial dysfunction can be used to refine stratification of subjects (otherwise) considered to be at relatively low risk, and to guide treatment for those who already show clinical manifestations, or have a high-risk profile. A better tool for coronary and systemic endothelial function assessment will also allow us to tease out the distinct role of concomitant vascular conditions, which may affect endothelial function and, at the same time, influence prognosis.20 Clearly, the clever approach by Iantorno et al17 needs to be reproduced on a larger scale, by different investigators, using different magnetic resonance imaging scanners. Efforts to visualize the left anterior descending coronary artery territory simultaneously with, or at least in very close temporal proximity to, IMA imaging are similarly welcome. However, the most exciting (and long awaited) consequence of it is to have in sight at last a methodology, which provides a direct and objective assessment of vascular reactivity, which allows clinicians and investigators to precisely assess endothelial function in the vast category of subjects with low or moderate cardiovascular risk profile, and which lends itself to being repeated over time, thus allowing one to assess the effects of therapy or lifestyle modifications on vascular health. The elegant approach devised by Iantorno et al17 is a major move forward in this important area, as it paves the road to an entirely new field of investigation to better understand the complex pathophysiology of endothelial function, and its role in the progression of cardiovascular diseases, ultimately to improve outcome of cardiovascular patients.

Disclosures

None.

References


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