EDITORIAL COMMENT
Statins, Skin, and the Search for a Test of Endothelial Function*

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Since their widespread introduction into clinical practice in the 1980s, statins have proven to be one of the most effective treatments to reduce morbidity and mortality in patients with vascular disease (1) and now represent one of the most prescribed drug classes in the world. Despite this, the mechanism whereby statins reduce vascular risk—whether it is exclusively via cholesterol lowering, or whether there might be beneficial effects mediated by non-lipid metabolites that are also altered during statin therapy—remains unclear. Given that vascular biology and physiology are improved in pig, monkey, and mouse models of statin treatment, wherein cholesterol levels do not change at all or even rise (2), there is at least prima facie evidence that the benefit of statins may extend beyond simple alteration in lipid levels.

A plethora of recent data has outlined many of the beneficial effects that statin therapy may have on atherothrombotic processes (1). These include inhibitory effects on monocyte adhesion to endothelial cells and platelet aggregation, reduction of plaque inflammation, attenuation of arterial wall hypoxia, and enhanced release of endothelium-derived vasodilators such as nitric oxide (NO).

Indeed, as statin therapy is associated with greater improvements in clinical outcomes than improvements in the degree of structural stenosis, it has been suggested that statin-related benefits in vascular function may be a key mechanism of the observed benefits of these drugs (3).

In this context, the current study of Binggeli et al. (4), published in this issue of the Journal, demonstrates another potentially beneficial effect of statin therapy on vascular function, with several different drugs in this class, by enhancing post-ischemic hyperemia in the skin circulation of hypercholesterolemic patients. Although this is not of direct clinical relevance per se, the authors suggest that these data are consistent with a statin-related increase in endothelial prostaglandin release, which may in turn have beneficial effects on vascular function in other territories. Furthermore, Binggeli et al. (4) propose that measurement of post-ischemic hyperemia in the skin circulation could prove to be a useful monitoring test for endothelial dysfunction, potentially suitable for use in clinical practice.

This study is therefore provocative and hypothesis-generating; however, further work needs to be done before accepting that the observed effect of statins in improving skin hyperemia is actually prostaglandin–mediated or that this non-invasive test will prove to be a useful clinical method for assessing early vascular dysfunction.

Regarding mechanism, the vascular responses to ischemia followed by reactive hyperemia are clearly complex, involving myogenic, neurogenic, and vasculogenic components, mediated by a variety of metabolic alterations and factors such as acidosis, hypoxia, adenosine, and NO (5). Although Binggeli et al. (4) have shown that inhibition of prostaglandin synthesis decreases hyperemic skin flow by approximately 30% in healthy young adults, and thus is an important contributor to the hyperemic response in skin, they have not yet demonstrated that the statin-related improvement in hypercholesterolemic subjects was actually due to enhanced prostaglandin release or bioavailability. In fact, as prostaglandins are synthesized by many cells other than endothelium (6), the contribution of the endothelium to post-ischemic hyperemia in the skin remains uncertain.

Previous research has demonstrated that the arterial endothelium does in general appear to be a very important player in the regulation of blood flow as well as in the maintenance of vascular health. By contrast, abnormal endothelial function appears to be a key event in the development of atherosclerosis and subsequently in determining cardiovascular risk (3,7). As normal endothelial functions include thromboresistance, inhibition of monocyte adhesion to the vessel wall, inhibition of smooth muscle proliferation, and maintenance of tonic vasodilation, it is hardly surprising that dysfunction of this important cell layer might predispose patients to pathologic conditions characterized by vasoconstriction, plaque development, and excessive thrombosis. One of the key mediators in normal endothelial function (interalia) is NO, which has a variety of atheroprotective effects beyond mere vasodilation (3).

It has been known for several years that impaired endothelium-dependent dilation in the systemic arteries can be observed in children and young adults at risk of atherosclerosis before plaque development (8) and that endothelial dysfunction in the epicardial coronary arteries can lead to abnormal vasoconstriction and myocardial ischemia (7). Furthermore, impaired endothelial function in the microcirculation has been associated with hypertension and microvascular angina (9). As several non-invasive or minimally invasive techniques have recently been described to allow the study of endothelial function in vivo, such tests have been used by many clinical research groups to define subjects at risk of atherosclerosis. Importantly, endothelial dysfunction in high-risk subjects appears to be at least partially reversible by certain therapeutic strategies, such as statin or angiotensin-converting enzyme inhibitor therapy.

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that are also associated with improved clinical outcomes (11). Thus, endothelial function testing has been widely used to assess potentially anti-atherogenic or anti-ischemic therapies by serial examination of arterial reactivity before and after intervention.

The recent demonstration that endothelial dysfunction is associated with adverse clinical outcomes in a variety of settings (12), such as obstructive and non-obstructive coronary disease and hypertension, has given further impetus to the search for a widely applicable and clinically useful test of endothelial function and dysfunction. The relevance of such a test might include the identification of high-risk subjects in a variety of clinical settings, such as primary prevention, evaluation of patients with chest pain, and/or pre-operative assessment of cardiovascular risk.

Despite this, the search for a simple non-invasive and reproducible test of endothelial function has proven difficult. Invasive catheterization of the coronary or indeed peripheral arteries with the infusion of vaso-active substances such as acetylcholine and nitrates (12) is a valuable research tool for studying endothelial and smooth muscle function in vivo but is clearly unsuitable for use in routine clinical practice. The most widely used non-invasive test for arterial endothelial health has been the ultrasound-based measurement of flow-mediated dilation (FMD) in systemic vessels such as the brachial artery (13). Flow-mediated dilation can be measured accurately and reproducibly and is mainly mediated by the release of endothelial NO. Also, there is good correlation between FMD in the peripheral and coronary arteries (14). Nevertheless, measuring FMD is technically difficult and therefore somewhat operator-dependent; the test is poorly standardized between different laboratories, and FMD may show important fluctuations throughout the day and after meals. Despite recent attempts to automate analysis of arterial FMD and despite the publication of guidelines for this procedure (13), much work needs to be done before FMD measurement can be accepted as a widely applicable diagnostic test.

In this context, the suggestion by Binggeli et al. (4) that post-ischemic hyperemia in the skin circulation might be a monitoring test of endothelial dysfunction for clinical practice requires careful scrutiny. Firstly, as noted above, it is unclear whether hyperemia in the skin is an endothelium-dependent response at all. Secondly, even if it is endothelially mediated, this phenomenon appears not to be dependent on NO. As NO mediates many of the important anti-atherogenic effects of the vascular endothelium, this would be a disadvantage to such a test. Furthermore, skin hyperemia appears to be a test of microcirculatory responses, which to date have not been correlated well with large-vessel disease, the level of the circulation that is affected by atherosclerosis. The relationship between the behavior of skin microvessels and those in skeletal and cardiac muscle is as yet unclear, and the reproducibility of skin hyperemia may be relatively poor, with a coefficient of variation of 21% documented in healthy controls (4).

Other aspects of endothelial function, apart from endothelium-dependent dilation, have recently been examined in vivo. Serum levels of soluble cell adhesion molecules, such as ICAM-1 and VCAM-1, are thought to reflect risk by indicating increased endothelial adheresiveness (15). Endothelial release of tissue plasminogen activator has also been measured in health and disease (16), as have serum levels of von Willebrand factor, thought to be released by dysfunctional endothelial cells (15).

There is little doubt that an effective test for vascular endothelial function would be a tremendous advance in diagnosing cardiovascular risk and in monitoring responses to treatment. Such a test ideally should be non-invasive, safe, and reproducible; it should distinguish between subjects with and without atherosclerosis, and it should be predictive of future events, when added to traditional risk-factor based predictive models. At this stage, no such test exists. Nevertheless, with the imaginative approach taken by groups such as Binggeli et al. (4) and the rapid pace of development of understanding endothelial function at both a scientific and a technical level, clinical testing of endothelial function should become possible in the near future.

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REFERENCES


