Endothelial Dysfunction in the Coronary Microcirculation: A New Clinical Entity or an Experimental Finding?

Editorial

The vascular endothelium modulates vascular tone by releasing a number of vasoactive substances including the endothelium-derived relaxing factor, now known to be either nitric oxide (1) or a related compound (2). Endothelium-derived nitric oxide mediates the vasodilatation produced by a number of neurohumoral substances, while attenuating vasoconstriction caused by others (for review, see reference 3). It is now generally accepted that several disease processes alter this important function of the endothelium in larger vessels (4–7). A rather surprising finding in experimental animals has been the observation that hypercholesterolemia can produce this "endothelial dysfunction" in microvessels, where overt atherosclerosis does not develop (8–11). Recently, observations regarding the effect of hypercholesterolemia on the peripheral and coronary microcirculation have been extended to humans (12, 13).

In this issue of *The Journal,* Egashira and co-workers (14) have extended these studies by demonstrating that not only hypercholesterolemia but other risk factors for coronary artery disease, in particular age greater than 50 years and hypertension, are also associated with impaired endothelium-dependent vasodilatation of the coronary microcirculation. These investigators used relatively new and accurate methodologies to study the effect of several risk factors on the coronary microcirculation. Among all patients, a substantial variability in the response of left anterior descending coronary flow to acetylcholine was observed. The degree of vasodilatation to acetylcholine demonstrated a correlation with serum cholesterol, and was reduced in both patients with hypertension and those greater than 50 years of age. Interestingly, smoking, male gender, and positive family history were not associated with an impaired response to acetylcholine. Responses to papaverine, an agent that does not require an intact and functioning endothelium to produce vasodilatation, were not altered by hypercholesterolemia or hypertension, and modestly reduced by age greater than 50 years, although not to the degree the acetylcholine response in this group was reduced.

In this study acetylcholine produced a greater degree of constriction of the proximal left anterior descending if this vessel had visible atherosclerotic lesions than if it did not. One potential criticism of the study relates to this issue. This difference in proximal diameter, however, unlikely contributed to the overall differences in coronary flow responses between the two groups, as the resistance offered by the larger coronary arteries is generally small. The authors reasonably concluded that their findings indicate a defect in endothelial function within the downstream resistance vessels.

What are the implications of endothelial dysfunction in the coronary microcirculation of individuals with hypercholesterolemia and other risk factors for coronary artery disease? The answer to this question remains to be determined. Coronary perfusion is regulated by numerous factors, including metabolic influences, neural input, humoral substances, myogenic tone, and the endothelium (for reviews see references 15 and 16). Many of these control mechanisms may be redundant, and it is generally assumed that metabolic control plays a predominant role. Nevertheless, there is now convincing data to suggest that endothelium-derived nitric oxide plays a major role in modulating basal coronary perfusion. Administration of inhibitors of NO synthase produce marked coronary constriction in both small (17) and large (18) animals.

Could alterations of endothelial function in the coronary microcirculation contribute to clinical syndromes of angina? There is no evidence to support this at present, but it is interesting to speculate that in some instances this may be correct. In particular, the puzzling syndrome of chest pain and normal coronary arteries (syndrome X) has been associated with impairments of endothelium-dependent vasodilatation in the coronary microcirculation (19), similar to the abnormality demonstrated in the present paper. The etiology of syndrome X is likely multifactorial, but at least in some instances may be due to the effects of multiple risk factors such as those identified by Egashira et al. Other chest pain syndromes that may involve endothelial dysfunction in the coronary microcirculation include typical angina pectoris in the setting of coronary disease (where small vessel constriction may further alter tissue perfusion), chronic hypertension, diabetes, myocardial ischemia following angioplasty (where vasoactive substances may be released into the coronary microcirculation), and numerous others. Obviously, testing of these patient subgroups using approaches similar to these used by Egashira and co-workers would be helpful.

Finally, it is interesting to ask, could correction of risk factors restore endothelial regulation of the coronary microcirculation? In experimental animals, regression of atherosclerosis by dietary lowering of the serum cholesterol results in a complete restoration of endothelium-dependent vascular relaxations in large vessels (20). Studies are currently underway to determine if lipid-lowering therapy is associated with an improvement in endothelial regulation of both coronary and forearm blood flow in humans, but have not yet been completed. Experiments like this have not been performed in microvessels in either experimental animals or in man. Further, it is not known if endothelial dysfunction due to hypertension can be improved by antihypertensive therapy. Obviously the process of aging would be difficult to alter.

In summary, the manuscript by Egashira et al. and other recent studies (12, 13) have elucidated a new pathophysiological entity. The clinical manifestations of endothelial dysfunction in the coronary microcirculation remain obscure, and the need (and capability) to correct this remains unknown. Because the endothelium plays such a crucial role in modulating vasomotor tone and regulating other aspects of vascular homeo-

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stasis, this defect may very likely contribute to the untoward effects of these risk factors.

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