Almost 2 decades ago, endothelin-1 (ET-1) was identified as one of the most potent vasoconstrictors in the complex but well-balanced regulation of vascular tone. Since then, through numerous clinical and experimental investigations, it has become evident that ET-1, beyond its function as a vasoactive peptide, also plays a seminal role in the atherogenic process by enhancing mitogenesis and inducing extracellular matrix formation. The role of ET-1 as an active participant in the atherogenic process is underscored by the observations that endothelin is highly and ubiquitously expressed in the extracellular space and the intracellular compartment (macrophages, myointimal cells, myofibroblasts, and endothelial cells) of human coronary atheromatous tissue.

Moreover, it has been demonstrated that circulating and tissue endothelin immunoreactivity correlates with the severity of human atherosclerotic disease. Taken together, these findings strongly suggest a major role for ET-1 in the evolution and progression of coronary atherosclerosis in humans. At the molecular level, nuclear factor-κB, a key transcription factor of the inflammation-cascade, is activated by ET-1 in human monocytes, which further supports the role of ET-1 in the development of inflammation, a key feature of atherogenesis, within the vessel wall.

Because of the development of endothelin antagonists suitable for experimental and human use, the functional role of ET-1 has been further elucidated. In experimental hypercholesterolemia, chronic endothelin receptor antagonism preserved coronary endothelial function and increased nitric oxide (NO) activity. Moreover, in the rodent atherosclerosis model, chronic ET_A receptor blockade not only normalized NO-mediated endothelial dysfunction but also significantly reduced atheroma formation. Similar results have been reported with a nonselective ET_A/ET_B receptor blocker in rabbits.

In this issue of Circulation, Sutherland et al extend the role of ET-1 in atherosclerosis and present their findings from a morphology- and immunohistochemistry-based study on internal mammary arteries (IMAs) collected from patients with coronary artery disease (CAD) undergoing coronary artery bypass graft surgery. They demonstrate that IMA specimens from CAD patients show increased medianecrosis, type-1 collagen, and ET-1, ET_A, and ET_B receptor expression. These findings underline the fact that the IMA is not simply a passive conduit vessel but is an autologous graft that responds to high levels of ET-1 in atherosclerosis with characteristic vessel-wall changes. In addition, they warrant further investigation regarding the potential use of ET-1 receptor antagonists in the medical regimen, which may further improve the already superior patency rate of the IMA in coronary artery bypass graft surgery. The concept that the IMA graft may profit from ET receptor blockade is supported by functional data showing that the IMA develops greater endothelium-dependent relaxation than vein grafts.

If the IMA responds to atherosclerotic stimuli such as ET-1 in a way that is similar to that of other arteries, why doesn’t it show the same rate of atherogenesis as the coronary arteries? Sutherland et al report several interesting observations that go beyond the initial scope of their study, but when taken together with previously published data may be able to answer these questions.

One important aspect of the study by Sutherland et al is the close association of atherosclerotic disease processes with the distribution of vasa vasorum at the media-adventitia border. As shown by Sutherland et al, there is increased and accentuated media necrosis, ET-1, and ET receptor expression in the media of the atherosclerotic IMA. It may be speculated that this may represent an imbalance between demand and perfusion and/or diffusion in this part of the vessel wall. Morphoanatomically, the media is “sandwiched” between 2 active endothelial surface areas: the main lumen and the vasa vasorum. Micro-computed tomography (CT)-based calculations show that up to 60% of the amount of endothelial surface area is also present in the outer vessel wall. The distribution of transmural pressure (Lamé’s law), however, only allows perfusion of those arterial and venous vasa vasorum that lay beyond the inner two thirds of the medial vessel-wall area. Moreover, the present study reports a high expression of ET-1 and its receptors in the IMA media, which may lead to endothelial dysfunction of the IMA, but the expression of endothelin and its receptors in the vasa vasorum may actually add up to a deleterious effect on vessel-wall perfusion. Indeed, functional analyses have shown that ET-1 plays a significant role in vascular tone of the vasa vasorum and hence may eventually result in increased malperfusion of the vasa vasorum-dependent vessel-wall areas with more local hypoxia, necrosis, and activation of atherogenic cascades. The importance of the vasa vasorum as an entry port and a supply route in addition...
to diffusion through the endothelium of the lumen is underlined by the presence of macrophages/monocytes in the adventitia and in vasa vasorum in the present study. Interestingly, micro-CT studies demonstrated that there is a low vasa vasorum density in the IMA compared with that seen in the native coronary artery, but the propensity for neovascularization in response to an atherogenic stimulus is more pronounced in the IMA. Both observations might provide the structural background for the low incidence of atherosclerosis in the IMA and may also help to explain the nonproportional increase in atherosclerosis after implantation.

Further micro-CT studies demonstrated that chronic endothelin receptor antagonism prevents the increase in vascular endothelial growth factor expression and vasa vasorum density of coronary arteries in experimental hypercholesterolemia. Hence, the potential success of chronic ET receptor blockade in atherosclerosis may be due in part to the inhibition of plaque neoangiogenesis, a factor that, unfortunately, has not been addressed in earlier studies.

Another interesting aspect is the increase in ETA receptors and its potential significance in CAD patients. The effect of ET-1 on nuclear factor-kB is mediated, at least in part, through ETA receptors, and studies on the human skin microcirculation have demonstrated that functional vasoconstrictive ETA receptors on vascular smooth muscle cells may contribute to the potentiating effects of high local concentrations of ET-1 on the vasoconstriction to noradrenaline and angiotensin II, which have been shown to be increased in atherosclerosis. Hence, the chronic administration of inhibitors of the endothelin system may lead to a further increased patency rate of IMA grafts by several mechanisms. Although additional assessment of the association of their findings with endothelial function and neoangiogenesis would have strengthened this study by Sutherland et al., their findings encourage further investigation on this unique and clinically important graft artery and the endogenous endotelin system as a mechanism for atherosclerosis. The choice of the most appropriate graft for coronary artery bypass surgery has been investigated by numerous clinical trials. Although it appears that 1-year patency is not significantly different, the majority of studies have demonstrated a better long-term patency rate of the IMA graft than with venous grafts.

Although atherogenesis appears to accelerate after implantation of the IMA, it remains unclear why this vessel is still superior to a venous graft. The IMA, in contrast to venous grafts, is exposed to the high-pressure circulation before implantation, and therefore the vessel-wall structure and function, such as its vascular reactivity properties, are already adjusted to these unique fluid-dynamic conditions. Moreover, the diversity in vascular wall structure and vasa vasorum distribution may contribute to the differential response. Thus, the sudden exposure to the high-pressure circulation causes changes that in the majority of cases cannot be compensated for chronically (and might even lead to acute graft occlusion).

In summary, the report by Sutherland et al. elaborates nicely that atherosclerosis is a pathological process ubiquitously distributed throughout the vessel wall and that the endogenous endothelin system may play a significant role in its evolution, progression, and complications. Moreover, it underscores the fact that the outer vessel-wall layers (and with them, the vasa vasorum) appear to play an important role in atherosclerosis and may be suitable as a future therapeutic target.

Currently, endothelin receptor antagonists are under investigation in clinical trials that mainly but not exclusively are focused on the treatment of acute and chronic cardiovascular diseases, including pulmonary hypertension and heart failure. There is only limited information on the role of endothelin receptor antagonists in the attenuation of atherosclerosis. The focus in the last decade was mainly on medical therapy for the reduction of CAD risk factors, such as elevated cholesterol and blood pressure. However, on the basis of recent experimental and clinical studies, including the present study, it may be speculated that this drug class plays a role in the early phase of atherogenesis, which is dominated by endothelial dysfunction and vasa vasorum neovascularization.

Disclosures

None.

References


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M. Gössl and A. Lerman

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