Adventitia as a Critical Player in the Functional Integrity of Arteries
– Additional Support for Novel Clinical Procedures –

Siu Ling Wong, BSc; Yu Huang, PhD

Adventitia, histologically defined as the outermost layer of the blood vessel and consisting of extracellular matrix and autonomic and sensory nerve endings, has been regarded as a rather inert scaffolding in the vascular wall compared with the active intimal endothelial and medial smooth muscle layers. Vascular diseases are traditionally believed to be initiated and regulated in an “inside-out” fashion. When the innermost endothelial layer is injured, vascular reactivity is dysregulated. Loss of endothelial cells promotes vascular inflammation, culminating in hypertension and atherosclerosis.

Article p1014

It was not until recently that the role of the adventitia was recognized, especially in failures of coronary artery bypass grafting (CABG) and restenosis after percutaneous coronary angioplasty, in association with damage to the adventitial layer, which incidentally leads to endothelial dysfunction. This unconventional “outside-in” mechanism may partly mediate neointimal formation, atherosclerosis, vascular dysfunction and inflammation in which pathogenesis occurs first in the adventitia and invades towards the intima. For example, allografts of aortic transplantation in rats result in neointimal hyperplasia, which is preceded by the transformation of adventitial fibroblasts into myofibroblasts and the liberation of pro-inflammatory cytokines and chemokines, including TGF-β1, MMP-7 and MCP-1. Balloon injury to porcine coronary arteries also causes similar activation of the adventitia, and infiltration of lymphocytes to the media and adventitia triggers local vascular inflammation. Besides which, periadventitial fat produces relaxing factor(s) that activates potassium channels in vascular smooth muscle. These studies provide clear evidence supporting the concept that adventitial and periadventitial components actively participate in vasoregulation.

In this issue of the Journal, Fischer et al demonstrate an essential role of adventitia in blood vessel biomechanics in vivo. Removal of the adventitia activated the underlying smooth muscle layer, leading to increased arterial stiffness and reduced conduit capability and arterial diameter, whereas such alterations did not occur in the in vitro preparations, suggesting active regulation of vascular function by the adventitia, rather than passive structural support. The authors also provide insights into how adventitial function may differ in the various types of arteries, in addition to regional differences in vessel thickness (muscular arteries have a thicker adventitial layer than elastic arteries). Fischer et al used bra-chocephalic trunks and femoral arteries to represent elastic and muscular arteries, respectively, and observed that the adventitia contributes to impedance of the former and compliance of the latter. This is probably the first demonstration of the function and structure of the adventitia in these 2 types of arteries.

The basic biomechanical study of Fischer et al may support the new concept of preserving the adventitia during CABG. The saphenous vein is the most commonly adopted conduit in CABG, but after harvesting and conventional graft preparation, perivascular tissue, including most of the adventitial layer, is always stripped and removed. Distention of the graft is essential to minimize venospasm. These procedures clearly injure the graft, leading to its occlusion. In view of this, a novel surgical procedure known as the “no-touch” technique has been introduced, representing a non-traumatic harvesting approach in which the vein is obtained together with intact surrounding perivascular tissue. This method reduces venospasm and increases the early patency of the graft after CABG. The reduction in venospasm eradicates the need for distention, and thus venous endothelial cells are better preserved. Tsui et al proposed that nitric oxide (NO) is the key to improved graft patency because the NO level of veins harvested using the no-touch technique is significantly higher than in those collected with the conventional stripping and distention method. All 3 NO synthase (NOS) isoforms are present in smooth muscle and adventitia. Dashwood et al have identified eNOS and NOS activity in perivascular adipocytes. Intriguingly, NOS isoforms in the adventitia are contributed by the vasa vasorum and perivascular nerves, indicating that the adventitia is neither quiescent nor passive in vascular tone regulation. Consistent with previous findings, early vasoconstriction immediately after adventitia removal may be caused by the sudden elimination of a basal relaxant effect of adventitia-derived NO, as observed by Fischer et al. This perhaps also explains why conventionally harvested veins always exhibit venospasm. NO is antiproliferative and antithrombotic, so preserving an intact saphenous vein with...
a pedicle of surrounding adipose tissue may delay or inhibit vascular inflammation associated with vein occlusion. Finally, the findings of Fischer et al suggest that the adventitia maintains the normal stiffness and compliance of arteries, partly implying a beneficial role of the adventitia in the conduit function of grafts and hence patency. Indeed, angioplasty in porcine coronary arteries also exhibit phenotypical alteration and migration of adventitial fibroblasts, causing neointimal formation, thus making the adventitia an attractive target for the prevention of post-angioplasty events. The potential approach of “outside-in” perivascular gene transfer therapy was reviewed recently.

Of note, earlier studies demonstrated that removal of the perivascular vasa vasorum during conventional stripping led to adventitial ischemia. The endothelium that overlaid the ischemic area was injured and denuded through cell loss, suggesting that nourishment from perivascular microvessels is important to endothelial cell health and integrity. Fischer et al also propose a hypothesis of the adventitia—endothelium interaction in arteries in relation to time-dependent changes in biomechanical parameters after adventitia removal. This concept may help to address how adventitia is functionally integrated with other components in the vascular wall, and warrants further investigation of: the complementary endothelium-dependent relaxing factors (EDRF); whether compensatory mechanisms are truly absent in endothelium-denuded arteries and in arteries from animals infused with eNOS inhibitors, if NO happens to be the EDRF involved; and what chemical signals the adventitia uses to cross-communicate with the endothelium. Nevertheless, how the adventitia of veins differs functionally from that of arteries and whether the adventitia plays a modulatory role in the arteriolization of grafted veins in connection with the clinical relevance remain to be explored.

References