Editorial

The Endothelium
Paracrine Mediator of Aortic Dissection

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For more than 30 years, the endothelium has assumed increasingly greater importance in our understanding of the development of vascular pathology. This includes the discoveries that the endothelium releases the powerful vasodilator and antiplatelet mediators prostacyclin and nitric oxide, as well as its role in governing permeability, inflammation, and monocyte/macrophage infiltration of the blood vessel. In this issue of Circulation, Fan et al1 show that boosting endothelial-derived oxidants in the mouse aorta by overexpression of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase isoform 2 (Nox2) during prolonged angiotensin II–induced hypertension results in a high incidence of infrarenal aortic dissection.

Aortic dissections are often associated with aneurysms, which may affect both thoracic (TAA) and abdominal (AAA) regions, but can occur also in the absence of aneurysm. There are currently no approved drug treatments against these deadly aortopathies. Limited treatment options include blood pressure control as a means of decreasing the risk of rupture and endovascular or open surgical repair, a procedure with high risk of morbidity and mortality. Although the elucidation of the mechanisms responsible for early aortic pathological changes that precede overt dissection remains very challenging in humans, animal models suggest that medial degeneration, consisting of vascular smooth muscle cell apoptosis and elastin fragmentation, are early features. The work by Fan et al identifies release from the endothelium of the proinflammatory cytokine cyclophillin A (cypA) on angiotensin II administration as a potential paracrine culprit mediating early degenerative events in vascular smooth muscle resulting in aortic dissection. Surprisingly, such a short-term dramatic effect was not a consequence of the hypertensive response to angiotensin II, because equal pressor doses of norepinephrine did not cause dissection. Instead, the authors present evidence that, when Nox2 is overexpressed in the endothelium, angiotensin II causes excessive aortic inflammation and remodeling, leading to dissection because the augmented production of oxidants promotes the secretion of cypA. Therefore, the novel model they present offers unique evidence of the powerful influence of the endothelium on arterial wall structure and insights into potential paracrine mediators within the arterial wall that may lead to aortic dissection. Despite the high rate of dissection and the dramatic magnetic resonance imaging pictures of the extent of the dissection along the aorta presented by the authors, they did not report on any sudden deaths, the most dreaded consequence of aortic dissection in humans. Hopefully, further understanding of the molecular mechanisms of dissection will provide therapeutic insights to prevent this cause of sudden death in humans.

Aortic dilatations and dissections, primarily in the thoracic region, are often a comorbidity of monogenic syndromes, such as Marfan, Loeys-Dietz, and Ehlers-Danlos syndromes, characterized by genetic alterations in extracellular matrix components, including fibrillin-1 and collagen. These gene mutations result in pathological aortic remodeling and enlargement, which can progressively worsen into a thoracic aortic aneurysm. Similarly, mutations in MYH11 (myosin, heavy chain 11, smooth muscle) and ACTA2 (actin, α2) 2 major vascular smooth muscle structural proteins, result in aneurysm. In addition, genetic mutations in transforming growth factor β (TGFβ)3, a cytokine with fibrotic effects on vascular smooth muscle, or TGFβ receptors (TGFβR1 and TGFβR2), downstream effectors (SMADs [SMA/MAD homologues]), or inhibitors (SKI [Sloan-Kettering Institute proto-oncogene])4 were implicated in the pathogenesis of aortic dilatation and dissection. Losartan, an angiotensin II receptor blocker commonly used as an antihypertensive medication, recently entered clinical trials for the treatment of thoracic aortic aneurysms in Marfan and related syndromes5 both for its ability to decrease the downstream effector TGFβ5 and the hemodynamic stress on the dilated aorta by lowering blood pressure. In contrast to purported deleterious actions in the thoracic aorta, TGFβ was protective in angiotensin II–induced AAA in normocholesterolemic mice by inhibiting inflammatory cell infiltration and consequent vascular smooth muscle cell apoptosis and extracellular matrix degradation.6 This underscores that molecular mechanisms may differ among the phenotypic spectrum of aortic aneurysms and dissections based on cause or location, making a “one-size-fits-all” therapeutic approach problematic. However, the fact that cypA mediates vascular smooth muscle cell proliferation and recruitment of inflammatory cells in several arterial disease models, including ligated carotid arteries, atherosclerosis, and angiotensin II–induced aneurysms,8 would suggest that cypA may be a common inflammatory mediator and a possible therapeutic target for several diseases of arterial remodeling characterized by oxidant overproduction and inflammatory cell infiltration.
Elastase infusions and calcium chloride instillation induce elastin fragmentation and mimic the structural defects of human aneurysmal aortas and are also features of mice bearing mutations for genes required for structural integrity of the aortic wall, such as fibrillin-1, fibrillin-4, and TGFβ receptors. In addition, apolipoprotein E or low density lipoprotein receptor null mice administered angiotensin II were used extensively as experimental models of aortic aneurysm, in part because of the reproducibility of the outcome but despite the fact that hypercholesterolemia is not an independent risk factor for aneurysms in humans. In the absence of the apolipoprotein E null genetic background, elevated doses of angiotensin II (commonly 3.2 mg·kg⁻¹·d⁻¹) are required to induce aneurysms in mice and occur with a lower incidence than in hypercholesterolemic mice, although they cause similar tissue pathology. The relevance of angiotensin II infusion models to the human pathology is still debated, primarily because direct comparisons between animal and human specimens at early stages of the disease are not feasible. The striking finding by Fan et al is that angiotensin II infusion, even at the modest dose of 1 mg·kg⁻¹·d⁻¹ in endothelial Nox2 transgenic mice, was sufficient to cause dissections in 45% of their normolipidemic mice.

Angiotensin II infusion in rodents has been used as a model of renin-dependent hypertension for more than 50 years. Despite the fact that the rapidity of development and severity of hypertension is not often reproduced in spontaneously hypertensive patients, the model continues to provide unique insights into the pathogenesis of hypertension and the mechanisms of its clinical sequelae. Two of the most exciting recent mechanistic observations provided by the model indicate the importance of NADPH oxidase in brain nuclei that control sympathetic nerve traffic and the involvement of T-cells in mediating the hypertensive response to angiotensin II. These 2 new directions stem from the original fundamental observations that angiotensin II stimulates NADPH oxidase–derived oxidants and contributes to vasoconstriction, hypertrophy and remodeling of the vascular wall, and atherosclerosis. The key NADPH oxidase involved contains the heme-binding subunit Nox2, or glycophorin 91 phagocyte oxidase, the isoform that accounts for superoxide anion production by neutrophils, macrophages, and other myeloid cells. A Nox2-deficient knockout mouse had diminished pressor and hypertrophic response to angiotensin II, but that study left open the question addressed by Fan et al of whether Nox2 expression in different cell types was important. Interestingly, Nox2, even in the normal aortic wall, is concentrated in the endothelium and adventitial fibroblasts, and these 2 sites also are where leukocytes increase during angiotensin II infusion. This inflammatory cell influx caused by angiotensin II is key as demonstrated by the fact that leukocyte infiltration, as well as the pressor and hypertrophic response, is diminished in a chemokine receptor knockout mouse. Fan et al show that the increase in reactive oxygen species that they induced in the endothelium leads to increased adhesion molecule VCAM1 (vascular cell adhesion molecule 1) expression throughout the aortic wall, providing evidence that the greater inflammatory response attributable to a paracrine mediator is at the root of the increased incidence of aortic dissection.

Fan et al also provide insights into the paracrine relations within the vascular wall that mediate the response to angiotensin II. Previous elegant studies showed that cypA in smooth muscle cells promotes inflammation and activation of proteolytic enzymes and that mice doubly deficient in cypA and apolipoprotein E were prevented from developing aortic aneurysms during angiotensin II infusion. In a clever series of studies using conditioned medium of cultured endothelial cells and aorta from endothelial Nox2 transgenic mice, Fan et al show that endothelial oxidants promote cypA production, which in turn “primed” smooth muscle cells through Erk (extracellular signal-regulated kinase) phosphorylation and increased oxidants. This, in turn, is responsible for the activation of proteolytic enzymes that destroy elastin and lead to dissection. The authors leave unaddressed the question of whether cell–specific genetic deletion of Nox2 in aortic endothelium might prevent much of the aortic pathology in response to angiotensin II, which would further highlight the importance of paracrine mediators.

It is apparent that the paracrine relations within the arterial wall induced by angiotensin II are multiple and complex, but that superoxide anion produced by NADPH oxidase, whether it be in endothelial cells, leukocytes, or adventitial fibroblasts, is key. It is made clear by Fan et al that endothelial oxidants can augment generation of cypA, but which oxidant species are involved and their cellular sites and enzymatic sources of origin is important to consider. In a supplemental figure, Fan et al show that an inhibitor of nitric oxide synthase prevents much of the angiotensin II–induced reactive oxygen species production by endothelial cells that overexpress Nox2, suggesting the possibility that uncoupled endothelial nitric oxide synthase and the generation of the reaction product of superoxide anion and nitric oxide, peroxynitrite, is at work. Indeed, the footprint of peroxynitrite, nitrotyrosine, is abundantly localized in the aortic intima and adventitia, but not in the media, after angiotensin II. In the media, evidence would suggest that hydrogen peroxide is the oxidant species at work, because angiotensin II–induced hypertrophy and aneurysm formation are prevented by smooth muscle–specific overexpression of catalase. Either peroxynitrite or hydrogen peroxide can contribute, by transcriptional and posttranscriptional mechanisms, to the increase in matrix metalloproteinase expression and activation that was shown so well by Fan et al to occur throughout the aortic wall and accounts for the elastin breaks and dissections they reported.

In considering multiple potential therapeutic targets to inhibit the molecular and cellular events leading to aortic dissection (Figure), it is important to realize that the same mechanisms that account for hypertension caused by angiotensin II are clearly different from those that account for arterial hypertrophy and remodeling. For example, inhibiting the acute activation of nuclear factor κB by replacement of nuclear factor κB inhibitor-α with nuclear factor κB inhibitor-β nearly abolished the intense fibrotic response to angiotensin II in the aorta and heart without affecting the pressor response. Either peroxynitrite or hydrogen peroxide can contribute, by transcriptional and posttranscriptional mechanisms, to the increase in matrix metalloproteinase expression and activation that was shown so well by Fan et al to occur throughout the aortic wall and accounts for the elastin breaks and dissections they reported.

In addition, other agonists, such as endothelin and thromboxane A₂, or cytokines, such as TNFα, can stimulate many of the pathways that angiotensin II does so potently and rapidly via the AT1 (type 1 angiotensin II) receptor, leaving the
Molecular mechanisms in the vascular wall leading to aortic dissection. In the presence of angiotensin II, endothelial Nox2-derived oxidants (O$_2^·$ and ONOO$^–$) stimulate endothelial cypA production, which acts as a paracrine factor to activate MMPs and ROS production in VSMCs. MMPs, in turn, degrade elastin, causing aortic dissection. Angiotensin II elicits an array of oxidants (O$_2^·$, ONOO$^–$, H$_2$O$_2$) and inflammatory responses (NF$\kappa$B) within the arterial wall via AT1Rs, which stimulate VSMC and fibroblast proliferation and inflammatory influx in the vascular wall, all contributing to remodeling and fibrosis. Angiotensin II also stimulates cypA production in VSMCs, further contributing to oxidants and inflammation. AT1R indicates type 1 angiotensin II receptor; cypA, cyclophilin A; eNOS, endothelial nitric oxide synthase; IL1$\beta$, interleukin 1$\beta$; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; NF$\kappa$B, nuclear factor $\kappa$B; ROS, reactive oxygen species; TGF$\beta$, transforming growth factor $\beta$; TNF$\alpha$, tumor necrosis factor $\alpha$; VCAM1, vascular cell adhesion molecule 1; and VSMC, vascular smooth muscle cell.

Disclosures

None.

References


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