The term elasticity, in materials science terms, indicates the degree to which energy is conserved during a deformation-recoil reaction. When a steel ball is dropped onto a rigid surface, it rebounds closer to its initial height than, say, a rubber ball. In that configuration, steel is said to be more elastic than rubber, because more of its potential energy is recovered during the reaction. In cardiovascular science, the term elasticity is sometimes appropriated to indicate compliance or deformability, but such license can sometimes lead to erroneous mechanistic constructs. A spoiled plum is deformable but, when dropped, interacts with the floor in a highly inelastic manner.

Aortic aneurysm is primarily responsible for more than 13,000 deaths and is a contributing factor in 61,000 hospital admissions.2-4 The overall risk of rupture, however, is relatively rare, occurring in younger patients, often enough during childhood, as a result of deficiencies in the inherent material properties of the aorta itself, along with putatively maladaptive tissue responses to subsequent vascular injury.

The diverse processes leading to catastrophic events share a common end result: loss of elasticity in the aortic wall (Figure). Hypertension and hyperlipidemia, especially when combined, evoke a vascular response to injury, mediated by oxidant stress and other effectors, propagated by inflammatory cell infiltration and matrix remodeling, culminating in loss of material elasticity.2-3 The cycle perpetuates itself by means of vessel dilatation (increasing LaPlacean distending pressure, and the added maladies arising from aortic valve regurgitation.

Since recently, maladaptive remodeling of the aorta was considered an inevitable feature of some inherited connective tissue diseases. Identification and management of exacerbating factors, eg, pulse-pressure, has resulted in a modicum of relief or cell therapy has sustained a level of hope for meaningful disease-modifying treatment for those most severely affected by inherited connective tissue diseases.5-6

But it is perhaps indicative of the inadequate state of affairs that among 16 registered therapeutic clinical trials for aortic diseases almost all are aimed at improved management of the catastrophic consequences of life-threatening aortic aneurysm, rather than modification of the underlying disease process. In effect, 7 of these forward-looking studies seek new ways to protect against (or repair) aortic rupture by means of placing a rigid (inelastic) buttress at strategic sites.6

In this issue of Circulation Research, Hanada et al report a spectacular spectrum of data from mice engineered to reduce expression of a key modulator of the material properties of the aorta, fibulin-4, which serves to organize assembly of elastic fibers.7 Whereas homozygous deletion of the gene encoding fibulin-4 is embryonically lethal, mice homozygous or heterozygous for the reduced expression allele can survive to adulthood. Gross anatomic and functional cardiovascular manifestations of this mutation resemble classic clinical disease: aortic dilatation, aneurysm formation, aortic valve dysfunction, increased pulse pressure, and cardiac remodeling.

Vascular dilatation and tortuosity are features of the clinical form of cutis laxa syndrome arising from a mutation resulting in reduced expression of fibulin-4.8 The findings are intrinsically fascinating. But the greater value of this work probably lies in the exhaustive characterization of the tissue responses to lost elasticity at the cellular and molecular level. It appears that energy lost when pulsatile blood flow interacts with the inelastic aorta is transduced chemically to produce a complex tissue injury response. Enthusiasm for these findings is predicated on the hypothesis that some of this response is either maladaptive or insufficient, and could thus potentially be manipulated to effect a disease-modifying result. The investigators identify a key mediator of the injury response, transforming growth factor-β (TGF-β) signaling, which is known to participate in the tissue response to other forms of injury in vascular tissue. Habashi et al previously demonstrated that TGF-β signaling is upregulated in a mouse model.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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of Marfan Syndrome, and that neutralization with blocking antibodies or the drug losartan prevented the Marfan vascular phenotype.9 Mutations in receptors for TGF-β underly vascular tortuosity and dilatation seen in the Loeys-Dietz Syndrome, indicating that abnormalities of TGF-β signaling are sufficient to initiate an aortic aneurysm syndrome in some cases.10 These findings, in large part, were responsible for initiation of a Phase III clinical trial of losartan, an angiotensin II receptor type I blocker which is already in wide use for treatment of hypertension, for patients with Marfan Syndrome, which began enrolling patients in January, 2007.6

In atherosclerosis, AT1 signaling is operative in almost every aspect of vascular injury and the response to injury (Figure). Low density lipoprotein cholesterol (LDL) upregulates the level of angiotensin II peptide as well as AT1 receptor expression in vascular wall.11 The rate-limiting enzyme for angiotensin II synthesis, angiotensin converting enzyme, colocalizes with oxidized LDL in atherosclerotic plaque and in stenotic aortic valves.12 AT1 signaling upregulates production of reactive oxygen species and cytokines, along with matrix metalloproteinases and elastase, all of which contribute to wall remodeling and reduction of wall elasticity. Leukocyte recruitment, fibroblast activation, and smooth muscle cell proliferation all occur as direct downstream effects of increased AT1 signaling in atherosclerotic plaque.13,14 It is not surprising, therefore, that blockade of angiotensin II synthesis or binding to its type 1 receptor yield reduction in disease progression15 and in clinical events in high-risk patients with atherosclerosis.16 In spite of these therapeutic advances, however, the diseases rage on, albeit perhaps at a slower rate or with slightly lower attack rate.1

The findings of these experimental and clinical studies may be greeted with some skepticism regarding their applicability across the whole spectrum of aortic aneurysm syndromes. Whereas Habashi et al found that blockade of TGF-β signaling alleviated the aneurysm phenotype in their mouse model of Marfan Syndrome,7 Dai et al reported a “healing” effect of overexpression of TGF-β in a different rat model of abdominal aortic aneurysm.17 In the latter case, deposition and organization of elastin were observed to be increased in the aneurysmal vessel wall, accompanied by decreased indicators of inflammation and a slower rate of aneurysm expansion. The notion that optimal cytokine signaling is neither an “all-or-none” phenomenon, nor fits neatly into a good versus bad dialectic, has become apparent in other settings as well.18 Nonetheless the findings reported by Hanada and colleagues6 hold great promise for elucidation of new and diverse aspects of the vascular response to injury. Specifically, it will be fascinating to learn the degree to which a single “magic bullet”, AT1 blockade, can ameliorate the ravages of inherited connective tissue syndromes. This growing body of work demonstrates the power of translational biomedical research across its whole spectrum, using iterative dialogue between clinicians, integrative physiologists, and molecular biologists. Energy invested in each of these pursuits sustains the other, and the cognitive interactions thus could be considered to be perfectly elastic.

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