

EDITORIAL COMMENT

Aortic Valve Mechanics

An Emerging Role for the Endothelium*

Craig A. Simmons, PhD

Toronto, Ontario, Canada

The aortic valve is a remarkable structure, capable of functioning for a lifetime in the most physically demanding environment in the body. While the valve's purpose—to prevent retrograde flow of blood back into the ventricle during diastole—is relatively simple, proper function is achieved only when physical interactions between the valve tissue and its fluid dynamic environment are choreographed appropriately. If either the tissue or fluid component is altered, valve function can be compromised. In the extreme case of a stiffened stenotic valve that has abnormal leaflet structure and opens incompletely, the consequences of compromised valve function are significant: stenosis carries an 80% 5-year risk of progression to heart failure, valve replacement, or death (1). However, even more subtle alterations in valve leaflet structure and mechanical properties may influence leaflet opening and coaptation, stress distributions in the leaflet tissue, coronary perfusion, and ventricular function (2,3). Thus, elucidation of the factors that influence valve mechanics will lead to a better understanding of how the valve functions, how disease alters its function, and how to engineer functional replacement valves.

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To date, valve mechanics has been largely viewed as an engineering issue, dictated solely by hemodynamics and tissue mechanics. However, with increasing appreciation for valve biology have come new insights about valve mechanics, and in particular, the role valve cells may play in regulating valve function. The most common and best studied valve cell type is the valve interstitial cell (VIC) that populates the leaflet extracellular matrix. VICs are predominantly fibroblast-like cells in normal adult valves, but can differentiate to contractile myofibroblasts in response to a

variety of biophysical stimuli (4,5) and during development and disease (6). Contractile responses of VICs have been demonstrated in intact valve tissue and in isolated cells in response to a variety of vasoactive agents (7–10). As expected, VIC responses are similar to those of vascular smooth muscle cells: 5-hydroxytryptamine (serotonin), endothelin (ET)-1, catecholamines, and histamine induce contraction, whereas nitric oxide (NO) induces relaxation. While the relevance of VIC-mediated contraction to valve function remains to be defined, it is speculated that contraction may play a role in tissue homeostasis, regulate tissue matrix organization, and influence tissue mechanical properties. In support of the latter, hypercontracted aortic valve tissue is significantly stiffer in flexion than nonstimulated tissue (11).

The potential for vasoactive agents to alter valve tissue mechanics is analogous to their role in regulating vascular tone and mechanical properties. It is well recognized that vascular smooth muscle tone and vessel compliance are regulated by the vascular endothelium, which releases several mediators, including NO, ET-1, and natriuretic peptides. In this issue of the *Journal*, El-Hamamsy et al. (12) demonstrate for the first time that the valvular endothelium can play a similar role in regulating aortic valve mechanical properties. Using intact porcine aortic valves *ex vivo*, the authors measured tissue elastic modulus (a measure of tissue stiffness) and contraction force in response to serotonin and ET-1. Tissue mechanical properties were measured with the tissue held in tension, stretched equally in the radial and circumferential directions. This configuration mimics the physiological loads to which the valve tissue is subjected by diastolic transvalvular pressure, but does not mimic the shear stress or flexural forces exerted on the valve.

The authors found that in this basal state, VIC-mediated contraction contributed to tissue stiffness, but the endothelium did not. In the presence of serotonin, however, the endothelium regulated tissue mechanical properties substantially. Stiffness and contraction were decreased in intact tissue samples when treated with serotonin. This effect was likely the result of endothelial release of NO and its induction of VIC relaxation, as inhibition of NO synthase or denudation of the endothelium reversed the effect of serotonin, causing an increase in tissue stiffness (and presumably VIC contractility). Exogenous ET-1, which is normally produced by the endothelium, also caused tissue stiffening, likely due to its induction of VIC contractility, as cytochalasin B, which depolymerizes actin filaments, inhibited tissue stiffening.

These important findings suggest that the endothelium plays a critical role in regulating valve mechanics and by extension, valve function and perhaps long-term durability. Dynamic, responsive adaptation of tissue mechanical properties may be a mechanism by which the valve ensures its proper motion and an appropriate stress distribution in the leaflets so as to avoid localized tissue microdamage in

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From the Institute of Biomaterials and Biomedical Engineering, Department of Mechanical and Industrial Engineering, and Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada. This work was supported by the Heart and Stroke Foundation of Canada (NA 6047) and the Canada Research Chair in Mechanobiology.

the face of changing hemodynamics. Loss of these adaptive mechanisms due to endothelial dysfunction (or the absence of endothelium in a damaged or tissue-engineered valve) could result in abnormal biomechanics, structural damage, and exacerbation of disease progression. This is a fascinating hypothesis that remains to be tested, as does the relevance of endothelial regulation of valve mechanics *in vivo*. The *ex vivo* measurements reported in the current study suggest that tissue elastic modulus can change substantially (by up to 30%) in response to serotonin. The response *in vivo* likely differs from that reported in the current study, as the biaxial test configuration and the method to determine tissue modulus based on the linear portion of the stress-strain curve represented supraphysiological load conditions in some experiments. Nonetheless, the novel work of El-Hamamsy et al. (12) clearly establishes that endothelial-*interstitial cell communication can modulate valve function and motivates future studies aimed at better defining the mechanisms and relevance in vivo.*

A priority and key extension of the current study will be to determine the role of blood flow-induced shear stress on endothelial regulation of valve function. This stimulus was absent in the *ex vivo* experiments by El-Hamamsy et al. (12), which may explain the lack of effect of the endothelium on basal tissue stiffness. In the vasculature, shear stress is an important determinant of endothelial regulation of vessel tone. For example, at branches and curvatures of the vasculature that experience low magnitude, oscillatory shear stress, NO synthase expression and NO release are reduced, and endothelium-dependent vasodilatation is impaired (13). The opposite may be the case in the valve, as *in situ* transcriptional profiling of the endothelium from opposite sides of normal aortic valves indicates that NO synthase messenger ribonucleic acid expression is higher on the aortic surface of the leaflets, a region that experiences disturbed flow (14). Thus, shear stress may regulate VIC contractility and tissue mechanics through the valve endothelium in a side-dependent manner and very differently than it does in the vasculature, consistent with mounting evidence that valvular and vascular endothelia are distinct phenotypes (15–18).

The potential for the endothelium to modulate the function of cells in the interstitium likely has broader implications that extend well beyond regulation of VIC tone to include modulation of valve homeostasis and pathobiology. In aortic valves, calcific lesions form preferentially in the fibrosa, the matrix layer below the endothelium on the aortic surface of the leaflets, whereas the opposite side of the leaflets (the ventricularis) is relatively disease protected. Focal lesion development is the result of pathological differentiation of VICs, including a recently identified subpopulation of valve mesenchymal stem cells with robust osteogenic calcification potential (19). Differentiation of these cells is likely modulated in part by side-dependent (and perhaps hemodynamically regulated) endothelial expression of growth factors and cytokines that act on VICs

locally to inhibit or stimulate fibrosis and calcification (14). Emerging evidence that calcification by VICs is modulated by matrix stiffness and cytoskeletal tension (5) suggests an additional mechanism by which endothelial regulation of tissue mechanics may impact valve homeostasis and pathology.

While these recent findings and those of El-Hamamsy et al. (12) are provocative, it is still too early to know what their *in vivo* and clinical implications will be. At minimum, they demonstrate that the valve, its cells, and their interactions are far more dynamic and complex than has been appreciated to date, and therefore there may be more opportunities to intervene early in calcific aortic valve sclerosis than were thought possible. The challenge moving forward will be to unravel the intricacies of valve biology and mechanics, and to integrate that knowledge with our understanding of genetic and environmental risk factors to discover early detection markers of aortic sclerosis and innovative, effective medical therapies for its prevention and treatment.

Reprint requests and correspondence: Dr. Craig A. Simmons, Department of Mechanical and Industrial Engineering, University of Toronto, 5 King's College Road, Toronto, Ontario M5S 3G8, Canada. E-mail: c.simmons@utoronto.ca.

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