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Mechano-potential etiologies of aortic valve disease

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ABSTRACT

Aortic valve leaflets experience varying applied loads during the cardiac cycle. These varying loads act on both cell types of the leaflets, endothelial and interstitial cells, and cause molecular signaling events that are required for repairing the leaflet tissue, which is continually damaged from the applied loads. However, with increasing age, this reparative mechanism appears to go awry as valve interstitial cells continue to remain in their 'remodeling' phenotype and subsequently cause the tissue to become stiff, which results in heart valve disease. The etiology of this disease remains elusive; however, multiple clues are beginning to coalesce and mechanical cues are turning out to be large predicators of cellular function in the aortic valve leaflets, when compared to the cells from the pulmonary valve leaflets, which are under a significantly less demanding mechanical loading regime. Finally, this paper discusses the mechanical environment of the constitutive cell populations, mechanobiological processes that are currently unclear, and a mechano-potential etiology of aortic disease will be presented.

1. Introduction

In the burgeoning field of mechanobiology, heart valves (HVs) have a unique position. The leaflets that make up the HVs are relatively 'simple' in architecture, and additionally, their biology is not excessively complicated due to significant innervations or vasculature. Both these characteristics are akin to articular cartilage and musculoskeletal tendons and ligaments, but HVs are unique in that they are always under significant forces due to the cardiac cycle. When a HV is open, the surface facing the passing blood is exposed to significant shear stress, while the other side experiences disturbed flow due to blood recirculation and eddy formation (Fig. 1A). When the HV is closed, blood pressure imposes a force normal on the leaflets preventing retrograde blood flow with a distinct orthogonal mechanical tissue response, largely due to an evolved and highly aligned collagen architecture (Fig. 1B).

This biomechanical response is of great significance for the HVs to function properly. Specifically, the leaflets are required to achieve very large strains with low stress in the radial direction in order to co-apt and close the orifice area; however, they must simultaneously withstand significant pressure from the blood to prevent retrograde flow. Thus, if one were to design a homogenous and isotropic material to function as a replacement valve leaflet, it may be able to achieve the high strain needed in the radial direction; however, there would not be ample strength to withstand the pressure and the leaflets would ultimately pull apart during closure, leading to regurgitation. To prevent this, HVs have developed an aligned collagen architecture in the circumferential direction that responds biomechanically with a sharp rise in stress with minimal strain.

The mechanobiologic consequence of the various stress modes experienced by the HV leaflets provides a platform to examine cellular response to mechanical stimuli. However, there are also confounding factors that make teasing out specific responses difficult. For instance, uncoupling effects of fluid shear stress and tissue deformation resulting from in plane stress is largely impossible. Additionally, the molecules that are produced in response to these stresses, which in turn act on the cells that are not under said deformation, offer further challenges (i.e. cytokines from endothelial cells that act on interstitial cells).

Here, I will focus on aortic valve (AV) leaflets specifically, and their low-pressure counterparts, the pulmonary valve (PV) leaflets, when appropriate. I will begin by moving from the outside of the tissue into the interstitial space and discuss recent advances in our understanding of how mechanical forces acting on the leaflets lead to biological changes in the cell population and subsequently leaflet tissue architecture and functional properties. The impetus for focusing on the AV is that it makes up ~63% of valve disease mortality numbers and ~53% of the 93,000 valve procedures performed per year in the US (Lloyd-Jones et al., 2009). These numbers will increase substantially in the coming years as our population continues to live longer.

Over the next 50 years, the population of Americans age 65+ will more than double—from 34 to 79 million (www.bioethics.gov 2005). In fact, the oldest of the old (85+) are currently the fastest growing segment of the population and will more than quadruple by 2050. These numbers are alarming in light of what is known of

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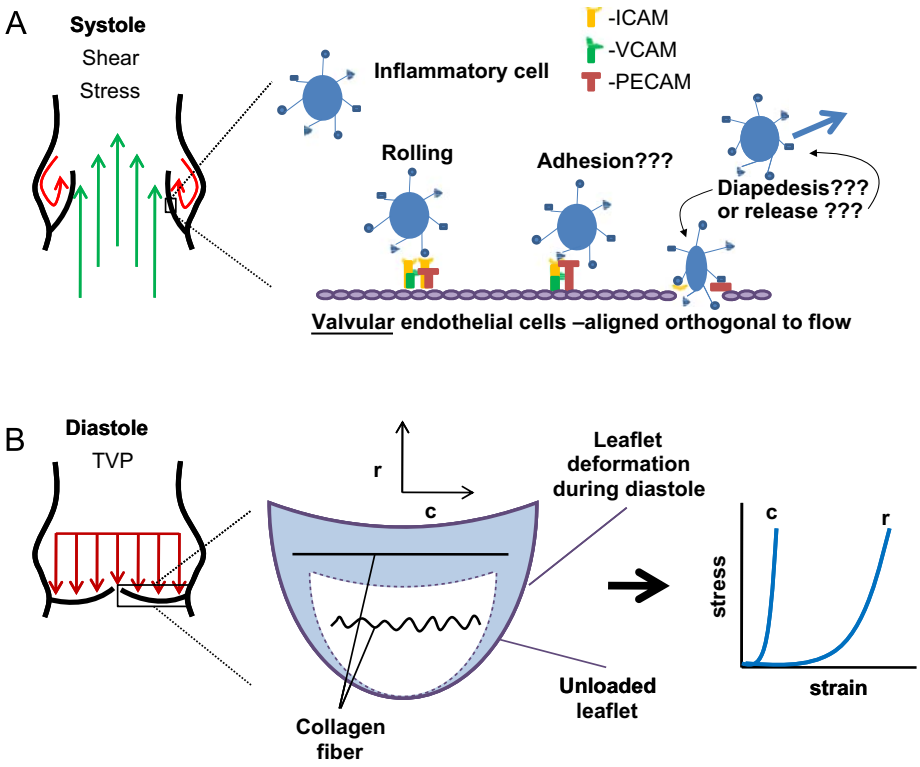

Fig. 1. Distinct stress modes applied to AV leaflets during the cardiac cycle. (A) Shear stress is applied to both sides of the leaflet during systole. On the side of flowing blood (ventricularis), the leaflets experience laminar shear stress. On the side of recirculation and eddy formation (fibrosa), the leaflets experience disturbed, oscillatory shear stress. This oscillatory shear stress is thought to activate cell adhesion molecules (i.e. ICAM, VCAM, and PECAM), which may or may not recruit inflammatory cells into the leaflet. (B) Diastolic pressure results in biaxial planar stretch of the leaflets. The leaflets exhibit an orthogonal stress–strain response due to the aligned collagen architecture in the circumferential direction. Under normal diastolic pressure (~80 mmHg), AV leaflets are strained to ~15% in the circumferential direction (c) (Thubrikar, 1990), due to the straitening of the collagen fibers, and ~50% in the radial direction (r) (Christie and Barratt-Boyes, 1995).

HV disease, particularly in the AV. AV disease develops in an escalating fashion after 65 years of age such that 48% of AVs are sclerotic by the age 85 (Stewart et al., 1997). Multiple studies demonstrate that sclerosis leads to stenosis and surgery 4–8 years after initial diagnosis (Cosmi et al., 2002; Faggiano et al., 2003). Together, the aging trends in the US combined with the progression of AV disease indicate an increasing trend in the number of patients affected and dollars spent on this pathology. In light of these projections, there is considerable interest in developing novel techniques to prevent early stage AV disease (before calcification) in the aging population, and developing strategies that utilize the AVs' inherent mechanobiological processes will likely be critical in achieving this goal. Thus, I will attempt to connect our current understanding of AV mechanobiology, including gaps that exist in our knowledge, with subsequent speculative directives toward research that will hopefully lead to novel preventative or treatment strategies in the coming years.

2. Shear stress and valve endothelial cells

The leaflets of all four HVs are sheathed by a single layer of valve endothelial cells (VECs) that have been shown to be morphologically different from vascular endothelial cells (Butcher and Nerem, 2004). Specifically, VECs are aligned perpendicularly to the direction of blood flow (Deck, 1986), whereas vascular endothelial cells are aligned parallel. This directionality may be programmed into the VECs as porcine VECs grown on collagen are reported to align perpendicular to flow *in vitro* (Butcher et al., 2004). VECs are believed to regulate tone, inflammation, thrombosis, and remodeling, and their dysfunction has been linked with multiple valve disorders (Leask et al., 2003). VECs have also been found to provide protection for valve interstitial cells (VICs) in a collagen gel/tissue engineering model by preventing a shift of the VICs to the myofibroblast phenotype (to be discussed in the next section) (Butcher and Nerem, 2006). However, this finding has not been substantiated in a native leaflet.

Within the proximal third of the leaflets, where they are innervated, there is believed to be a feedback mechanism between the VECs and VICs wherein the nerves transmit information regarding released substances from the VECs (Marron et al., 1996). While it has not been demonstrated to date for HVs, mechanosensitive release of cytokines from vascular endothelial cells has been shown to cause changes in vascular smooth muscle cell structure and function (Davies, 1997); thus, there is a likelihood that this occurs in valvular tissue. There has been speculation that there exists some physical communication between the VECs and VICs via gap junction. However, to date none has been observed between the two cell populations (Filip et al., 1986), indicating that signaling between the two is likely biochemical. A very recent publication supports this notion, as treatments of intact VECs on porcine leaflets with various neurohumoral stimulants (endothelin 1, serotonin, etc.) resulted in contraction or relaxation of the tissue in both the circumferential and radial directions (El-Hamamsy et al., 2009). Previously, multiple biochemicals have been found to alter AV leaflet stiffness via VIC contraction (Kershaw et al., 2004; Merryman et al., 2006); however, this is the first evidence that VECs directly communicate with the VICs to alter leaflet mechanical properties.

Some of the most compelling work in the area of VEC mechanobiology in recent years is by Simmons et al., (2005).