Growth and remodeling of atrioventricular heart valves: A potential target for pharmacological treatment?
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Abstract
Atriocentric heart valves, that is, the mitral valve and the tricuspid valve, play vital roles in our cardiovascular system. Disease of these valves is, therefore, a significant source of morbidity and mortality. Unfortunately, current treatment options are suboptimal with significant rates of failure. It was only recently that we have begun to appreciate that the atriocentric heart valve leaflets are not just passive flaps, but actively (mal)adapting tissues. This discovery sheds new light on disease mechanisms and provides, thus, possible pathways to new treatments. In this current opinion piece, we examine the state of our knowledge about the (mal)adaptive mechanisms (physiological and pathological growth and remodeling) of the atriocentric heart valves. Furthermore, we review the evidence that suggests that valve maladaptation may be a target for pharmacological treatment of diseased valves which, in the future, could transform clinical practice.

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Background
The mitral valve and the tricuspid valve, collectively referred to as the atriocentric valves, separate the left and right atria from their respective ventricles. They function as check valves that ensure unidirectional blood flow through the heart. During diastole, they open to allow for ventricular filling. During systole, they close under the transvalvular pressure gradient to prevent backflow or regurgitation of blood. These vital functions depend on a well-orchestrated interplay between the valves’ components, that is, the valve leaflets, the valve annulus, the chordae tendineae, and the papillary muscles, refer Figure 1a. In this role, their central components, the valve leaflets, are exposed to hemodynamic shear stresses, radial tensile forces at the chordal insertion sites, circumferential tensile forces at their annular insertion, biaxial stretch due to the transvalvular pressure, and compressive forces in the coaptation zone. This complex loading regime is cyclically repeated with every heartbeat for billions of times throughout our lifetime [1,2]. Ostensibly, these loading modes determine the valves’ microstructure and consequently their mechanical properties [3]. As a result, the valve leaflets are complex laminate structures with four distinguishable layers, the atrialis, the spongiosa, the fibrosa, and the ventricularis. Each layer shows a distinct composition and organization of the structural elements elastin, collagen, and glycosaminoglycans. Grossly, elastin is diffusively distributed in the atrialis and ventricularis. On the other hand, collagen is primarily organized circumferentially throughout the entire leaflet structure but is most dense and organized in the fibrosa. However, in the atrialis hemodynamic shear stresses can result in the deposition of more radially oriented collagen. Finally, glycosaminoglycans are most prominently found in the spongiosa [4].

Heart valve leaflets are not passive flaps but active tissues. Valvular interstitial cells (VICs) are the primary cell types that maintain a distinct extracellular matrix organization. Although there is much to be understood about VICs and their role in valve extracellular matrix maintenance, they likely maintain a homeostatic equilibrium through degradation and deposition of structural proteins [5]. It appears that disruption of this mechanobiological equilibrium elicits a phenotypical change in VICs from a quiescent state to a synthetic state (also called fibrotic state in the pathological setting) [6]. Subsequently, increased matrix turnover may result in growth and remodeling [7]. The stimuli interrupting the tissue’s equilibrium may be physiological or pathological, leading to adaptive and maladaptive changes, respectively [8]. Thus, VICs may play a central role in both physiological growth and remodeling (e.g. during pregnancy) and pathological growth and remodeling (e.g. in response to cardiomyopathy) and thus could be viable targets for pharmacological treatment.

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Growth & remodeling in health

During pregnancy, an increased demand in oxygen to support fetal development drives an increase in maternal blood volume by up to 45% [9]. This volume overload results in cardiovascular adaptation, refer Figure 1a. Increases in both tricuspid valve and mitral valve orifice area have been reported in patients [10,11]. For example, between the gestational ages 5 and 38 weeks, mitral valve orifice area in pregnant women increases by approximately 12%. This increase in orifice area correlates with an increase in leaflet size, likely as a compensatory mechanism to maintain proper coaptation and to prevent pregnancy-induced regurgitation. In fact, in cows, mitral valve leaflets have been reported to grow as much as 33% during gestation. Interestingly, this increase in area is accompanied by an increase, or at least maintenance, of thickness. The simultaneous increase in area and maintenance of thickness implies that this change is not (entirely) due to elastic deformation but also due to the addition of mass, that is, growth. This increase in mass is accompanied by an increase in total collagen content. In addition, the microstructure of mitral leaflets remodels during pregnancy. For example, it has been reported that collagen fibers lose organization in the leaflet bellies and increase their fiber crimp length [12]. Not surprisingly, these morphological and structural changes are accompanied by changes in mechanical properties [13]. Specifically, mitral valve leaflet stiffness first decreases in early pregnancy before normalizing in late pregnancy. However, there appears to be a disconnection between the monotonically increasing leaflet size and thickness and the biphasic, nonmonotonic changes in leaflet stiffness. This incongruency may imply that factors other than leaflet thickness, collagen content, and collagen organization determine leaflet stiffness.

Although the teleologic reasons for mitral valve growth and remodeling in pregnancy are clear, the actual stimuli that elicit this response are not. One obvious contender is increased leaflet tension after annular dilation. As the heart is adapting to increased oxygen demands by ventricular hypertrophy, dilation of the periannular tissue increases the valves’ orifice areas. These geometric changes alter the radius of curvature of the leaflets and, through Laplace’s law, their leaflet tension. Presumably, those alterations elicit the phenotypical changes in VICs and promote tissue growth and remodeling. Alternatively, or additionally, systemic changes in hormones during pregnancy such as relaxin [14] may directly or indirectly promote VIC activation and physiological tissue growth and remodeling. As of today, there is little evidence in favor of either hypothesis.

Growth & remodeling in disease

Valve leaflets respond not only to physiological stimuli as in the case of pregnancy but also to pathological stimuli in disease, refer Figure 1a. It was first observed that
patients with heart failure had stiffened leaflets that appeared fibrotic upon histological analyses [15]. Specifically, leaflets from patients with heart failure had remodeled to have more glycosaminoglycans, more collagen, less water content, and were thicker. Those compositional and structural changes also led to less leaflet extensibility [16]. Subsequently, it was shown in a longitudinal study design in sheep models of heart failure and ischemic cardiomyopathy that mitral valve leaflets may lengthen and increase in area within short time periods (order of few weeks) [17,18]. Motivated by these early reports on mitral valve growth and remodeling, Chaput et al [19] demonstrated in patients with functional mitral regurgitation and dilated cardiomyopathy that mitral valve leaflets increase in size in both patient populations. In addition, patients who demonstrated signs of regurgitation had smaller leaflet area to orifice area ratios (i.e. less leaflet to prevent backflow for a given outflow opening) [19,20]. These data suggested that (i) mitral valve leaflets in humans can grow in response to disease, ostensibly, to prevent regurgitation after annular dilation and (ii) regurgitation correlates with insufficient leaflet area increase. Detailed studies in pigs by the same group carefully delineated the potential stimuli for mitral valve growth and remodeling, Chaput et al [21] and Dal-Bianco et al [22,23] were able to isolate the effects of mechanical stretch alone from mechanical stretch plus ischemia and found that mechanical stretch alone (via papillary muscle displacement-induced leaflet tethering), in the absence of regurgitation or ischemia, resulted in leaflet growth and thickening. Moreover, the addition of ischemia to the same mechanical stimulus increased both leaflet growth and thickening. In detailed studies, they demonstrated that leaflet tethering induces transforming growth factor (TGF-β)–mediated endothelial-to-mesenchymal transition, refer Figure 1b. Interestingly, they also found that addition of ischemia not only enhanced TGF-β–mediated endothelial-to-mesenchymal transition and, thus, growth and remodeling but also altered the underlying biological pathways. Specifically, they found that in animals that underwent mechanical stretch (via tethering) plus ischemia leaflets stained additionally for hematopoietic CD45, VCAM-1, MMP-2/9, Ki67 and demonstrated signs of neovascularization [24,25]. The latter changes are all indicative of acute tissue remodeling and proliferation with possible involvement of circulating bone marrow–derived cells. Thus, leaflet growth and remodeling may be enhanced through infarct-mediated inflammatory cytokines. Most recently, it was also demonstrated that alterations in leaflet stress state via device implantation may similarly induce growth and remodeling [26]. Specifically, implantation of annuloplasty devices in pigs with ischemic mitral regurgitation demonstrated elevated levels of collagen expression associated with increased TGF-β. Biological changes in these studies were accompanied by increased leaflet stiffness.

In summary, data from patients with heart failure, with ischemic mitral regurgitation, and dilated cardiomyopathy, as well as several animal models of the same diseases indicate that (i) mitral valve leaflets can actively adapt to changes in their mechanobiological state (owing to ventricular remodeling and annular dilation or device implantation) toward preventing regurgitation, (ii) regurgitation correlates with insufficient adaptation, (iii) leaflets also thicken and stiffen which is counter-productive to proper coaptation mechanics, and (iv) TGF-β appears to be heavily involved in this adaptation response.

**Growth and remodeling as a pharmaceutical target**

Given the important role of atrioventricular heart valves in cardiovascular physiology, their failure is associated with significant morbidity and mortality. The primary failure modes are due to excessive narrowing of the valve’s orifice, that is, valve stenosis, or due to leakage of the valve, that is, valve regurgitation. Although atrioventricular valve stenosis is observed, atrioventricular valve regurgitation is far more common. In fact, mitral regurgitation is the most common valvular disease [27]. In contrast to the aortic valve, where open heart surgery is being slowly but surely replaced with less-invasive, transcatheter techniques [28], atrioventricular valve regurgitation is primarily addressed surgically [29], although transcatheter systems are under development [30]. The most common approach to atrioventricular heart valve repair is valve annuloplasty during which the implantation of a prosthetic ring is meant to reshape the valves’ annulus and to reestablish proper valve coaptation [31]. Although an established technique, mitral and tricuspid valve repair is notoriously suboptimal with up to 30% of certain repairs failing within a few years of surgery [32].

Atrioventricular heart valves can grow and remodel. In health, this ability prevents valve insufficiency in pregnancy [10–12]. In disease, the leaflets’ growth and thickening response is not clearly defined. On the one hand, leaflet area increase is a potentially beneficial response, whereas, on the other hand, fibrotic leaflet thickening and stiffening are detrimental [19,21,24]. Thus, pharmacological regulation of both responses — promotion of the former, suppression of the latter — may open novel pathways for supporting surgical repair.

Likely target systems for pharmacological intervention are the renin–angiotensin system and the TGF-β system and its receptors [33]. Importantly, both systems interact as the main effector of the renin–angiotensin system, and angiotensin II activates TGF-β production, refer Figure 1c. These systems play critical roles in the pathogenesis of other types of cardiovascular diseases, including coronary artery disease, aneurysms,
stroke, and cardiac fibrosis [34]. In those pathologies, inhibition of the renin—angiotensin system (and, indirectly, of the TGF-β system) has been beneficial. Specifically, administration of angiotensin II receptor antagonists (blockers)(ARBs), short ARBs, and angiotensin-converting enzyme inhibitors have been mostly successful. Experience with treatment in those pathologies may inspire pharmacological strategies for treating (mal)adaptation in the atrioventricular heart valves. For example, Wylie-Sears et al [35] have recently explored systemic administration of losartan (an ARB) in an animal model of leaflet tethering plus ischemia. They found that administration of losartan suppressed leaflet thickening significantly, while allowing for leaflet area increase. These changes correlated with downregulation of all previously mentioned markers of tissue fibrosis and reorganization: TGF-β, presence of CD45-positive cells, VCAM-1, K67, and neovascularization. The authors suggested that losartan decreases production of TGF-β, its receptor, and angiotensin II—induced release of latent TGF-β [35–37]. Thus, losartan appears to be modifying the growth and remodeling response to disease in atrioventricular heart valves and may, therefore, be a promising first step toward optimizing atrioventricular heart valve treatment by pharmacological means. Note, because losartan also lowers blood pressure and affects myocardial remodeling after ischemia, the authors modified their experimental approach to correct for those confounding effects.

Future directions

Atrioventricular heart valve growth and remodeling is a young research area with mostly early findings. Thus, there remains much to be understood about growth and remodeling in health and disease. In health, we are lacking a fundamental understanding of the pathways that initiate growth and remodeling. For example, we have a limited understanding of the stimuli that initiate growth and remodeling in pregnancy (i.e. hormonal versus mechanical). Identification of the physiological mechanisms of growth and remodeling may uncover novel targets for pharmacological treatment in disease. In the disease setting, one significant open question is, of course, the translatability of basic scientific findings to the clinical setting and identification of additional targets and pharmacological agents. Specifically, as in most other tissues, the role of the renin—angiotensin system and its interactions with the TGF-β system are only incompletely understood. Future work on characterizing these systems and the downstream effect of their modulation will hopefully suggest additional strategies to control atrioventricular heart valve (mal)adaptation. In conclusion, understanding growth and remodeling of the atrioventricular heart valves is not just of interest to basic science but also to clinical science. Identification of pharmacological targets and agents that may support open heart surgery (or transcatheter approaches in the future) may improve currently poor outcomes for a broad spectrum of patients.

Conflict of interest statement

Nothing declared.

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References

Papers of particular interest, published within the period of review, have been highlighted as such.

- of special interest


This work suggests that (mal-)adaptive changes in the heart valves of patients with heart failure may contribute to disease. Specifically, the authors observed that valves in patients with heart failure were stiffer, which may result in suboptimal valve closure and thus promote valve dysfunction.


This article provides evidence for a (mal-)adaptive mechanism in patients with functional mitral regurgitation. If further suggests that leaflet growth may compensate for increased orifice area in these patients and thus may be beneficial.


This manuscript is the first to suggest that not just disease, but also intervention may elicit a (mal-)adaptive response in aortocinotric heart valves. Thus, it suggests that surgical and interventional approaches need to be evaluated not just for their acute mechanical effects on the host tissue, but also for the long-term effects that changes to the tissue’s mechanics may elicit.

This article proposes and tests Losartan, an angiotensin II receptor antagonist, as a possible pharmacological agent to modulate the (mal-) adaptive response of the atrioventricular heart valves. Thus, it takes a first step toward translating a basic scientific discovery about the (mal-) adaptation of the atrioventricular heart valves into clinical practice.