# Myocardial remodeling with aortic stenosis and after aortic valve replacement: Mechanisms and future prognostic implications

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Aortic valve stenosis is a common cause of left ventricular pressure overload, a pathologic process that elicits myocyte hypertrophy and alterations in extracellular matrix composition, both of which contribute to increases in left ventricular stiffness. However, clinical and animal studies suggest that increased myocardial extracellular matrix fibrillar collagen content occurs later in the time course of left ventricular pressure overload at a time coincident with severe abnormalities in diastolic function followed by the development of symptomatic heart failure. Aortic valve replacement remains the most effective treatment for elimination of chronic pressure overload secondary to aortic stenosis but has traditionally been recommended only after the onset of clinical symptoms. Long-term follow-up of patients with symptomatic aortic stenosis after aortic valve replacement suggests that valve replacement may not result in complete reversal of the maladaptive changes that occur within the myocardial extracellular matrix secondary to the pressure overload state. To the contrary, residual left ventricular extracellular matrix abnormalities such as these are likely responsible for persistent abnormalities in diastolic function and increased morbidity and mortality after aortic valve replacement. Defining the mechanisms and pathways responsible for regulating the myocardial extracellular matrix during the natural history of aortic stenosis may provide a means by which to detect crucial structural milestones and thereby permit more precise identification of the development of maladaptive left ventricular remodeling. (J Thorac Cardiovasc Surg 2012;143:656-64)

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Aortic stenosis (AS) is a common disease in which failure of the aortic valve to completely open imposes an abnormally high-pressure load on the left ventricle (LV). Irrespective of the cause of AS, the ensuing pressure overload results in the manifestation of 2 distinct but overlapping processes.[1-3] The first process is characterized by concentric left ventricular hypertrophy (LVH), and, as demonstrated by the Law of Laplace, the increased wall thickness and mass act to limit the increase in wall stress created by the AS-induced pressure overload state.[2,4] The second process occurs within the myocardial extracellular matrix (ECM) and leads to progressive myocardial fibrosis, reduced ventricular compliance, and impairments in diastolic filling (ie, diastolic dysfunction).[5-10] It is this second phase of progressive LV myocardial fibrosis that contributes to the progression of LV diastolic dysfunction and eventually to the presentation of the signs and symptoms of heart failure.[6,10]

Aortic valve replacement (AVR) remains the single most effective intervention for long-standing elimination of pressure overload in patients with AS. The current guidelines for AVR in patients with AS include those with severe AS and the presence of symptoms such as heart failure.[11] In the absence of precluding factors, the presence of symptoms with AS mandates consideration for AVR to avoid a 25% yearly mortality rate associated with disease of this extent.[12] However, there are several lines of evidence to suggest that this paradigm for timing of AVR could be improved. First, forestalling AVR until heart failure symptoms manifest implies that the development of the decompensated maladaptive phase has already occurred. As a result, significant and deleterious structural LV myocardial remodeling has likely already ensued along with the attendant changes in LV diastolic function.[6] Although imaging and functional studies such as echocardiography can quantify indices of LV diastolic function (eg, filling rates and relaxation times), abnormalities in these indices will only become detectable once the structural changes within the myocardium and in particular the myocardial ECM have already become manifest. Thus, once physiologically and subsequently clinically significant LV diastolic dysfunction has occurred with AS, significant and irreversible changes within the myocardial ECM have been established. Second, significant clinical and experimental evidence exists to suggest that when AVR is performed only after the development of LV diastolic dysfunction and heart failure symptoms, the LV myocardial remodeling process that ensued from long-standing AS may not be readily reversible.[5-7,13] Myocardial fibrosis secondary to long-standing and progressive AS may persist for years after AVR[6] and can contribute to the persistence of postoperative heart failure symptoms.[13,14] Therefore, although the

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**Abbreviations and Acronyms**

ARB = angiotensin receptor blockade
AS = aortic stenosis
AVR = aortic valve replacement
BNP = B-type natriuretic peptide
CT = cardiotrophin
ECM = extracellular matrix
LV = left ventricle, left ventricular
LVH = left ventricular hypertrophy
MMP = matrix metalloproteinase
mRNA = messenger RNA
TGF = transforming growth factor
TIMP = tissue inhibitor of matrix metalloproteinase

use of current guidelines to determine appropriate timing of AVR has yielded reasonable surgical outcomes, this approach may result in the incomplete reversal of the deleterious changes present within the LV myocardial matrix of patients with symptomatic AS.

To improve the timing for AVR, it is essential to identify the mechanistic underpinnings that contribute to the development of maladaptive LV remodeling. Because increased myocardial fibrosis and myocardial stiffness represent hallmarks of maladaptive LV remodeling with AS,[10,15] the determinants of ECM remodeling likely play an instrumental role. Although elucidation of molecular and biochemical pathways that contribute to myocardial ECM remodeling, fibrosis, and LV dysfunction will provide clinically relevant prognostic information, translation of these basic ECM pathways into diagnostic and prognostic applications that can be used to direct appropriate timing for AVR within the context of AS is necessary. Accordingly, the purpose of this review is 2-fold. The first goal is to examine the results obtained from clinical and relevant preclinical studies of AS and AVR with respect to adverse LV ECM remodeling and the attendant effects on LV form and function. Although significant structural and ECM changes occur within the aortic valve itself with AS, the focus of this review is to examine the consequences of the pressure overload with AS, as it applies to the myocardium. The specific focus of this goal will be to examine the temporal and structural LV remodeling that exists in the ECM compartments during the development and progression of AS-induced LVH and heart failure and after relief from this pressure overload state with AVR. We will attempt to coalesce the findings generated in these studies to provide an updated hypothesis of the molecular pathways that regulate myocardial ECM remodeling with AS and after AVR. The second goal of this review is to examine molecular pathways that contribute to myocardial ECM structure and composition and identify those pathways that may yield relevant biomarker signatures with respect to the natural history of AS. This goal will allow development of methods to improve the timing of AVR.

## CLINICAL INVESTIGATIONS OF AORTIC STENOSIS

Although increased myocyte size is one critical feature of pressure overload-induced LV remodeling, the development of abnormalities within the ECM represents a maladaptive structural milestone in the progression of decompensated heart failure.[5-7,16-18] Changes in ECM composition and structure and accumulation of ECM components, such as increased fibrillar collagen content, have been shown to impair LV diastolic filling and decrease LV distensibility in hypertensive heart disease[16,17] and clinical AS.[7,10,13,19,20] These pressure overload-induced changes in ECM structure and composition play a mechanistic role in the progression of heart failure. There are several clinical studies that support this conclusion and clearly relate myocardial ECM content to LV diastolic mechanics during the progression of AS-induced pressure overload and during the regression of AS-induced pressure overload after AVR. These investigations are briefly described next.

A specific set of cellular and extracellular events occur during the development of AS and after AVR. Investigators from the University Hospital, Zurich, Switzerland, provided much of what is known regarding the effects of clinical aortic valve stenosis on myocardial structure and function before and after AVR.[5-8] Patients with AS demonstrated significantly increased LV myocardial interstitial fibrosis compared with control patients.[6-8] Moreover, LV relaxation, filling, and stiffness were abnormal in patients with AS.[6] However, there were no changes in LV systolic performance in patients with AS.[5,6] Thus, these investigations are important in that they linked changes within the LV extracellular compartment with the clinical syndrome of pressure overload-induced diastolic dysfunction and heart failure. These same investigators examined the effects of AVR on components of the myocardial ECM.[6] Specifically, AVR was associated with changes in interstitial fibrosis at both early ($22 \pm 8$ months) and late ($81 \pm 24$ months) time points compared with preoperative values. Interstitial fibrosis remained elevated over control values late after AVR and failed to normalize (Figure 1). Whether the persistent LV structural abnormalities noted by these investigators achieve clinical significance remains a matter of debate; however, it is noteworthy that these colleagues demonstrated that approximately 20% of patients with AS exhibited some degree of exercise intolerance 5 to 10 years after AVR.[14] A more recent clinical investigation conducted by Weidemann and associates[15] lends credence to the assertion made by these initial investigators