REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Left Ventricular Hypertrophy in Valvular Aortic Stenosis: Mechanisms and Clinical Implications

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ABSTRACT

Valvular aortic stenosis is the second most prevalent adult valve disease in the United States and causes progressive pressure overload, invariably leading to life-threatening complications. Surgical aortic valve replacement and, more recently, transcatheter aortic valve replacement effectively relieve the hemodynamic burden and improve the symptoms and survival of affected individuals. However, according to current American College of Cardiology/American Heart Association guidelines on the management of valvular heart disease, the indications for aortic valve replacement, including transcatheter aortic valve replacement, are based primarily on the development of clinical symptoms, because their presence indicates a dismal prognosis. Left ventricular hypertrophy develops in a sizeable proportion of patients before the onset of symptoms, and a growing body of literature demonstrates that regression of left ventricular hypertrophy resulting from aortic stenosis is incomplete after aortic valve replacement and associated with adverse early postoperative outcomes and worse long-term outcomes. Thus, reliance on the development of symptoms alone without consideration of structural abnormalities of the myocardium for optimal timing of aortic valve replacement potentially constitutes a missed opportunity to prevent postoperative morbidity and mortality from severe aortic stenosis, especially in the face of the quickly expanding indications of lower-risk transcatheter aortic valve replacement. The purpose of this review is to discuss the mechanisms and clinical implications of left ventricular hypertrophy in severe valvular aortic stenosis, which may eventually move to center stage as an indication for aortic valve replacement in the asymptomatic patient.
 • *The American Journal of Medicine (2015) 128, 344-352*

KEYWORDS: Aortic stenosis; Aortic valve replacement; Indications; Left ventricular hypertrophy; Mechanisms; Mortality

Valvular aortic stenosis is the second most prevalent adult valve disease in the United States, occurring in 4% of patients aged more than 75 years,[1] and causes progressive pressure overload leading invariably to life-threatening complications. Surgical aortic valve replacement and, more recently, transcatheter aortic valve replacement effectively relieve the hemodynamic burden and improve symptoms and survival of affected individuals.[2-4] Indications for aortic valve replacement are primarily based on the development of clinical symptoms, such as syncope, angina, or dyspnea, because their presence indicates a dismal prognosis.[5] However, patient-reported symptoms may be misleading, because up to two thirds of "asymptomatic" patients with severe aortic stenosis develop symptoms during exercise stress testing and thus are at risk.[6] Furthermore, progressive left ventricular hypertrophy and diastolic dysfunction develop in a sizeable proportion of patients before the onset of symptoms.[7] According to current American College of Cardiology/American Heart Association guidelines on the management of valvular heart disease, a left ventricular ejection fraction less than 50% is a class IIA indication for aortic valve replacement, whereas left ventricular hypertrophy, even if severe, is not an indication for aortic valve replacement.[8] Several studies demonstrate that regression of left ventricular hypertrophy from aortic stenosis is incomplete after aortic valve

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2014.10.054

replacement and associated with adverse early postoperative outcomes and worse long-term outcomes.[7,9-14] As shown in our conceptual **Figure 1**, reliance on the development of symptoms alone without consideration of structural abnormalities of the myocardium for optimal timing of aortic valve replacement potentially constitutes a missed opportunity to prevent postoperative morbidity and mortality from severe aortic stenosis.[9]

In clinical decision-making, the considerable risk of open heart surgery has to be weighed against the usually low risk for sudden cardiac death in the asymptomatic patient with severe aortic stenosis,[15] but also against the risk for progressive left ventricular hypertrophy and irreversible myocardial damage. With the advent of transcatheter aortic valve replacement as a potentially lower-risk treatment option for severe aortic stenosis, the risk–benefit ratio may shift in favor of earlier intervention, and thus it will become essential to recognize adverse prognostic indicators and early signs of left ventricular decompensation before symptom development. In addition, pressure overload–induced hypertrophy in chronic hypertension indicates poor outcomes and therefore is an important treatment target. Likewise, left ventricular hypertrophy from aortic stenosis may be an important treatment target. The purpose of this review is to discuss the mechanisms and clinical implications of left ventricular hypertrophy in severe valvular aortic stenosis, which may eventually move center stage as an indication for aortic valve replacement in the asymptomatic patient.

CLINICAL SIGNIFICANCE

- Left ventricular hypertrophy results from aortic stenosis and is associated with adverse early and long-term postoperative outcomes.
- The risk of open heart surgery has to be weighed against the usually low risk of death in asymptomatic patients but also against the risk for irreversible myocardial damage.
- Transcatheter aortic valve replacement may become a lower-risk treatment option for severe aortic stenosis, shifting the risk–benefit ratio in favor of earlier intervention.

THE NATURAL HISTORY OF AORTIC STENOSIS

Aortic valve calcification is common in patients after the age of 65 years and typically progresses from the base of the leaflets toward the edges, at which point leaflet motion becomes restricted.[16] In a large retrospective study[17] of patients with nonstenotic aortic valve thickening at baseline, aortic stenosis developed in 16%. The mean time interval to moderate aortic stenosis was 6 years and to severe aortic stenosis was 8 years, but it occurred at a more rapid pace, occurring in as little as 2 years in a subset of patients.[17] Once aortic stenosis is in the moderate range, the average rate of progression of mean transvalvular pressure gradient is 7 mm Hg per year, corresponding to an annual increase in aortic valve velocity by 0.3 m/s with an average annual decrease of aortic valve area by 0.1 cm^2.[1,18-20] Although the average time for the progression from moderate to severe aortic stenosis is fairly similar between studies,[1,18-20] it is highly variable among individuals.[21] Therefore, the management of aortic stenosis in the absence of symptoms remains a challenging task for clinicians, who may miss the optimal time for preventing complications from aortic stenosis. When patients are followed closely in specialized valve centers, outcomes in patients with asymptomatic severe aortic stenosis have been reported to be similar as in the age-matched general population. However, these studies have been conducted in tertiary referral centers, and outcomes in less specialized care models and more lenient follow-up may not be comparable. The majority of patients develop symptoms in a relatively short time period (67% in 4 years[22] and 74% within 5 years),[23] underscoring the progressive nature of severe aortic stenosis. The 3 cardinal symptoms are evidence of left ventricular decompensation: (1) syncope from episodic systemic hypotension from reduced cardiac output or arrhythmic or vasodepressor response, (2) dyspnea from increased left ventricular end-diastolic pressure, and (3) angina from microvascular ischemia secondary to elevated left ventricular pressure and relative insufficient vascularization of the hypertrophied left ventricle. Once these symptoms occur, severe aortic stenosis has a dismal prognosis with a 5-year mortality rate of up to 88%[24,25] if left untreated; thus, such symptoms are a clear indication for aortic valve replacement. At the present time, as operative outcomes continue to improve and transcatheter aortic valve replacement is becoming a potential option for even lower-risk patients, reevaluation is warranted on whether the development of symptoms and frank left ventricular dysfunction are sufficiently sensitive indicators to identify appropriate timing of aortic valve replacement and to achieve optimal long-term patient outcomes.

LEFT VENTRICULAR HYPERTROPHY IN AORTIC STENOSIS

From Compensatory Remodeling to Clinical Decompensation

Chronic left ventricular pressure overload from hemodynamically significant aortic stenosis causes both increases in myocardial muscle mass and changes in left ventricular geometry as compensatory mechanisms to reduce wall stress and maintain cardiac output.[26-28] On a cellular level, recruitment of contractile elements occurs in parallel with fibroblast activation and pathologic increases in cardiac extracellular matrix (ie, fibrosis).[29] In addition, the inability