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CONTEMPORARY AORTIC VALVE THERAPY

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Introduction

Aortic valve disease imparts a pressure or volume overload on the left ventricle (LV). If this load is severe and prolonged, it eventually leads to LV damage, congestive heart failure (CHF), and death. These mechanical problems ultimately require mechanical correction in the form of valve replacement or repair, and the timing and types of mechanical therapy will be the main thrusts of this article.

Aortic Stenosis

Therapy to Retard Progression

While in much of the world rheumatic fever is a major cause of aortic stenosis (AS), this etiology is rare in developed countries where calcific disease is the major cause. For much of the 20th century, this process was referred to as calcific degeneration, implying a "wear and tear" phenomenon that lead to injury and calcification of the valve. However, a seminal paper by Otto et al. described the histopathology of early AS in patients who died of causes other than AS.[1] She reported findings similar to those of atherosclerosis (Figure 1). Additional data strengthened the relationship between calcific AS and coronary artery disease.[2-8] These data led to the hypothesis that statins, so effective in treating coronary artery disease, might also be effective in retarding the progression of AS. Although several retrospective or non-randomized studies suggested that statins might indeed be effective,[9-12] the two

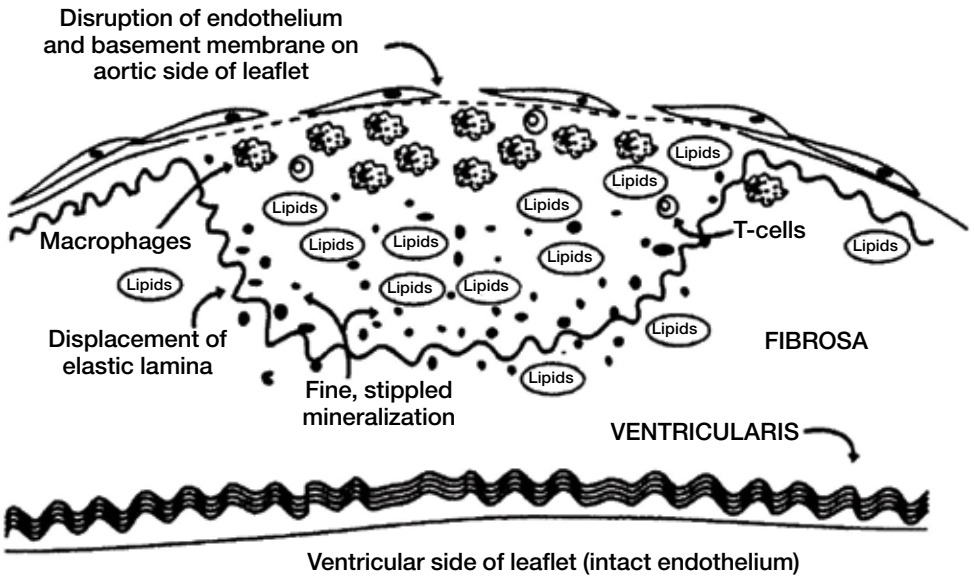

Figure 1. A schematic representation of the early lesion of aortic stenosis emphasizes the presence of macrophages and lipids similar in nature to the plaque of coronary disease. Taken from Otto et al. with permission.[1]

randomized placebo-controlled trials of statins in moderate to severe AS showed no benefit.[13, 14] While the use of these agents might be effective if applied earlier in the course of the disease, it would require a very large and extended trial to prove the concept. In the meantime, much has been learned about the nature of the AS lesion; inflammation is prominent, and there is abnormal signaling in the pathways that control tissue calcium deposition.[15-22] These observations in turn could lead to new targets to prevent disease progression. For now, however, AS remains a surgical disease with medical therapy limited to clinical investigation.

Timing of Surgery

The Symptomatic Patient. One of the most straightforward decisions in cardiology is managing the patient with severe AS (often defined as an aortic valve area of < 1.0 cm^2) who has developed the typical symptoms of angina, syncope, or dyspnea. *Death occurs on average in five years after the onset of angina, three years after the onset of syncope and within two years after the onset of the symptoms of heart failure* with *an overall 75%* mortality rate at three years without aortic valve replacement (AVR) (Figure 2).[23, 24] *Yet the prognosis is* excellent following AVR. Thus, urgent valve replacement is indicated once patients develop symptoms unless severe co-morbidities prevent AVR.

The Asymptomatic Patient. A much greater challenge is the patient with asymptomatic AS. The prognosis is excellent in such patients,[25] although some asymptomatic patients do suffer sudden death; there is the constant fear that a patient may deny or fail to recognize symptoms, causing a missed opportunity for AVR therapy. In view of this concern, some recommend AVR for most patients with severe AS irrespective of symptomatic status. However, these concerns must be weighed against the operative risk of AVR, which is about 3% overall and about 1% for asymptomatic patients without co-morbidities. Several factors may put some asymptomatic patients at higher-than-average risk for sudden death, and in such patients management favors AVR even when symptoms are absent. These factors include abnormal exercise performance on a formal exercise test,[26] very severe AS[27] (aortic valve area < 0.6 cm^2), heavy valve calcification and rapid progression of disease,[28] and a rising brain naturetic hormone (BNP).[29]

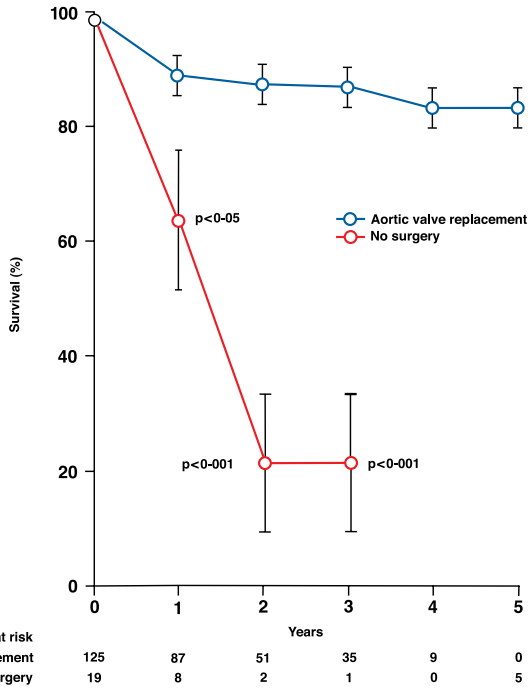

Figure 2. Survival of patients with symptoms of aortic stenosis. Taken from Schwartz et al. with permission.[24]

The Patient with Low Ejection and Low Gradient. The patient with a low ejection fraction (EF) and high transvalvular gradient (mean gradient > 40 mm Hg) poses little problem in management. Such patients have severe afterload mismatch and improve dramatically when the load is reduced by AVR.[30] On the other hand, patients with a low gradient and low EF have reduced LV function not from afterload mismatch but rather from severe myocardial damage and reduced contractility.[30] Such patients have an operative risk of AVR as high as 50%.[31-35] Three negative prognostic benchmarks — ultra-low gradient,[35] lack of inotropic reserve,[33] and BNP > 550 pg/ml[34] — have been noted for this group of patients. Thus, in one study operative risk was 18% for patients with a mean gradient > 20 mm Hg but 35% for patients with a gradient of < 20 mm Hg.[35] For patients whose stroke volume increases by > 20% during dobutamine infusion, operative risk is 10% but jumps to 30% for patients without such inotropic reserve.[33] In another report, perioperative mortality was 50% if BNP exceeded 550 pg/ml.[34]

The Patient with Normal Ejection Fraction and low Gradient. It is generally held that patients with severe aortic stenosis and a normal EF will generate a transaortic gradient > 40 mm Hg.[27] Recently, however, researchers have identified a group of patients who have concentric remodeling without hypertrophy.[36] Such patients have small, thick-walled LVs. Because LV volume is small, an abnormally low stroke volume is generated despite a normal EF; as a consequence, the transvalvular gradient is also low. The low gradient can easily be misinterpreted to indicate that the AS is not severe. However, this group of patients, if symptomatic, has as dire a prognosis as other patients with symptomatic AS, yet they have an excellent outcome with AVR.[37]

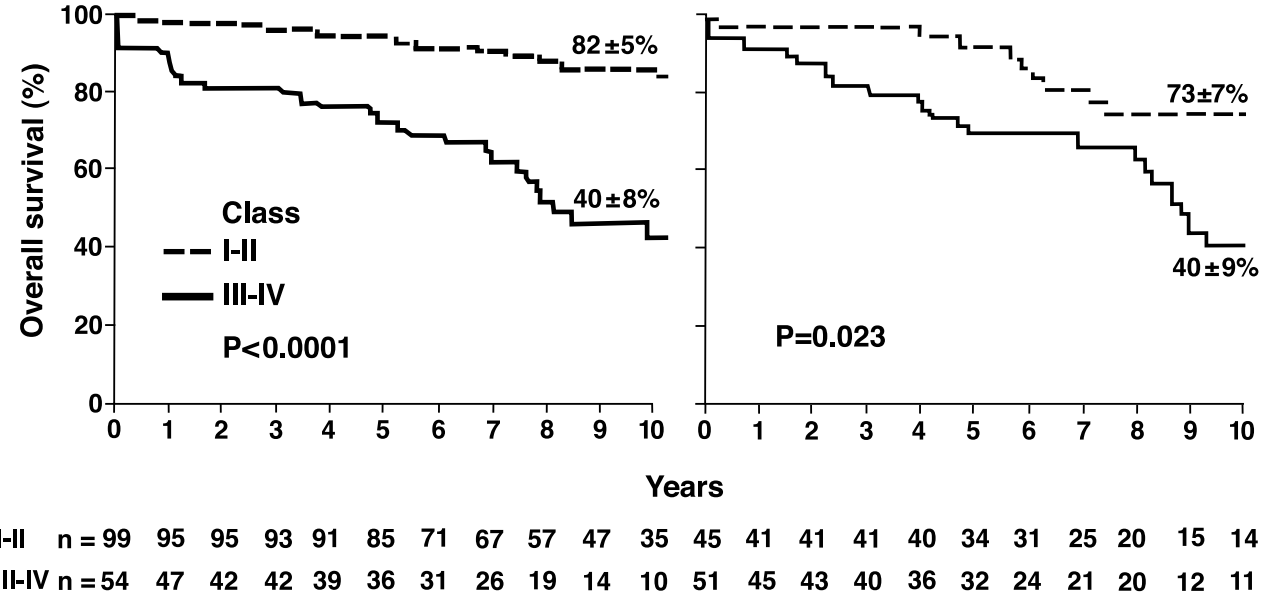

Figure 3. Outcome of patients with AR and reduced ejection fraction (left panel) and normal ejection fraction (right panel) is shown. In either case, advanced symptoms greatly reduced survival following AVR. Taken from Klodas et al. with permission.[45]

Percutaneous Valve Replacement

It has been estimated that only about half the patients with severe AS ever undergo AVR.[38, 39] Aortic stenosis is a disease of aging, and while advanced age is not considered a contraindication for AVR, many older patients have significant co-morbidities that preclude heart surgery or put them at very high risk for AVR. Further, even if the elderly patient survives surgery, older patients may require a prolonged period of rehabilitation in order to return to their preoperative level of functioning. Fortunately, percutaneous AVR (PAVR) is rapidly developing as a potential alternative to standard surgical AVR.[40] *Pioneered by Cribier and Webb,* [41, 42] this technique has received approval for use of two different valves (Edwards SAPIEN and Medtronic Core Valve) in Europe, where it is estimated that more than 10,000 valves have been implanted already. Trials are well underway in the United States, and general availability is probably imminent.

Briefly, in PAVR the native valve is first dilated using a large balloon catheter before valve deployment. The Edwards SAPIEN valve is a bioprosthetic stented valve crimped onto a balloon catheter and advanced to the aortic annulus, where the balloon is inflated and the valve deployed, anchored by the stent. The Core Valve is also a bioprosthesis attached to a self-expanding nitinol cage that is advanced to the annulus, where expansion seats the valve. *These valve can be implanted percutaneously retrograde, percutaneously antegrade using the transseptal approach and transapically.* Technologically, the delivery systems are advancing so rapidly that successful implantation is approaching 100%. Mortality is less than predicted for this very high-risk group of patients. Randomized trials comparing PAVR to surgical implantation in operable patients and to medical therapy in inoperable patients are also underway. If the trials are successful, they will likely pave the way for FDA approval and, in the near future, general availability in the United States.

Chronic Aortic Regurgitation

Severe chronic aortic regurgitation (AR) is a disease of combined LV pressure and volume overload that is remarkably well tolerated for many years.[43, 44] Indications for AVR include the onset of symptoms or the occurrence of LV dysfunction; the combined incidence of either event is about 4% per year, so that even 10 years after the onset of severe AR, most patients have safely avoided AVR.

Medical Therapy

While AR has always been classified as a volume overloading lesion, it is now well recognized that afterload is also increased in this disease, which also creates systolic hypertension. Thus AR really exerts a combined pressure and volume overload on the LV. Afterload is often measured as systolic wall stress, where stress (σ) = pressure (P) x radius (r) / 2 thickness (h). Both pressure and radius increase in AR, and while increased thickness partially offsets the increases in

the numerator terms, stress is usually elevated.[43] It is not surprising that afterload-reducing vasodilators have been investigated as possible therapies for AR. Scognamiglio et al. randomized asymptomatic patients with severe AR and normal LV function to receive either digoxin or nifedipine.[45] In that study, it appeared that administration of nifedipine safely delayed the need for AVR by about two years. However, a second study comparing nifedipine to a true placebo and to enalapril found no benefit to vasodilator therapy, with a trend toward harm in the enalapril group.[46] As a consequence of these conflicting data, no firm recommendation about the use of vasodilators or any other medical therapy for AR can be made. However, if heart failure has intervened and the patient has been deemed inoperable, standard heart failure therapy including ACE inhibitors should be employed.

Timing of surgery

Aortic valve replacement or repair should be performed when severe AR causes even mild symptoms (Figure 3) or when it causes LV dysfunction.[47] Severe AR is defined echocardiographically as a jet width > 65% of the LV outflow tract, a vena contracta > 0.6 cm, a regurgitant volume of 60 cc, a regurgitant fraction > 0.5, or a regurgitant orifice area > 0.3 cm.[2, 27] LV dysfunction is defined as an EF of < 0.5.[27] Other echocardiographic signs of LV dysfunction include an end diastolic dimension of > 70 mm or an end systolic dimension > 50-55 mm.[48]

Aortic valve repair is in its relative infancy compared to mitral valve repair, with about 15% of valves being repaired in the United States. This figure may change as techniques improve, driven by the advantage of sparing patients the risks inherent to prosthetic valves.[49]

Acute AR

Acute severe AR, as might occur with leaflet destruction from infective endocarditis, is a wolf in sheep's clothing.[50] Death may be imminent even though the hyperdynamic signs of chronic AR are absent. In chronic AR, the volume regurgitated into the LV during diastole is compensated by LV dilatation, which allows the LV to generate increased total stroke volume, in turn producing a wide pulse pressure. This increased stroke volume and wide pulse pressure produce the myriad physical findings in chronic AR, for example, Hill's sign, Quincke's pulse, etc. In acute AR, however, there is no time for LV dilatation, thus both the increased stroke volume and the signs it causes are absent. Early closure of the mitral valve caused by high LV filling pressure reduces the intensity of s_1. The precordium is quiet, and the only sign of AR may be a short diastolic murmur. Yet mortality from this disease may be as high as 90% once even mild heart failure is manifest.[51] Blood pressure is usually low, near shock levels, but pressor agents used to increase blood pressure only worsen the amount of AR present. Vasodilators used to reduce the AR worsen hypotension. Fortunately, AVR done even within 48 hours of a positive blood culture is rarely complicated by infection of the prosthesis, particularly when a homograft valve replacement is used.[52, 53] Thus AVR should follow within 24 hours of the onset of even mild symptoms or signs of CHF in the presence of severe acute AR, especially if echocardiographic demonstration of mitral valve pre-closure is present.[54]

Conclusion

Aortic valve disease exerts a pressure and/or volume overload on the left ventricle; if severe and protracted, these loads become lethal. These mechanical problems have only mechanical solutions that should be applied when even mild symptoms occur and at the first hint that LV dysfunction is developing. The advent of a percutaneous approach to valve disease will usher in a new dimension in therapy, offering treatment to patients once denied surgical therapy because of extravalvular medical problems

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