Severe Aortic Stenosis With Low Systolic Gradient
The Good and Bad News

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Severe calcific aortic stenosis (AS) is an important clinical entity because (1) it is the most common valve lesion being considered for valve replacement in the United States,[1] especially in older people. (2) More people are living longer. In 1996, 36 million people in the United States were ≥65 years old, and by 2020, this number is expected to increase by 75%. (3) Aortic valve replacement (AVR) improves the survival of symptomatic patients.[1,2] The relative survival of those ≥65 years old is better than those <65 years old.[1,2] (4) The symptomatic state and abnormal LV function improve or normalize in most patients.[1,2]

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Patients with a mean aortic valve gradient (AVG) ≤30 mm Hg have been of concern. They may have severe AS even if left ventricular (LV) ejection fraction (EF) is normal. The clinical problem is magnified in those in whom LVEF is severely reduced because of uncertainty about the cause of low LVEF and patient outcome after AVR.

In this issue of *Circulation*, Connolly and coworkers[3] from the Mayo Clinic present important data that clarify several issues but also raise other issues that need to be addressed. Of 52 patients 71±11 years old (mean±SD) with aortic valve area (AVA) of 0.7±0.2 cm^2, mean AVG <30 mm Hg, and LVEF <0.35, 86% were in NYHA functional classes III and IV. The *good news* is that after AVR, (1) the 3-year survival was 62%; (2) of the survivors, 47% were asymptomatic and 30% were minimally symptomatic (the improvement in symptomatic state is impressive); and (3) LVEF improved by 0.10±0.14.

Most patients were in clinical heart failure (HF) (LVEF <0.35; 86% were in clinical classes III/IV[3]), and their survival was not significantly different from that of previously described patients living in Olmstead County in HF, without AS, in classes III/IV.[4] The patients had many comorbid conditions[3]: previous MI in 33%, coronary artery disease (CAD) in 69%, other systemic arterial disease in 44%, systemic hypertension in 54%, diabetes mellitus in 29%, chronic obstructive pulmonary disease in 14%, and liver disease in 8%. Of 41 patients who survived AVR, 10 (24%) died over the next 4 years; details of medical therapy were not provided. The 4-year mortality of 24% is similar to that of patients without AS in chronic HF in functional classes II to IV. For example, in the MERIT-HF[5] and CIBIS II[6] trials, the annual mortality in the treated groups was 7.2% and 8.8%, respectively. Furthermore, the 3-year survival of 62% is better than the 1- to 2-year survival of ≤10% of patients with severe AS in HF treated medically.[7,8] These data are compatible with the hypothesis that AVR eliminated the mortality related to severe AS, which resulted in an overall improvement in survival.

Therefore, it is important to examine in detail the causes of death. By multivariate analysis, the only predictor of the 21% operative mortality was a small prosthesis size[3] (47% mortality for valve prosthesis size ≤21 mm versus 15% for prosthesis sizes ≥23 mm). This emphasizes the importance of the problem of valve prosthesis–patient mismatch[9] and raises the issue of whether patients who need valve sizes ≤21 mm[10] should receive a stentless valve, which would leave the patient with a larger valve orifice. Homografts are an alternative choice, but the documented valve deterioration rate at ≥10 to 12 years is of concern.[11] Age and functional class were not statistically significant predictors of operative mortality.[3] However, operative mortality was 9%, 17%, and 30% in those <65, 65 to 74, and ≥75 years old, respectively, and was 15% and 24% in those in classes III and IV, respectively. Possible reasons for statistical nonsignificance were the relatively small number of patients in each subgroup and the fact that almost all patients were in classes III/IV and thus cannot be compared adequately to the few in classes I/II. In the 1990s and with early AVR, the operative mortality is likely to be lower.

The causes of late death were less easy to fathom by statistical analyses[3]; mean AVG, AVA, age, and preoperative LVEF were not predictors of mortality at 3 years; only an improvement in functional class was a predictor. The survival in the present group of patients was statistically significantly worse than in others the Mayo group have previously reported who had severe AS and LVEF <0.35 but had a mean AVG >30 mm Hg (Figure 1b of the article by Connolly et al).[3] However, review of this Figure[3] shows that (1) at 3 years, the difference between the 2 groups is small; and (2) at 5 years, the difference is larger, but there are only 3 patients at risk in the group with an AVG <30 mm Hg (Figure 1a), and most of the difference can be accounted for by the difference in operative mortality.

It seems to me that the important cause of mortality was most likely associated comorbid conditions, in particular, irreversible myocardial damage. To be noted: (1) LVEF

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improved modestly, from 0.24±0.07 to 0.32±0.14.[3] However, in 9 of 10 patients who died late, postoperative LVEF had been obtained, and in all but 1 patient, LVEF was still ≤0.30. In 3 of 9 patients, LVEF fell; in 1, it did not change; and in 1, it increased from 0.25 to only 0.27, suggesting that in these patients, the LV dysfunction was irreversible or only partly reversible. (2) The 3- and 5-year survivals of those without CAD were 71% and 71% and in those with CAD, 58% and 28% (P=NS because of small sample size).[3] (3) As emphasized above, the long-term mortality was not different from that of patients without severe AS in HF who were in classes II to IV.

The mortality is the *bad news*. What are the problems and what should be done?

1. Severe AS is being diagnosed late because 86% of patients were already in classes III/IV when first seen at this referral center.[3] In a study from another center, severe AS was misdiagnosed in 34% of the patients, most of whom were also in classes III/IV.[12] The likely reasons for failing to diagnose early, severe AS in older patients include the following. (a) Patients may present in HF, they may have associated hypertension and other comorbid conditions, carotids are frequently not parvus, the ejection murmur is soft and may be heard only at the apex (Gallavardin's phenomenon), and the murmur is different but classic for this age group (described as "cooing," "musical," or "seagull sound").[1] Thus, the patients may be diagnosed as having HF with mitral regurgitation. (b) Even if the patients are not in HF and this classic murmur is heard at the sternal border or even at the apex, the patient may be diagnosed as having an innocent murmur or aortic sclerosis or mitral regurgitation. Thus, it is important to recognize the differences in the clinical picture of the older patients and to obtain an echocardiographic/Doppler study in all such patients and emergently in those in HF.

2. Even if the echocardiographic/Doppler study is obtained, there is an inappropriate *fixation* on gradient(s). None of the echocardiographic techniques measure intravascular pressures directly; several assumptions are made, and there are problems with such measurements that were recently reviewed.[13] Furthermore, (a) peak gradients measured by Doppler occur in early systole and are a problem in normals and in those with AS[13]; (b) no matter how a gradient is measured, it is dependent on stroke volume (not cardiac output directly, because the gradient is a per-beat function) and on systolic ejection time, both of which are dependent on LV preload, afterload, and myocardial contractility, and is also influenced by aortic pressure and thus may change rapidly[1,13]; and (c) a mean AVG <50 mm Hg may be associated with severe, moderate, or even mild AS.[13–15] Thus, it is important and prudent to determine the AVA; severe AS is AVA ≤1.0 cm^2 (≤0.60 cm^2/m^2).[15,16] In the Mayo study, the AVA was 0.7±0.2 cm^2.[3]

3. If there is reasonable concern that AS may not be severe in the patient who has a low gradient but has severe AS on the basis of calculated AVA, it is appropriate to perform a stress test; intravenous dobutamine is the frequently used stress. During intravenous dobutamine, it is important to (a) determine heart rate, stroke volume, systolic ejection time, and mean AVG and (b) calculate the AVA. This will help to ensure that the dose of dobutamine used had the desired hemodynamic change and will allow a proper evaluation of severity of AS. Reliance on gradients alone may be misleading, because they may and do increase not only in severe AS but also in mild/moderate AS. Right and left heart catheterization with simultaneous LV and ascending aortic pressures (after pressure recovery, 2 to 3 cm above the valve) and cardiac output measurements afford more complete information. In patients with severe AS, AVA may increase a little, by up to 10% to 20%, but usually not to the moderate range of AS.

4. Comorbid conditions pose a serious risk to the patient early and late and should be treated and controlled. Consideration should be given to early AVR for severe AS in the presence of serious comorbid conditions, even if the patient is asymptomatic from the severe AS and the LVEF is normal.

5. In an earlier study of severe AS and HF, LVEF had increased from 0.34±0.03 to 0.63±0.05.[17] In the study by Connolly et al, LVEF did not improve at all or not to a marked degree, indicating that LV dysfunction was more irreversibly damaged. There are at least 3 reasons why LV dysfunction may be irreversibly damaged. (a) Associated CAD may cause myocardial injury, which is particularly deleterious in the hypertrophied heart with severe outflow obstruction.[1] (b) In AS, the LV systolic dysfunction initially is most likely a result of afterload mismatch,[18] which can be reversed in the early stage[1] if AS is relieved. In aortic regurgitation, the duration of afterload mismatch is ≤12 months[19]; in AS, this duration is unknown and may be ≤3 to 6 months and perhaps even shorter in the presence of associated, significantly obstructive CAD. (c) A combination of these 2 reasons. In the study by Connolly et al, 33% had a previous MI and 69% had CAD; the duration of LV dysfunction and of symptoms is not described. Thus, to appropriately manage the patient with severe AS, (a) one should know the extent and severity of associated CAD, especially in those ≥35 years old and/or in the presence of symptoms; (b) patients with severe AS and associated CAD should have early (as soon as possible)[1,2] AVR and myocardial revascularization even if they are asymptomatic; and (c) patients with severe AS and LV dysfunction should have coronary angiography and early (immediate)[1,2] AVR in the earliest phase of LV dysfunction even if they are asymptomatic; if they also have associated CAD, AVR plus myocardial revascularization is emergent.[1,2]

In conclusion, the study by Connolly et al shows that the *good news* about severe AS with AVG ≤30 mm Hg and LVEF <0.35 is that AVR (plus myocardial revascularization, if needed) results in (1) most likely, an improved survival because of elimination of mortality of severe AS; (2) some improvement of LVEF in many patients; and (3) marked improvement of symptomatic status.

The *bad news* is that the results are not as good as one would like. In addition to treatment of comorbid conditions and of HF, the improvements will come from (1) early clinical diagnosis; (2) avoidance of a fixation on gradients and greater concentration on AVA; (3) proper use of an appropriate dobutamine stress test; (4) early AVR (plus myocardial revascularization if needed) in selected subgroups of patients with severe AS, even if they are asymptomatic;

and (5) after AVR, aggressive treatment of comorbid conditions and HF by 1999 standards.

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