Impact of Preoperative Symptoms on Postoperative Survival in Severe Aortic Stenosis: Implications for the Timing of Surgery

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Background. **The impact of symptoms on the natural history of patients with severe aortic stenosis (SAS) has been well documented. By contrast, the implications of preoperative symptoms on postoperative outcomes remain poorly defined.**

Methods. **The long-term survival of 812 patients greater than 65 years old with SAS undergoing bioprosthetic aortic valve replacement (AVR) was analyzed according to their preoperative symptoms.**

Results. **Operative mortality was larger in New York Heart Association (NYHA) III-IV than in NYHA I-II patients (10% vs 6%, $p = 0.036$). Abrupt symptomatic deterioration from NYHA I to NYHA III-IV within the month preceding surgery was observed in 18% of NYHA III-IV patients and resulted in an increased operative mortality (17% vs 5% in NYHA I, $p = 0.035$). Long-term survival was also significantly worse in NYHA III-IV than in NYHA I-II patients (56% vs 72%, $p = 0.002$). Reduced long-term survival of NYHA III/IV patients was observed in subgroups with a left ventricular ejection fraction (LVEF) 0.50 or greater (58 vs. 74%, $p = 0.008$) and in those with a systolic pulmonary artery pressure (SPAP) less than 40 mm Hg (60% vs 74%, $p = 0.014$). By contrast, the presence of class III-IV symptoms did not influence outcome in patients with a LVEF less than 0.50 (51 vs. 55%, $p = 0.34$) or with a SPAP 40 mm Hg or greater (43% vs 48%, $p = 0.78$).**

Conclusions. **In patients with SAS, preoperative NYHA III-IV symptoms, particularly of recent onset, are independently associated with excess short- and long-term postoperative mortality. This was particularly evident in patients with normal LV function or pulmonary artery pressures. These findings plead in favor of an earlier surgical correction of SAS, before the onset of severe symptoms, especially in low-risk patients.**

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The poor outcome of patients with symptomatic severe aortic stenosis (SAS) has been well documented. Averaged survival after the onset of symptoms of congestive heart failure, angina, or exertion syncope has been reported to be less than 2 to 3 years [1–4]. Because the appearance of symptoms identifies a critical point in the natural history of SAS and because aortic valve replacement (AVR) not only results in symptomatic relief but also improves left ventricular (LV) function and survival [5–7], the most recent European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines consider symptomatic SAS as a class I indication for surgery [8, 9].

The optimal timing of surgery in asymptomatic SAS is more controversial. Although earlier studies have shown that the prognosis of patients with no or minimal symptoms was relatively benign and that surgery could be safely delayed until symptoms develop [1], recent evidence has accumulated that suggests the opposite. First, large natural history studies have recently shown that asymptomatic patients with SAS incur a 6% to 15% yearly mortality rate, most of the fatalities being attributable to congestive heart failure and to a lesser extent to sudden cardiac death [10–12]. Second, with increasing severity of SAS, LV dysfunction can eventually develop, which in turn greatly increases operative risks [13–15]. Third, the development of irreversible myocardial fibrosis in pressure-overloaded LVs is a frequent cause of postoperative diastolic LV dysfunction and persistent heart failure symptoms, even after successful AVR [16, 17].

In spite of these arguments, the 2008 ACC/AHA guidelines have remained reluctant to propose surgery to patients with no or minimal symptoms, arguing that the risk of AVR exceeds any potential benefit in these patients [18]. Although the recent 2012 ESC guidelines have been somewhat less restrictive [19], the overall consensus

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remains that most patients with asymptomatic SAS should be managed conservatively and referred to surgery only once symptoms, LV dysfunction, or both have developed.

Because current guidelines have only concentrated on the relationship between natural history data and symptoms but have failed to consider their potential impact on postoperative mortality, we examined the outcome of elderly patients with calcified SAS who underwent bioprosthetic AVR at our institution between 2000 and 2010 and explored the potential impact of preoperative symptoms and their mode of onset on immediate and long-term postoperative survival.

Material and Methods

Study Population

Since the year 2000, all patients with valvular heart disease seen at the Cliniques Universitaires St-Luc are enrolled into a prospective registry where baseline and follow-up demographics, and clinical and echocardiographic data are collected and stored. Informed consent is obtained from each patient, and the study protocol was approved by the Internal Review Board of our institution.

Between January 1, 2000 and August 31, 2010, 1,249 patients who presented with SAS, defined as an aortic valve area less than 1 cm^2, and who subsequently underwent bioprosthetic AVR, were enrolled into this registry. From this initial cohort, 812 patients older than 65 years were selected to be included into the present study. Exclusion criteria were concomitant severe aortic or mitral regurgitation (n = 23), prior valvular surgery (n = 30), missing or poor quality preoperative echocardiographic images (n = 284), and no or mild aortic valve calcifications (n = 2) [19].

Patients with concomitant coronary disease were not excluded. The most recent information on postoperative events was obtained between September and November 2010. Cardiac events and causes of death were ascertained by contacting the patients' physicians, the patients themselves or their family, or by reviewing death certificates. Follow-up times were measured from the time of surgery. Follow-up was 99% complete. The 9 patients who were lost for follow-up were censored at the time of last medical contact.

Echocardiography

All patients underwent a comprehensive examination, including M-mode and two-dimensional echocardiography, as well as Doppler examinations. All tests were conducted by experienced sonographers. Transvalvular gradients, aortic valve area, LV diameters, and ejection fraction were calculated as recommended [20]. Systolic pulmonary artery pressure was considered to be equal to the systolic transtricuspid pressure gradient as calculated by the modified Bernoulli equation and could be measured in 61% of the patients.

Symptomatic Status

Preoperative functional status was graded according to the New York Heart Association (NYHA) classification during the month preceding surgery. Patients were considered to be in NYHA I if they were free of any symptoms. Patients were considered to be in NYHA II if they complained of mild symptoms (ie, dyspnea or angina) during ordinary activity. Patients were considered to be in NYHA III if they had experienced heart failure or angina during less-than-ordinary activity. Finally, patients were considered to be in NYHA IV if they had experienced heart failure or angina while at rest. Patients with exercise-induced syncope were considered to be in NYHA III. Patients who experienced transient NYHA III or IV symptoms and did return in lower NYHA classes due to medical treatment were considered to be in either NYHA III or IV.

Statistical Analysis

All analyses were performed using the SPSS 15.0 software (SPSS, Inc, Chicago, IL). Continuous variables were expressed as mean ± 1 SD, categoric variables as counts and percentages, and follow-up times as mean and range. Comparison of groups used standard t test, χ^2 test, or a Fisher exact test when appropriated.

The impact of symptoms on operative mortality was analyzed by use of a χ^2 test or a Fisher exact test. The impact of symptoms on long-term survival after AVR was analyzed using the Kaplan-Meier method. For each patient included in the study, the corresponding average age-specific annual mortality rates of the Belgian general population were obtained. Multivariate logistic regression analysis was used to adjust for the effects of baseline patients characteristics on operative mortality. Finally, a Cox model was used to adjust for the effects of baseline patients characteristics on overall survival. Relative hazards ratio for each specific covariate of the final models was computed as the exponential of the regression coefficient [21]. A p value less than 0.05 was considered indicative of a statistically significant difference.

Results

Symptomatic Status

Before surgery, 62 patients were in NYHA I, 298 in NYHA II, 359 in NYHA III, and 93 in class IV. Among the 452 patients who were operated on for NYHA III-IV symptoms, 81 (18%) were in NYHA I one month before AVR and became abruptly symptomatic during the month preceding surgery. No differences were found between NYHA I and NYHA II patients. At baseline, Society of Thoracic Surgeons (STS) score was larger in NYHA IV patients compared with NYHA III patients ($p < 0.001$).

Operative Mortality

Sixty-three patients (8%) died within 1 month of AVR or during the same hospitalization. The cause of death was