

Balloon Aortic Valvuloplasty in Adults: Failure of Procedure to Improve Long-Term Survival

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Objectives. This study sought to determine the long-term outcome of adult patients undergoing percutaneous balloon aortic valvuloplasty.

Background. Percutaneous balloon aortic valvuloplasty has been offered as an alternative to aortic valve replacement for selected patients with valvular aortic stenosis. Although balloon aortic valvuloplasty produces an immediate reduction in the transvalvular aortic gradient, a high incidence of restenosis frequently leads to recurrent symptoms. Therefore, it is unclear whether balloon aortic valvuloplasty impacts on the long-term outcome of these patients.

Methods. Clinical, hemodynamic and echocardiographic data were collected at baseline in 165 patients undergoing balloon aortic valvuloplasty and examined for their ability to predict long-term outcome.

Results. The median duration of follow-up was 3.9 years (range 1 to 6). Ninety-nine percent follow-up was achieved. During this 6-year period, 152 patients (93%) died or underwent aortic valve replacement, and 99 (60%) died of cardiac-related causes. The probability of event-free survival (freedom from death, aortic valve replacement or repeat balloon aortic valvuloplasty) 1, 2 and 3 years after valvuloplasty was 40%, 19% and 6%, respectively. In

contrast, the probability of survival 3 years after balloon aortic valvuloplasty in a subset of 42 patients who underwent subsequent aortic valve replacement was 84%. Survival after aortic valvuloplasty was poor regardless of the presenting symptom, but patients with New York Heart Association functional class IV congestive heart failure had events earliest. Univariable predictors of decreased event-free survival were younger age, advanced congestive heart failure symptoms, lower ejection fraction, elevated left ventricular end-diastolic pressure, presence of coronary artery disease and increased left ventricular internal diastolic diameter. Stepwise multivariable logistic regression analysis found that only younger age and a lower left ventricular ejection fraction contributed independent adverse prognostic information (chi-square 14.89, $p = 0.0006$).

Conclusions. Long-term event-free and actuarial survival after balloon aortic valvuloplasty is dismal and resembles the natural history of untreated aortic stenosis. Aortic valve replacement may be performed in selected subjects with good results. However, the prognosis for the remainder of patients who are not candidates for aortic valve replacement is particularly poor.

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Percutaneous balloon aortic valvuloplasty has been used as an alternative to surgical valve replacement for patients with calcific aortic stenosis since 1986 (1). Acutely, balloon aortic valvuloplasty usually reduces the aortic valvular gradient, increases the calculated aortic valve area and improves left ventricular ejection fraction (2-4); yet, short- and intermediate-term follow-up data indicate that cardiac hemodynamic variables may revert to their pre-valvuloplasty baseline as early as 2 h after the procedure (5). Within 6 months, 75% of patients

who have undergone an aortic valvuloplasty exhibit hemodynamic evidence of restenosis (6-8). Therefore, it is unclear whether balloon aortic valvuloplasty favorably alters the long-term outcome of patients with symptomatic aortic stenosis.

The present study describes the long-term outcome (median follow-up 3.9 years, range 1 to 6) of 165 patients undergoing balloon aortic valvuloplasty for severe aortic stenosis. It also defines the clinical, invasive and echocardiographic variables related to long-term outcome after this procedure.

Methods

Patients. Between November 11, 1986 and April 30, 1991, 165 patients with symptomatic valvular aortic stenosis underwent balloon aortic valvuloplasty at Duke University Medical Center. All patients had been previously evaluated by both a cardiologist and a cardiothoracic surgeon. Balloon aortic val-

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valvuloplasty was most often performed because the operative mortality rate associated with valve replacement was estimated to exceed 15%. Exceptions include 17 operative candidates who requested balloon valvuloplasty as an alternative to surgical valve replacement and 4 who underwent palliative balloon aortic valvuloplasty during severe noncardiac illnesses.

Forty-two of the original 165 study patients underwent aortic valve replacement after undergoing balloon aortic valvuloplasty. The entire study cohort was analyzed according to whether the patient had balloon aortic valvuloplasty alone or subsequently progressed to surgical valve replacement.

Valvuloplasty procedure. Balloon aortic valvuloplasty was performed after informed consent had been obtained in accordance with a protocol approved by the Duke University Medical Center Institutional Review Board. The retrograde technique was used in 164 patients. The anterograde technique was used in one patient. Balloon dilation was sequentially performed with single or double balloons of progressively larger effective diameters. Left ventricular and aortic pressures were simultaneously measured immediately before and after balloon aortic valvuloplasty with dual-sensor, high fidelity micromanometer catheters (Millar Inc.). R wave gated masked-mode digital subtraction left ventriculography and supravalvular aortography were obtained before and after valvuloplasty in 150 patients. Oxygen consumption was measured with a metabolic cart, and Fick cardiac output was obtained. The effective aortic valve area was calculated using the Gorlin formula (9). Coronary artery disease was defined as >50% lumen narrowing of a major epicardial coronary.

Echocardiography. Transthoracic echocardiographic data were obtained with a Hewlett-Packard 77020A phased-array sector scanner immediately before valvuloplasty. Left ventricular end-diastolic dimension was measured from the parasternal view using M-mode or two-dimensional imaging. Mitral regurgitation was evaluated by color flow Doppler technique and graded in a semiquantitative fashion from 0 (absent) to 4+ (severe).

Clinical follow-up. Patient status was evaluated by physician interview and examination before balloon aortic valvuloplasty and 3, 6 and 12 months afterward. The status of patients surviving >1 year after valvuloplasty was assessed thereafter by annual telephone interviews. Final telephone follow-up was performed in May 1992. When patients developed symptoms of aortic valve restenosis, they were treated with either continued medical therapy, a second balloon aortic valvuloplasty or aortic valve replacement. End points were achieved when the patient died, underwent aortic valve replacement, underwent repeat balloon aortic valvuloplasty or survived to the last day of possible contact (May 20, 1992). If death occurred, telephone interviews with both the primary care physician and family were obtained to classify the cause of death as either cardiac or noncardiac. Duration of follow-up was defined as the time from the date of balloon aortic valvuloplasty to the last day of contact.

Statistics. Continuous variables are expressed as the median and 25th and 75th percentiles. Categorical variables are expressed as percentages.

The Kaplan-Meier method (10) was used to characterize post-aortic valvuloplasty actuarial and event-free survival. The actuarial survival rate was calculated from the time of the initial balloon aortic valvuloplasty until death. The event-free survival was calculated from the time of initial aortic valvuloplasty until death, repeat balloon aortic valvuloplasty or aortic valve replacement. Survival for all patients was censored at the time of last contact.

The Cox proportional hazards regression method (11) was used to examine the univariable association of clinical, catheterization and echocardiographic variables with event-free survival. Multivariable associations within these same groups (clinical, catheterization and echocardiography) were also evaluated. Those variables found significant within each of these three groups were combined, and, with stepwise regression techniques, a model of the multivariable association of all potential variables was derived. A subgroup analysis comparing the actuarial survival of patients treated with balloon aortic valvuloplasty alone or subsequent aortic valve replacement was performed. The actuarial survival of these subgroups was corrected for differences in their baseline characteristics. Comparison of baseline subgroup characteristics was made using the Wilcoxon two-sample test for the continuous variables and the chi-square test with two degrees of freedom for the dichotomous variables. A Cox proportional hazards model (11) was then developed that included the important baseline characteristics of age, ejection fraction, gender, angina, congestive heart failure, syncope and mitral regurgitation.

Results

Baseline characteristics. Balloon aortic valvuloplasty was performed in 165 patients. Eighty-two percent of the procedures were performed in the years 1987 to 1989 (Fig. 1), and all patients were eligible for at least 1 year of clinical follow-up. This cohort was elderly and highly symptomatic; 39% had angina, 79% had congestive heart failure and 33% had had syncope (Table 1). Fifty-two percent of patients had significant coronary artery disease in at least one vessel.

Hemodynamic results. Balloon aortic valvuloplasty immediately reduced the peak-to-peak transvalvular pressure gradient from 68 (50, 88) to 38 (28, 50) mm Hg. Median aortic valve area increased from 0.5 (0.4, 0.6) to 0.7 (0.6, 0.9) cm². Left ventricular systolic pressure decreased from 205 (180, 233) to 178 (155, 200) mm Hg and left ventricular end-diastolic pressure from 20 (15, 28) to 15 (10, 23) mm Hg. Left ventricular ejection fraction increased a median of 3% (0%, 6%) from a prevalvuloplasty median of 53% (32%, 61%).

Long-term outcome. Follow-up data were available for 164 patients (99%). During the period of follow-up, 152 (93%) patients died or underwent aortic valve replacement, and 99 patients (60%) died of cardiac-related causes. The patient with the longest event-free survival died of cardiac

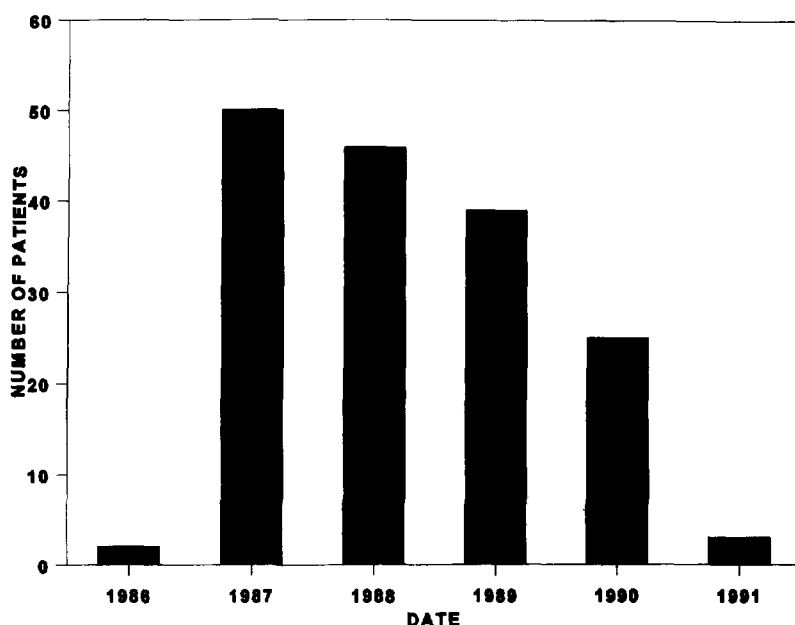


Figure 1. Number of balloon aortic valvuloplasty procedures by year.

causes 4.3 years after undergoing a balloon aortic valvuloplasty. Surgical aortic valve replacement was performed during the postvalvuloplasty period in 42 patients (25%), and 31 patients (19%) underwent a second balloon aortic valvuloplasty.

The probability of event-free survival 1, 2 and 3 years after balloon aortic valvuloplasty was 40%, 19% and 6%, respectively (Fig. 2). Event-free outcome 1 year after balloon aortic valvuloplasty was similar for patients with angina, syncope and New York Heart Association congestive heart failure classes I to III. However, comparison of the event-free survival curves

in Figure 3 suggests that patients with class IV congestive heart failure had major events earliest. The median time from balloon valvuloplasty to death or aortic valve replacement was 10.5 (3.7, 21.3) months.

If actuarial survival is defined as existence free of death, then the median actuarial survival after balloon aortic valvuloplasty was 1.8 (0.7, 4.5) years; survival 1, 2 and 3 years after the procedure was 64%, 48% and 37%, respectively (Fig. 2). Examining actuarial survival by postvalvuloplasty treatment reveals a great disparity in survival patterns. Survival 1 year after balloon aortic valvuloplasty was 52% in patients treated

Table 1. Baseline Characteristics

Characteristic	All Patients	BAV Only	BAV + AVR	p Value*
Age (yr)	78 (72, 83)	80 (74, 83)	73 (68, 75)	0.001
Men/women	71/94	49/74	22/20	NS
Symptom				
Angina (NYHA class III or IV)	64 (39%)	43 (35%)	21 (50%)	NS
CHF (NYHA class III or IV)	131 (79%)	101 (82%)	30 (72%)	NS
Syncope	54 (33%)	39 (32%)	15 (36%)	NS
No. of coronary arteries narrowed >50%				
				0.005†
0	80 (48%)	50 (42%)	30 (71%)	
1	39 (24%)	32 (26%)	7 (17%)	
2	22 (13%)	20 (16%)	2 (5%)	
3	23 (14%)	20 (16%)	3 (7%)	
Ejection fraction (%)	53 (32, 61)	52 (31, 61)	56 (37, 61)	NS
Echocardiography				
LVIDD (cm)	4.7 (4.1, 5.4)	4.6 (4.0, 5.6)	4.7 (4.3, 5.5)	NS
MR ≥2+	47 (28%)	41 (34%)	6 (14%)	0.02

*Balloon aortic valvuloplasty (BAV) only versus patients who subsequently underwent aortic valve replacement (BAV + AVR). †Zero- versus one-vessel coronary disease. Data presented are median (25th, 75th percentile), number of patients or number (%) of patients. CHF = congestive heart failure; LVIDD = left ventricular diastolic internal diameter; MR = mitral regurgitation; NYHA = New York Heart Association functional class.

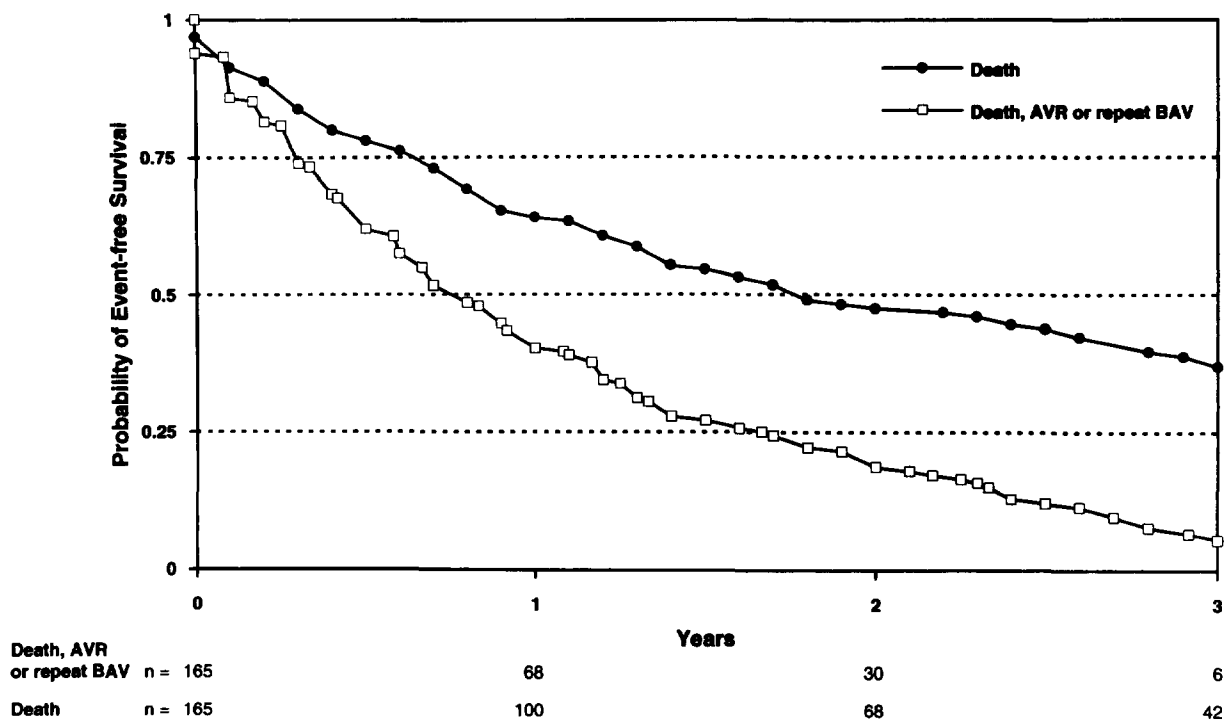


Figure 2. Actuarial and event-free survival after balloon aortic valvuloplasty illustrating the probability of actuarial and event-free survival from the date of initial balloon aortic valvuloplasty. Events are defined as death, aortic valve replacement (AVR) or a second balloon aortic valvuloplasty (repeat BAV).

with balloon valvuloplasty alone versus 95% in patients treated by balloon valvuloplasty and subsequent aortic valve replacement (Fig. 4). Even after correcting for important differences in the baseline characteristics of age, ejection fraction, gender, angina, congestive heart failure, syncope and mitral regurgitation, the difference in actuarial survival between the balloon valvuloplasty only and balloon valvuloplasty plus aortic valve replacement groups remained highly significant (chi-square 36.4, $p < 0.00001$).

The forty-two patients who underwent elective aortic valve replacement did so 0.6 (0.2, 1.3) years after undergoing balloon aortic valvuloplasty. The duration of postoperative follow-up in this group, defined as the time elapsed from the date of aortic valve replacement to May 20, 1992 was 3.3 years. One hundred percent follow-up of this subgroup was achieved, and the probability of survival 1 year after aortic valve replacement was 88%. At the time of last contact, there were 17 deaths in this subgroup (40%), including 1 operative death, 5 nonoperative noncardiac deaths and 11 nonoperative cardiac deaths. Of the remaining 25 survivors, only 2 (8%) had New York Heart Association class III or IV heart failure, and 1 (4%) had class III or IV angina.

Predictors of patient outcome. The baseline clinical, hemodynamic and echocardiographic variables and their univariable association with any major cardiac event (death, repeat balloon aortic valvuloplasty or aortic valve replacement) are shown in Table 2. Younger age and functional class IV congestive heart failure were the only clinical variables associated with a major cardiac event. Other predictors of major adverse events were the presence of coronary artery disease, low ejection fraction,

high left ventricular end-diastolic pressure and increased left ventricular internal diastolic diameter. No procedural variables predicted event-free survival, including the reduction in aortic valvular gradient or the increase in aortic valve area. In multivariable analysis, only younger age and a lower left ventricular ejection fraction contributed independent adverse prognostic information. Jointly, they had a chi-square of 14.89 ($p = 0.0006$).

Discussion

Patient outcome. The long-term outcome of adults undergoing balloon aortic valvuloplasty has been incompletely described. Previous studies (1-4,6-8,12-15) evaluating the outcome after balloon aortic valvuloplasty have been limited by reporting only short- and midterm outcome and have not examined clinical, hemodynamic and echocardiographic data in the same cohort of patients (15). Therefore, prognostic information available from a complete patient evaluation has not previously been available. The present study describes the outcome (up to 6 years) of 165 consecutive patients undergoing balloon aortic valvuloplasty for severe, symptomatic aortic stenosis. The long-term outcome after balloon aortic valvuloplasty in this cohort is poor, as illustrated by a 94% probability

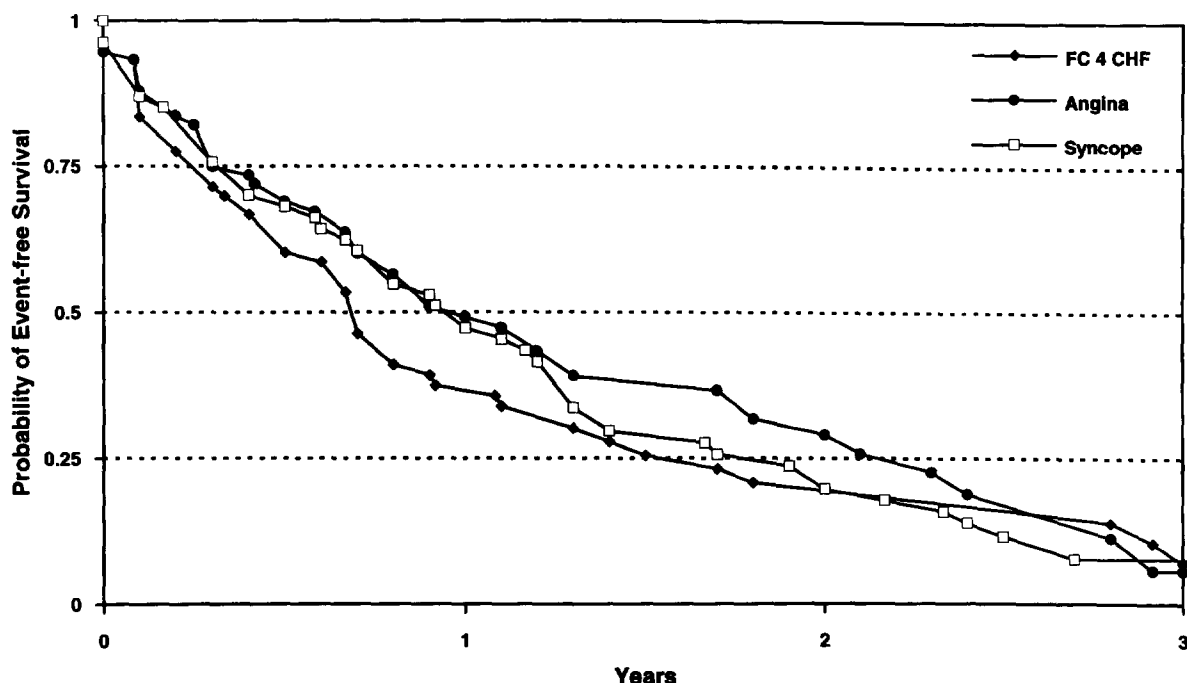


Figure 3. Event-free survival after balloon aortic valvuloplasty was similar for patients with syncope, angina and functional class IV congestive heart failure (FC 4 CHF). Patients with congestive heart failure tended to have events earliest.

of death, aortic valve replacement or repeat balloon aortic valvuloplasty within 3 years of the initial procedure. In our model, event-free survival is best predicted by patient age and left ventricular ejection fraction.

The long-term nature of the present study allows comparison of the outcome in these patients with what is known of the natural history of untreated aortic stenosis. In their early review of studies based on postmortem examinations, Ross and

Braunwald (16) emphasized the poor prognosis of patients with symptomatic aortic stenosis. Symptoms had existed for <4 years in 80% of the patients who died of aortic stenosis; the average survival of patients with angina was 5 years, with syncope 3 years and with congestive heart failure 2 years (16). However, the epidemiology of the etiology of aortic stenosis has changed from these earlier studies from rheumatic to degenerative calcific aortic stenosis (17), and the correlation between survival and type of symptom now appears poor (18). The presence of any symptom, and not the type of symptom, portends a poor prognosis (18,19), and the study by O'Keefe et al. (20) illustrates the particularly poor prognosis of candidates for balloon aortic valvuloplasty. They found that the 1-, 2- and

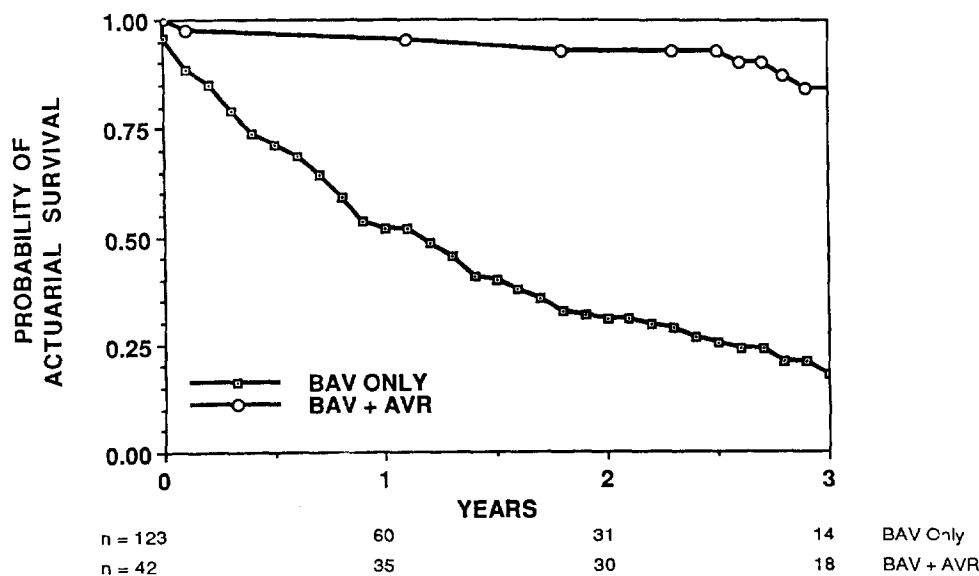


Figure 4. Actuarial survival from the date of balloon aortic valvuloplasty in patients who subsequently underwent aortic valve replacement (BAV + AVR) and those treated by balloon aortic valvuloplasty alone (BAV only).

Table 2. Baseline Univariable Predictors of Event-Free Survival

Findings	Chi-Square	p Value	Sign of Coefficient
Clinical			
Age	11.87	0.0006	-
CHF NYHA class IV	5.08	0.02	+
Angina	2.01	0.16	+
Female gender	1.50	0.22	-
Syncope	0.65	0.42	-
Catheterization			
Ejection fraction	8.78	0.0031	-
LVEDP	5.08	0.02	+
Cardiac output	2.80	0.09	-
Coronary disease	4.00	0.045	+
Aortic valve area	1.00	0.32	-
Peak gradient	0.67	0.41	-
Aortic insufficiency	0.02	0.88	+
Echocardiographic			
LVIDD	6.58	0.01	+
MR $\geq 2+$	0.099	0.75	+

LVEDP = left ventricular end-diastolic pressure; other abbreviations as in Table 1.

3-year actuarial survival rate of 50 elderly patients (mean age 77 years) referred to the Mayo Clinic with symptomatic aortic stenosis, in whom aortic valve replacement or balloon valvuloplasty was not performed, was 57%, 37% and 25%, respectively. In our elderly study cohort (mean age 76 years), the event-free survival rate 1, 2 and 3 years after balloon valvuloplasty was 40%, 19% and 6%, respectively, and the corresponding actuarial survival rate was 64%, 48% and 37%, respectively. After exclusion of the 42 patients who underwent aortic valve replacement after balloon aortic valvuloplasty, the 1-, 2- and 3-year postvalvuloplasty actuarial survival rate of the remaining patients was 52%, 31% and 18%, respectively. Although a comparison cohort such as that of O'Keefe et al. (20) cannot fully substitute for an age-matched control group, the similar survival patterns of the Mayo group and our valvuloplasty group suggest that balloon aortic valvuloplasty does not alter the dismal long-term prognosis of patients with aortic stenosis.

Predictors of outcome. Previous studies (1-8,11-14) of short-, mid- and long-term outcome after balloon aortic valvuloplasty illustrate its beneficial palliative effect on aortic stenosis symptoms and hemodynamic variables. However, the benefit is of brief duration, and most patients develop evidence of restenosis within 6 months of valvuloplasty (6-8). The present study indicates that long-term event-free survival is best predicted by patient age and left ventricular ejection fraction. Other studies (12,13,15,21) have found that the best predictors of clinical improvement after valvuloplasty are variables reflecting left ventricular function. The present study demonstrates that variables of left ventricular function, including functional class IV congestive heart failure symptoms, reduced ejection fraction and increased left ventricular internal diastolic diameter, are also powerful predictors of long-term event-free survival.

The data indicate that younger age is associated with a poorer event-free survival but better actuarial survival. This apparent contradiction may be explained by the way patients were treated after their initial balloon aortic valvuloplasty. If one analyzes the event-free survival of the entire 165-patient cohort, "nonsurvivors" include the 42 patients treated with balloon valvuloplasty who then had valve replacement, the 12 patients who underwent a repeat balloon valvuloplasty and all the patients who died during follow-up. The few remaining event-free survivors were a particularly elderly subgroup who may have been excluded from subsequent procedures because of coexisting medical conditions. The very advanced age of this small remaining subgroup thereby directed the analysis of event-free survival toward the conclusion that younger patients had poorer event-free survival.

As the actuarial survival analysis demonstrates, the best possible outcome for the patients in our study was not to be "event free." Instead, subsequent aortic valve replacement was associated with the greatest probability of actuarial survival. Patients in group receiving follow-up aortic valve replacement were a younger subset of the 165 patient study cohort, and their superb actuarial survival influenced the conclusion that younger age was associated with improved actuarial survival.

Aortic valve replacement. In an era when aortic valve replacement may be performed in selected patients >70 years old with low operative risk and excellent long-term results (22-24), the utility of balloon aortic valvuloplasty appears limited. It has been thought of as a viable alternative for the especially frail and elderly patient. During our early experience with balloon aortic valvuloplasty, all of our patients were seen by a cardiovascular surgeon who agreed with the assessment of high surgical risk and the appropriateness of balloon aortic valvuloplasty. Aortic valve replacement was recommended only after symptomatic restenosis developed. The 42 patients in the present study who underwent aortic valve replacement after balloon aortic valvuloplasty did surprisingly well, with a 1-year median actuarial survival rate of 95% from the time of balloon valvuloplasty and 88% from the time of operation. This result compares with a median 1-year actuarial survival rate of only 52% in the remaining patients treated by balloon aortic valvuloplasty alone. Remarkably, only 1 of the 42 surgical patients died of procedure-related causes.

Study limitations. The present study was not randomized with regard to use of medical therapy, balloon aortic valvuloplasty and aortic valve replacement for high risk patients with severe aortic stenosis. During the 5-year period of patient enrollment, the criteria for performing delayed aortic valve replacement versus a second balloon aortic valvuloplasty were evolving. The fact that an individual patient may have undergone an initial balloon aortic valvuloplasty and a subsequent aortic valve replacement does not imply that the patient's condition improved during the interval between the two interventions; rather, it is a reflection of our growing understanding of the limited utility of balloon aortic valvuloplasty.

The present study lacks an age-matched control cohort for the entire study group and for the 42 patients who progressed

to aortic valve replacement. The study group is generally an especially elderly and ill group in whom balloon aortic valvuloplasty was pursued because of perceived excessive surgical risk. The lack of a matched control group may obscure any potential benefit conferred by the balloon aortic valvuloplasty.

In addition, the 42 patients who proceeded to delayed aortic valve replacement had significant demographic differences from the 123 patients who continued with medical treatment. The surgical group was younger, included more men than women and had less coronary artery disease, a slightly higher median ejection fraction and less mitral regurgitation than the balloon valvuloplasty-only group. Because the subgroup proceeding to delayed aortic valve replacement was in general healthier than the balloon valvuloplasty-only group, a selection bias was introduced that most likely accounts for some of the survival difference between the two groups. However, after a statistical adjustment for these differences in baseline characteristics, the difference in survival between the groups remained statistically significant.

The conclusions of this study are limited to an adult patient cohort and should not be extrapolated to pediatric patients, where balloon aortic valvuloplasty may be performed with more favorable results (25).

Conclusions. Long-term event-free and actuarial survival after balloon aortic valvuloplasty is dismal and resembles the natural history of critical aortic stenosis. Aortic valve replacement may be performed in selected patients after balloon valvuloplasty with good results; however, the prognosis of the remainder of medically treated patients is particularly grim. Because the beneficial effects of balloon aortic valvuloplasty are transient, this procedure is most appropriately used when short-term palliation is desired, such as in patients with a reduced life expectancy because of comorbid illness. Over the longer term, balloon aortic valvuloplasty does not appear to alter the natural history of untreated aortic stenosis.

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