Late incidence and predictors of persistent or recurrent heart failure in patients with mitral prosthetic valves

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Objective: The study's objective was to examine factors associated with persistent or recurrent congestive heart failure after mitral valve replacement.

Methods: Patients who underwent mitral valve replacement with contemporary prostheses (N = 708) were followed with annual clinical assessment and echocardiography. Cox proportional hazard models were developed to evaluate the impact of demographic, comorbid, and valve-related variables on the occurrence of congestive heart failure after mitral valve replacement, defined as the composite outcome of New York Heart Association class III or IV symptoms or death caused by congestive heart failure postoperatively. Factors associated with all-cause mortality were also examined. Models were bootstrapped 1000 times.

Results: The total follow-up was 3376 patient-years (mean 4.8 ± 3.7 years, range 60 days to 17.1 years). Freedom from New York Heart Association III or IV symptoms or death caused by congestive heart failure was $96.1\% \pm 0.8\%$, $82.7\% \pm 1.7\%$, $66.4\% \pm 3.0\%$, and $38.8\% \pm 6.9\%$ at 1, 5, 10, and 15 years, respectively. Preoperative New York Heart Association class, left ventricular grade, atrial fibrillation, coronary artery disease, smoking, persistent tricuspid regurgitation, and redo status predicted congestive heart failure postoperatively (all $P < .05$). Patients who underwent mitral valve replacement for pure mitral stenosis had less congestive heart failure events after surgery than those with regurgitation or mixed disease. Prosthesis size and elevated transprosthesis gradients were not predictive of freedom from congestive heart failure after mitral valve replacement. Atrial fibrillation, persistent tricuspid regurgitation, and surgical referral for mitral valve replacement at an advanced functional stage were also risk factors for all-cause mortality.

Conclusions: This study identifies the incidence of and risk factors for congestive heart failure and death late after mitral valve replacement. Although prosthesis size has no effect, other potentially modifiable factors such as atrial fibrillation, persistent tricuspid regurgitation, and late surgical referral have a negative impact on freedom from congestive heart failure and overall survival after mitral valve replacement.

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lthough mitral valve replacement (MVR) is no longer the surgical treatment of choice for mitral valve disease, it remains commonly used for some indications, such as redo mitral surgery and the treatment of advanced stenotic or mixed lesions, endocarditis, or ischemic mitral insufficiency. As for other valve operations, an important goal of MVR is to prevent or cure symptoms of congestive heart failure (CHF) and decrease the likelihood of CHF-related death,¹ but few studies have systematically examined the impact of patient- and prosthesis-related characteristics on this outcome. This study addresses this question with a

TABLE 1. Prevalence and mean values of preoperative variables

	Mechanical (N = 493)	Bioprosthetic (N = 215)	P
Female gender	62.1%	58.8%	.41
Age (y)	59.1 ± 11.2	64.6 ± 13.2	<.001
Body surface area (m ²)	1.85 ± 0.22	1.81 ± 0.21	.024
NYHA class			.17
I	11.7%	13.5%	
II	24.4%	19.7%	
III	43.9%	39.9%	
IV	20.1%	26.9%	
Left ventricular grade			.54
1	50.8%	51.7%	
2	30.6%	29.3%	
3	12.7%	17.2%	
4	6.0%	1.7%	
LVEDP (mm Hg)	16.1 ± 5.4	16.4 ± 11.3	.63
Coronary artery disease	29.4%	32.4%	.42
Chronic atrial fibrillation	23.9%	25.0%	.75
Primary operative indication			.29
Stenosis	21.7%	18.1%	
Insufficiency	29.6%	33.3%	
Mixed disease	48.6%	48.7%	
Previous mitral replacement	18.3%	5.1%	<.001

Values are reported as mean ± SD or percentages.

LVEDP, Left ventricular end-diastolic pressure; NYHA, New York Heart Association.

cohort of patients followed after MVR and complements another article that focused on the same issue after aortic valve replacement (AVR).² Furthermore, in light of our AVR data, this study also ascertains whether prosthesis size has an impact on specific functional CHF end points after MVR. Previous studies on mitral prosthesis size may have been limited (similar to other studies that examined this issue in patients after AVR) by the nonspecificity of all-cause mortality as a clinical indicator of cardiac performance after valve replacement.

Methods

Study Population

The general methodology of this study has been described.² Briefly, adult patients (aged ≥18 years) who underwent MVR between 1976 and 2001 at our institution were followed annually in a dedicated valve clinic with clinical and laboratory examinations. The preoperative characteristics of the cohort are presented in Table 1.

Because of the potential impact of the prosthesis on the outcome of interest, patients who received valves that have since been withdrawn from the North American market were excluded from the analyses. Patients who underwent operation after 1990 had preservation of the posterior leaflet and chordae whenever feasible. The study cohort included 708 adult patients who underwent replacement of the mitral valve with prostheses that are still commercially available today (Table 2) and who survived the

TABLE 2. Implanted mitral prostheses and manufacturer valve size

	Number implanted (median size; min-max)
Mechanical	
Medtronic Hall	215 (29; 23-33)
St Jude Medical	193 (29; 25-33)
Carbomedics	85 (31; 27-33)
Bioprosthetic	
Medtronic Hancock I	100 (29; 23-35)
Medtronic Hancock II	95 (29; 25-33)
Edwards Perimount	20 (29; 27-33)

perioperative period. The total follow-up was 3376 patient-years, with a mean duration of 4.8 ± 3.7 years (range 60 days-19.9 years). Seventy-seven percent of patients had an average of 3.6 postoperative transthoracic echocardiograms performed at our institution on an annual basis.

Definition of Heart Failure

Heart failure after valve replacement was defined as (1) New York Heart Association (NYHA) functional class III or IV for more than 4 consecutive weeks or (2) death in which the primary or main contributing diagnosis was CHF. The clinical impression was corroborated with physical examination, chest radiograph, electrocardiogram, and echocardiography findings. Cases of primary non-structural dysfunction resulting from severe paravalvular leaks, valve thrombosis, or endocarditis were excluded as heart failure events for the purpose of this study.

Statistical Analyses

Data were imported and analyzed in Intercooled Stata 8 (Stata, College Station, Tex). Patients were censored at the time of their last follow-up visit if they had not experienced at least 1 episode of NYHA functional class III or IV for 4 weeks or more, or had died from a CHF-related event. Deaths from an unknown cause were not considered to result from CHF. Crude, stratified, and risk-adjusted survival, heart failure event rates, and failure rates are reported as mean ± SE or as mean (95% confidence interval [CI] lower bound, 95% CI upper bound).

Cox proportional hazards models were developed by incorporating variables that had a *P* value of .10 or less on univariate analysis and by forcing into each model patient- and prosthesis-related variables (eg, age, gender, comorbidities, atrial fibrillation, and valve type) that constituted potential confounders regardless of their univariate *P* value. Variables used in the models are presented in Tables 3 and 4. To account for positive or negative confounding, no automated model selection procedure was used, and reported variables, unless collinear with a Spearman's rank correlation coefficient of 0.30 or greater and a *P* value less than .01, were used simultaneously. Each model was evaluated with a score test and rejected if the *P* value was .05 or greater. Final models were subjected to 1000 bootstrap replications, and bias-corrected estimates of 95% CIs were tabulated for significant covariates.

TABLE 3. Predictors of New York Heart Association class III or IV symptoms or CHF-related death

	Hazard ratio	95% CI	P	Bias-corrected 95% CI*
Significant independent predictors:				
Atrial fibrillation	1.97	1.37-2.82	<.001	1.26-2.75
Preoperative NYHA class†	1.42	1.14-1.77	.002	1.13-1.77
Preoperative left ventricular gradet	1.41	1.02-1.94	.038	1.02-1.96
Coronary artery disease	1.58	1.06-2.35	.025	1.03-2.38
Smoking	2.09	1.14-3.82	.017	1.06-3.53
Redo mitral valve replacement	2.00	1.30-3.07	.002	1.18-3.11
Tricuspid insufficiency	2.46	1.11-5.43	.027	0.29->10 ⁵
Pure mitral stenosis	0.57	0.33-0.99	.049	0.30-0.96
History of previous stroke	3.13	1.24-7.92	.016	1.23-5.87
Nonsignificant variables included in the model:				
Age at surgery (per year increase)	1.01	0.99-1.03	.15	—
Male gender	1.03	0.68-1.55	.89	—
Preoperative diastolic pulmonary artery pressure (per mm Hg)†	1.01	0.98-1.03	.49	—
Body surface area	1.10	0.41-2.94	.85	—
Diabetes mellitus	1.69	0.78-3.68	.18	—
Bioprosthetic (vs mechanical) valve	1.02	0.69-1.51	.91	—
Bileaflet (vs tilting disk) mechanical valves§	1.28	0.81-2.01	.29	—
Manufacturer valve size (per one size increase)†	0.94	0.86-1.03	.18	—
Peak transprosthesis gradient (per mm)‡	1.01	0.96-1.06	.75	—
Mean transprosthesis gradient (per mm)‡	1.04	0.94-1.16	.45	—
Peak transprosthesis gradient ≥90th percentile‡	0.74	0.30-1.80	.50	—
Mean transprosthesis gradient ≥90th percentile‡	1.25	0.60-2.61	.55	—

CI, Confidence interval; NYHA, New York Heart Association.

*Derived from 1000 bootstrap model simulations (reported for significant predictors only).

†‡Collinear variables that were successively but not simultaneously included in the model.

§Within subset of mechanical valves.

TABLE 4. Predictors of all-cause death

	Hazard ratio	95% CI	P	Bias-corrected 95% CI*
Significant independent predictors:				
Age at surgery (per year)	1.04	1.01-1.06	.001	1.01-1.06
Atrial fibrillation	2.30	1.10-4.81	.027	1.06-4.57
Preoperative NYHA class†	1.28	1.00-1.63	.048	1.00-1.63
Preoperative left ventricular gradet	1.47	1.03-2.09	.033	1.04-2.02
Coronary artery disease	1.81	1.16-2.81	.009	1.12-2.74
Number of pack-years smoked (per pack-year)	1.02	1.00-1.04	.039	1.00-1.04
Tricuspid insufficiency	2.17	1.30-3.63	.003	0.10->10 ⁶

CI, Confidence interval; NYHA, New York Heart Association.

Nonsignificant variables also included in the model were male gender, preoperative diastolic pulmonary artery pressure,† body surface area, pure mitral stenosis, redo mitral valve replacement, bioprosthetic (vs mechanical) valve, manufacturer valve size, peak‡ and mean‡ transprosthesis gradients, and peak‡ and mean‡ transprosthesis gradient ≥90th percentile.

*Derived from 1000 bootstrap model simulations.

†‡Collinear variables that were successively but not simultaneously included in the model.

Results

Cumulative Incidence of Heart Failure Events After MVR

The freedom from the composite outcome of NYHA functional class III or IV symptoms or CHF-related death in patients who survived and were followed in a clinic 2 months or more after MVR was 96.1% ± 0.8%, 82.7% ±

1.7%, 66.4% ± 3.0%, and 38.8% ± 6.9% at 1, 5, 10, and 15 years, respectively. Figure 1 shows the freedom from NYHA class III or IV symptoms not leading to CHF-related death (Figure 1, A), the freedom from CHF-related death (Figure 1, B), and the freedom from all-cause death (Figure 1, C) in patients with mechanical and bioprosthetic mitral valves.

Figure 1. Cumulative incidence of heart failure events and death after MVR. Unadjusted Kaplan-Meier estimates of the freedom from NYHA class III or IV symptoms (A), heart failure-related death (B), and all-cause death (C) in patients with mitral mechanical and bioprosthetic valves.

Risk Factors for Heart Failure

Patient-related factors. Table 3 displays the risk factors for heart failure late after MVR. Significant independent predictors included atrial fibrillation (hazard ratio [HR]: 2.0), preoperative functional class (HR: 1.4 per class increase), left ventricular grade (HR: 1.4 per unit increase), coronary artery disease at the time of surgery (HR: 1.6), smoking (HR: 2.1), redo MVR (HR: 2.0), moderate-to-severe tricuspid insufficiency at follow-up echocardiography (HR: 2.5), and a history of stroke preoperatively (HR: 3.1). Patients who underwent MVR for pure mitral stenosis had a lower cumulative incidence of heart failure events

after surgery (HR: 0.6) than those with mitral insufficiency or mixed disease, independent of confounding factors.

Prosthesis-related factors. In contrast with patients with aortic prostheses,² prosthesis size did not significantly predict freedom from heart failure after MVR, regardless of whether body surface area was accounted for in the model.

The median transprosthesis peak and mean gradient for patients with a mitral prosthesis were 11 mm Hg and 4 mm Hg, respectively, and the 90th percentile values for peak and mean aortic gradients were 19 mm Hg and 7 mm Hg, respectively. Peak and mean transprosthesis gradients had

no significant impact on the freedom from heart failure after MVR either as a linear relationship or as a dichotomous predictor defined by a gradient at or above the 90th percentile value of the cohort.

Risk Factors for All-Cause Death

Table 4 displays the risk factors for all-cause death late after MVR in the study cohort. Significant independent predictors were age, atrial fibrillation, preoperative functional class, left ventricular grade, coronary artery disease, number of pack-years smoked, and persistent tricuspid insufficiency at follow-up. Again, no significant effect of prosthesis size on crude survival was detected.

Discussion

In this study we identified risk factors for persistent or recurrent CHF after MVR from a cohort of patients prospectively followed after surgery. Risk factors for the composite outcome of CHF symptoms or CHF-related death after MVR included chronic atrial fibrillation, advanced preoperative NYHA class, advanced LV grade, smoking, tricuspid insufficiency, and preoperative history of stroke. MVR for pure mitral stenosis was associated with significantly less CHF events during follow-up than if MVR had been performed for mitral regurgitation or mixed disease.

These data have practical relevance in light of some of the current controversies related to the operative management of patients with mitral valve disease. First, patients with atrial fibrillation have an increased risk of persistent or recurrent CHF after MVR, raising the question of whether the use of a concomitant maze procedure might modify this risk. Previous data have demonstrated that all-cause mortality after mitral valve surgery is lower for patients in sinus rhythm than for those in atrial fibrillation³ and that, as expected, freedom from atrial fibrillation after MVR is higher in patients who concomitantly undergo a maze procedure.^{4,5} Our data support the premise that the maze procedure may be beneficial with respect to CHF outcomes and all-cause mortality after MVR, and may provide the basis for a randomized, controlled trial that would examine the impact of this procedure not only on electrophysiologic, anticoagulation, and stroke outcomes but also on CHF end points and functional capacity after MVR and mitral valve repair.

Another finding of relevance in this study is that persistent tricuspid insufficiency at follow-up was independently associated with an increased risk of CHF and all-cause death after MVR, regardless of the severity of symptoms preoperatively. Although this significant finding was not robust on bootstrap resampling simulations because of the relatively small number of linked events, it nevertheless suggests that the commonly held view stipulating that the performance of tricuspid valve repair in patients after MVR

is dictated by the presence of congestive symptoms may be unfounded, and that an aggressive approach toward repair of tricuspid insufficiency in patients after MVR might positively impact on freedom from CHF late postoperatively. In this regard, other investigators have also suggested that even asymptomatic, functional tricuspid insufficiency may warrant tricuspid valve repair, because tricuspid insufficiency may not improve and even worsen with time, especially in the presence of atrial fibrillation.⁶

Other aspects of patient management were also identified as potential CHF risk modifiers in this study. For example, it is possible that newer trends in the management of patients with mitral valve disease, such as the referral of patients for valve surgery before symptom development, may have an independent positive impact on the freedom from CHF after MVR.

An important negative finding of this study was that mitral prosthesis size, within the usual range used for MVR in adults, did not correlate with functional outcome, freedom from CHF death, or overall survival after MVR. These findings are in contrast with recent work from our group that examined similar outcomes after AVR and that showed aortic prosthesis size had a significant independent effect on freedom from CHF.² Yazdanbakhsh and colleagues⁷ indicated that a small valve area index is a risk for early mortality after MVR (with congestive failure being the main cause of death), but these authors, as those in the present study, found no impact of mitral prosthesis size on late mortality after MVR. In this regard, it is plausible that early outcomes of surgeries such as MVR may be particularly susceptible to selection bias, which can persist despite rigorous multivariate analysis.⁸

Smoking was another potentially modifiable risk factor for CHF after MVR that was identified in this study. Although smoking and its associated impairments in functional capacity may have resulted in more pseudo-CHF symptoms reported from smokers than nonsmokers, a recent study from our group indicated that smoking is an independent risk factor for structural bioprosthesis degeneration, which may help explain the impact of smoking on CHF outcomes observed in the present study.⁹ Additional evidence pertaining to native valves previously suggested that cigarette-derived toxins play a biologic role on the structural integrity of valves through premature calcification.^{10,11}

It is noteworthy that within the number of risk factors identified, a history of stroke may have been a risk factor for subsequent stroke¹² or a marker of advanced cardiovascular disease and thus a potential positive confounder of poor functional status that could not be fully discriminated from advanced NYHA class symptoms during the follow-up period.

Finally, the results of this study also indicate that patients with pure mitral stenosis who undergo MVR have a signif-

icantly better long-term functional outcome than those with mitral insufficiency or mixed disease and that MVR provides relatively good functional results in patients for whom mitral commissurotomy is not feasible. This issue may warrant further research to determine whether MVR is better than a suboptimal mitral valve repair in a patient with advanced mitral stenosis whose valve is poorly amenable to commissurotomy.

Limitations

This study was not of randomized design. It is possible that unidentified confounders or selection bias may have influenced results despite the use of specific end points and bootstrapped methods. Statistical overfitting also may have enhanced some associations, with one possibility being the significant relationship of tricuspid insufficiency with CHF outcomes and death, which could not be verified by bootstrap resampling because of the relatively small number of linked events.

Patients lost to follow-up may have had important subsequent outcomes that were not accounted for in the analyses, and the mean follow-up of the study, although extending to 19.9 years, was only 4.8 years. Inferences therefore apply mostly to intermediate-term outcomes.

Some entries were incomplete in the database. Although no data were imputed and the sample size of each analysis was floated with respect to the number of complete entries, this approach may have prevented the demonstration of some associations by increasing type II statistical error, because some potential predictors were evaluated with sub-total samples.

Other than for a general consensus to preserve the sub-valvular mitral apparatus in patients of the cohort who underwent operation after 1990, specific details pertaining to the preservation technique used in each patient were not available from the database. Their impact on CHF outcomes could therefore not be examined in this study.

Conclusions

This study identified risk factors for the development of CHF after MVR. Potentially modifiable factors such as

advanced NYHA class and left ventricular grade may be impacted by earlier referral for valve surgery. Other risk factors such as postoperative atrial fibrillation and tricuspid insufficiency warrant further research to define the impact of concomitant surgical procedures oriented at these conditions on the cumulative incidence of CHF after MVR.

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