Long-Term Mortality Effect of Early Pacemaker Implantation After Surgical Aortic Valve Replacement

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Background. **The need for pacemaker implantation is a well-described complication of aortic valve replacement. Not so well described is the effect such an event has on long-term outcome. This study reviewed a 21-year experience at the Mayo Clinic (Rochester, Minnesota) with aortic valve replacement to understand the influence of early postoperative pacemaker implantation on long-term mortality rates more clearly.**

Methods. **This study retrospectively reviewed the records of 5,842 patients without previous pacemaker implantation who underwent surgical aortic valve replacement from January 1993 through June 2014. The median age of these patients was 73 years (range, 65 to 79 years), the median ejection fraction was 62% (range, 53% to 68%), 3,853 patients were male (66%), and coronary artery bypass graft operation was performed in 2,553 (44%) of the patients studied. Early pacemaker implantation occurred in 146 patients (2.5%) within 30 days of surgical aortic valve replacement.**

Results. **The median follow-up of patients was 11.1 years (range, 5.8 to 16.5 years), and all-cause mortality rates were 2.4% at 30 days, 6.4% at 1 year, 23.1% at 5 years, 48.3% at 10 years, and 67.9% at 15 years postoperatively. Early pacemaker implantation was associated with an increased risk of death after multivariable adjustment for baseline patients' characteristics (hazard ratio, 1.49; 95% confidence interval, 1.20, 1.84; $p < 0.001$).**

Conclusions. **Early pacemaker implantation as a complication of surgical aortic valve replacement is associated with an increased risk of long-term death. Valve replacement–related pacemaker implantation rates should be important considerations with respect to new valve replacement paradigms, especially in younger and lower-risk patients.**

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Pacemaker implantation is a well-described complication that occurs in approximately 5% of patients within 30 days of surgical valve replacement [1–3]. Although there is evidence that supports the concept of pacemaker-induced heart disease, previous cardiac surgical studies failed to document any long-term detrimental effect related to pacemaker implantation [4–9]. Such studies, however, may have been limited by either a small number of valve replacement recipients or a short duration of follow-up [4, 6, 7]. To understand the influence of early pacemaker implantation on mortality rates more clearly, we reviewed our 21-year experience at the Mayo Clinic in Rochester, Minnesota in a large cohort of patients who underwent surgical aortic valve replacement.

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Patients and Methods

The Institutional Review Board approved this study. We retrospectively reviewed the records of 5,842 patients without a history of previous pacemaker implantation who underwent isolated surgical aortic valve replacement with or without coronary artery bypass graft operation from January 1993 through June 2014. There were 146 patients who had early pacemaker implantation within 30 days of valve replacement (study group, 2.5%) and 5,696 patients who did not have pacemaker implantation within 30 days of valve replacement (unexposed group, 97.5%). The endpoint of the study was all-cause mortality.

Baseline characteristics, performance of coronary artery bypass graft operation, and the need for early postoperative pacemaker implantation with 30 days of surgical aortic valve replacement were taken from the electronic medical record and the institution's Division of Cardiovascular Surgery database. Data were recorded based on definitions set forth in The Society of Thoracic Surgeons Adult Cardiac Surgery Database (Chicago, IL). Vital status was determined through review of the

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medical record, correspondence (ie, from patient, family, or referring physicians), and yearly Accurint (LexisNexis, New York, NY) review.

Categorical data were recorded as count (percentage) and continuous variables as median (interquartile range). The Society of Thoracic Surgeons predicted risk of death was also reported as mean ± standard deviation. Differences between groups were determined by χ^2 test or Wilcoxon rank sum test, as appropriate. The Kaplan-Meier product limit method was used to estimate mortality curves, with unadjusted comparison of rates based on the Wilcoxon test. To account for the 30-day follow-up period used to define pacemaker group membership, we considered day 30 as the time origin for all group-stratified Kaplan-Meier analyses, thereby excluding a small percentage of patients who died before that point.

The association of permanent pacemaker implantation with survival time, after adjustment for suspected confounding factors, was analyzed with multivariable Cox proportional hazards model regression. Given the possibility of exposure over 30-day follow-up, pacemaker implantation was assessed as a time-dependent variable in the Cox proportional hazards model based on Andersen and Gill's counting process formulation. To display estimates of mortality after covariate adjustment graphically, a separate Cox proportional hazards model was developed on 30-day survivors that was stratified by pacemaker group and adjusted for baseline covariates at their mean levels in the combined sample. From this model, adjusted mortality estimates were determined by the Kalbfleisch-Prentice product limit estimator based on the discrete underlying hazard formulation [10].

Because some covariates in the final adjustment model were infrequently missing, subset analysis resulting from casewise deletion was used to derive the adjusted effect of pacemaker. To address the adequacy of excluding those patients with incomplete data, sensitivity analysis was performed by refitting the model on the full cohort after imputing missing values. Single imputation based on the Markov chain Monte Carlo method was undertaken to estimate missing values for a given variable by using available data from the other baseline covariates [11]. An alpha level of 0.05 was used to define statistical significance. All analyses were carried out in SAS statistical programming language (version 9.4, SAS Institute, Inc, Cary, NC).

Results

Baseline characteristics of the 5,842 patients included a median age of 73 years (range, 65 to 79 years), male sex in 3853 patients (66%), performance of coronary artery bypass graft operation in 2,553 patients (44%), and The Society of Thoracic Surgeons predicted risk of mortality of 4.3 ± 4.1% (median, 3.0%; interquartile range, 1.8 to 5.4%).

Additional baseline patients' characteristics and operative data are reported in Table 1 and are grouped according to those patients who underwent early pacemaker implantation and those who did not. In comparison with the unexposed group, patients who underwent pacemaker implantation were older, had reduced ejection fractions, received operation in an earlier calendar year, and were more likely to have diabetes, previous valve operations, greater New York Heart Association functional class dyspnea, mitral valve regurgitation grade moderate or severe, and operation in a nonelective status ($p < 0.05$ for each, from unadjusted analyses) (Table 1).

Pacemaker device implantation included a dual-chamber pacemaker in 119 patients (82%), a single-chamber pacemaker in 19 patients (13%), a single-chamber pacemaker with an intracardiac defibrillator in 3 (2%), a dual-chamber pacemaker with an intracardiac defibrillator in 2 (1%), a biventricular pacemaker in 2 (1%), and a biventricular pacemaker with an intracardiac defibrillator in 1 (1%). Indications for pacemaker implantation included atrioventricular conduction system block in 114 patients (78%), bradycardia in 13 (9%), tachycardia-bradycardia syndrome in 12 (8%), and prevention in 7 (5%).

In-hospital death occurred in 120 patients (2%) and included 1 patient who underwent pacemaker implantation, whereas operative death occurred in 153 patients (2.6%) and similarly include 1 patient who underwent pacemaker implantation. The observed-to-expected mortality ratio for all patients was 0.6 (2.6/4.3), whereas the ratio was 0.1 (0.7/5.6) in patients who underwent pacemaker implantation and 0.6 (2.7/4.3) in those who did not undergo pacemaker implantation.

The median follow-up of patients was 11.1 years (range, 5.8 to 16.5 years), and all-cause mortality rates were 2.4% at 30 days, 6.4% at 1 year, 23.1% at 5 years, 48.3% at 10 years, and 67.9% at 15 years postoperatively. Duration of follow-up did not differ significantly between groups with and without early pacemaker implantation (median, 12.9 years vs 11.0 years; $p = 0.340$). During the follow-up period, death occurred in 93 patients (64%) in the pacemaker implantation group and in 2,660 (48%) patients in the unexposed group.

Among all patients alive on day 30 (n = 5,702), median survival was 7.3 years (range, 3.6 to 11.5 years) in the pacemaker implantation group and 10.7 years (range, 5.9 to 18.1 years) in the unexposed group. Mortality rates appeared to be consistently higher over time in patients with pacemaker implantation (32.8% at 5 years, 64.7% at 10 years) compared with those patients who did not undergo pacemaker implantation (20.9% at 5 years, 46.6% at 10 years). Among the 30-day survivors who had complete data with regard to known important baseline characteristics (n = 4,846), pacemaker implantation was associated with increased mortality rates from both unadjusted and adjusted analysis ($p < 0.001$ for each) (Fig 1).

To explore this association further in an analysis that was not conditional on 30-day survival, pacemaker implantation was assessed as a time-dependent covariate in Cox proportional hazards model analysis. In the multivariable model adjusting for baseline patient and operative variables, Cox proportional hazards model analysis on 4,969 (85%) subjects with complete data