Relation of Prolonged Pacemaker Dependency After Cardiac Surgery to Mortality

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Permanent pacemaker implantation (PPI) represents a rare complication after cardiac surgery, with no uniform agreement on timing and no information on follow-up. A multicenter retrospective study was designed to assess pacemaker dependency (PMD) and long-term mortality after cardiac surgery procedures. Between 2004 and 2016, PPI-patients from 18 centers were followed. Time-to-event data were evaluated with semiparametric regression Cox models and semiparametric Fine and Gray model for competing risk framework. Of 859 (0.90%) PPI-patients, 30% were pacemaker independent (PMI) at 6 months. PMD showed higher mortality compared with PMI (10-year survival 80.1% ± 2.6% and 92.2% +2.4%, respectively, log-rank p-value < 0.001) with an unadjusted hazard ratio for death of 0.36 (95% CI 0.20 to 0.65, p< 0.001 favoring PMI) and an adjusted hazard ratio of 0.19 (95% CI 0.08 to 0.45, p< 0.001 with PMD as reference). Crude cumulative incidence function of restored PMI rhythm at follow-up at 6 months, 1 year and 12 years were 30.5% (95% CI 27.3% to 33.7%), 33.7% (95% CI 30.4% to 36.9%) and 37.2% (95% CI 33.8% to 40.6%) respectively. PMI was favored by preoperative sinus rhythm with normal conduction (SR) (HR 2.37, 95% CI 1.65 to 3.40, p< 0.001), whereas coronary artery bypass grafting and aortic valve replacement were independently associated with PMD (HR 0.63, 95% CI 0.45 to 0.88, p = 0.006 and HR 0.807, 95% CI 0.65 to 0.99, p = 0.047 respectively). Time-to-implantation was not associated with increased rate of PMI. Although 30% of PPI-patients are PMI after 6 months, PMD is associated with

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Permanent pacemaker implantation (PPI) after cardiac surgery for brady-arrhythmia's and/or atrio-ventricular (A/V) conduction defects occurs in up to 1%to 3% of patients after coronary artery bypass graft (CABG), 5% after mitral valve replacement (MVR), and reportedly up to 12% after aortic valve replacement (AVR).[1−3]. Brady-arrhythmia's requiring pacemaker implant include sick sinus syndrome, atrial fibrillation with slow ventricular response, and several degrees of A/V block.[3] Although pacemaker dependency decays with time, depending on the type of indication, new or recurrent conduction disturbances may develop at variable time points after hospital discharge.[2,4,5] However, data addressing this topic are heterogeneous, dependent on local protocols, and, therefore, poorly informative.[3] Current guidelines consider advanced second or third degree A/V block lasting at least 7 days after cardiac surgery as a class I indication for PPI, but the evidence is based on relatively small studies ranging between 150 and 250 patients, with short-term follow up.[6,7] Also, the impact of a PPI after cardiac surgery on survival is not known. Based on these premises we developed a multicenter working group to thoroughly investigate the actual incidence of PPI after cardiac surgery procedures in a large population. The purposes of this study were to evaluate the pacemaker dependency after PPI, to describe the influence of pre-operative sinus rhythm with normal conduction (SR) on pacemaker dependency and to assess the long-term mortality after PPI.

Methods

The study population was retrospectively extracted, analyzing the institutional databases of 18 cardiac surgery units that are part of the G.I.R.O.C. (Italian Group for Research Outcome in Cardiac Surgery) and adhered to the study protocol. The requirement for PPI was determined by the cardiologist, the cardiac surgeon and the electrophysiologist of each center. All datasets analyzed were collected and responded to the requirements of a minimum dataset of predefined variables. Patients who underwent cardiac surgery from January 2004 to December 2016 requiring postoperative PPI during the hospitalization related to cardiac surgery procedures were included in the study. Patients with preoperative indication to PPI, who underwent implantable cardioverter defibrillator or cardiac resynchronization therapy treatment, were excluded. Preoperative and demographic information, operative data, and perioperative mortality and complications for all patients were retrieved from the institutional databases.

The primary outcomes included pacemaker dependency at follow-up and long-term mortality. The secondary outcome described the influence of pre-operative SR on pacemaker dependency. Pacemaker dependency was defined as the absence of intrinsic rhythm on a postdischarge assessment performed by reducing the pacemaker frequency below 40 beats per minute (bpm) during 15 seconds. The presence of SR with associated conduction status and the presence of supraventricular arrhythmia were also recorded. Patients were considered pacemaker independent (PMI) if they had SR or atrial fibrillation with an adequate ventricular response at 40 bpm. Follow-up information was obtained by direct patient visit and electrophysiology analysis on simple EKG tracings. Patient data collection was truncated on December 31, 2016; patients who did not experience the events were considered as rightly censored. The study was conducted after approval of the individual Ethical Committees at each institution (Principal Investigator Ethical Committee approval nr.1467, date March 4, 2014).

Normally distributed variables (by Kolmogorov-Smirnov test) are reported as mean and standard deviation, non-normally distributed variables are reported as median and quartiles. Pairwise comparison was performed with student's *t* test or Mann-Whitney U-test in case of continuous variables and chi-square with Fisher's exact test in case of categorical variables. Following discharge, the primary events were managed as time-to-event data and analyzed with nonparametric and semiparametric methods. Discharge from hospital after surgery was defined as beginning of follow-up and all intraoperative deaths and in-hospital were excluded from time-to-event analysis. Time-to-event distributions were separately analyzed according to primary event-type (death, cardiac death and freedom from pacemaker dependency), using Kaplan-Meier estimates and Cox regression for the time-to-death analysis and Fine & Gray models in competing risk framework for time-to-cardiac death (with no-cardiac death as competing risk) and time-to-freedom from pacemaker dependency (with death as competing risk). The variables selection for the Cox models was performed by a forward stepwise regression (probability of stay = 0.10, probability of entry = 0.05). For time-to-cardiac death and time-to-freedom from pacemaker dependency, nonparametric analyses of the outcome variables of interest were computed with the cumulative incidence function (CIF), and subdistribution hazards and comparisons were computed by means of Fine and Gray test. Direct regression modeling of the effect of covariates on CIF was performed through the semi-parametric proportional hazard model for the subdistribution hazards proposed by Fine and Gray, allowing for time-varying effect of the covariates. The variables selection for the Fine & Gray models was performed by a forward stepwise regression with the Bayesian Information Criterion as selection criteria. Hazards proportionality and time-dependent effects were checked with the analysis of Shoenfeld residuals, Kolmogorov-Smirnov test, and Cramer von Mises test. Missing values occurred for variables with a max of 3%. The center effect was evaluated with mixed effect model with center as random effect. Missing values were substituted by means of multiple imputation, as described in order to reduce bias and increase statistical power. For all analyses, we used R 3.3.1

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Results

Patient population included 94.693 cardiac surgery procedures from January 2004 to December 2016. During this period, 859 patients (0.90%) underwent PPI within 30 days after surgery. Table 1 shows the baseline characteristics of the study groups. Median time from cardiac surgery to PPI was 8 days (ranging from 2 to 10 days).

Seven patients who underwent PPI (7/859, 0.81%) died during their primary hospitalization and no death was PPI related. Eighty patients died after discharge (9.4%). Survival rate at 1, 5, and 12 years were 96.8% (95% CI: 95.6% to 98.0%), 90.4% (95% CI: 88.3% to 92.6%), and 85.1% (95% CI: 81.9% to 88.5%) respectively. Cardiac mortality rates at 1, 5, and 12 years were 2.2% (95% CI: 1.2% to 3.2%), 4.4% (95% CI 2.9% to 5.8%), and 6.2% (95% CI 3.9% to 8.4%) respectively. Figure 1, Panel A shows the Kaplan-Meier estimates for the long-term survival curves, of patients with PMD at follow-up and those who restored A/V conduction (PMI) (Log-rank p-value < 0.001), based on 4642.53 patient-years follow-up and a median follow-up of 61.8 months. Figure 1, Panel B shows the CIFs of the cardiac death between PMD and PMI, with noncardiac death as a competing risk and vice-versa (Gray test p-value = 0.057 and 0.008 respectively). The unadjusted hazard ratio for overall mortality was 0.39 (95% CI 0.22 to 0.69, p-value = 0.001), in favor of PMI. The adjusted hazard ratio was 0.22 (95% CI 0.09 to 0.52, p-value < 0.001) with PMD as reference group, thereby confirming association of PMD with increased long-term mortality (Table 2). No center effect was pointed out in the regression modeling. The long-term predicted survival curves with 95% CI, are shown in Figure 1 Panel C. The assumption of hazards proportionality for the Cox model was confirmed by the analysis of Schoenfeld residuals (per-variable Grambsch-Therneau test p-value > 0.05 for all regressors). Hence, PMI qualified as an independent protective factor for long-term mortality after surgery and PPI.

Figure 2, Panel A reports the CIFs of restored pacemaker-independent rhythm at follow-up. Crude CIF at 6 months, 1 year, and 12 years were 30.5% (95% CI 27.3% to 33.7%), 33.7% (95% CI 30.4% to 36.9%), and 37.2% (95% CI 33.8% to 40.6%) respectively. As evident in Figure 1, more than 30% of patients with postoperative PPI returned to a prevalent non-PMD rhythm. Direct regression modeling of the effect of covariates on CIF of PMI demonstrated that PMI was favored by preoperative SR (HR 2.17, 95% CI 1.50 to 3.12, p value < .001), whereas AVR (HR 0.87, 95% CI 0.68 to 1.11, p= .084), and CABG (HR 0.60, 95% CI 0.42 to 0.83, p= 0.006) were independently associated to PM dependency (Kolmogorov-Smirnov test and Cramer von Mises test p-values > 0.05), and MVR was not significant (HR 0,848 95% CI 0,659 to 1,090, p = 0.2). No center effect was pointed out in the regression modeling. Preoperative SR qualified as an independent factor favoring PMI after PPI. Figure 2 Panel B shows the adjusted CIF of PMI in patients with preoperative SR and nonpreoperative SR.

Table 1
Baseline characteristics of patients (n = 859)

Pre-operative Data and Co-morbities Variables	Study Group (n = 859)
Age, mean (SD) (years)	68,7 (12,4)
Women	443 (51,6%)
Hypertension	537 (62,5%)
Active endocarditis	45 (5,2%)
Diabetes mellitus (requiring drug treatment)	184 (21,4%)
Previous stroke	47 (5,5%)
Chronic renal failure	48 (5,6%)
Dialysis	9 (1,1%)
Chronic pulmonary disease	123 (14,3%)
Pulmonary hypertension (systolic PA pressure >55 mm Hg	172 (20,0%)
Extracardiac arteriopathy*	124 (14,4%)
Previous myocardial infarction	81 (9,4%)
Recent myocardial infarction	36 (4,2%)
Left ventricular ejection fraction, mean (SD), %	54,2 (11,4)
NYHA Class III/IV	410 (47,7%)
Previous cardiac surgery	105 (12,2%)
Urgent status of operation	27 (3,1%)
ECG	
Sinus rhythm	640 (74,5%)
Left bundle branch block	87 (10,1%)
Right bundle branch block	88 (10,2%)
Bi-fascicular block	9 (1,0%)
Left anterior fascicular block	71 (8,3%)
Left posterior fascicular block	5 (0,6%)
First-degree atrioventricular block	88 (10,2%)
Second-degree atrioventricular block	26 (3,0%)
Atrial fibrillation	186 (21,7%)
Surgery	
Coronary artery bypass grafting	239 (27,8%)
Aortic valve replacement	387 (45,1%)
Aortic root surgery	44 (5,1%)
Mitral valve surgery	375 (43,6%)
Tricuspid valve surgery	178 (20,7%)
Myxoma excision	4 (0,5%)
Atrial septal defect closure	16 (1,9%)
Ventricular septal defect closure	9 (1,0%)
Surgery for atrial fibrillation	47 (5,5%)

* any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids.

Discussion

To our knowledge, this is the largest study on patients who underwent PPI after cardiac surgery with an extended long-term follow up. Our incidence of PPI was 0.90%, in accordance with published reports.[4,8,9] Merin et al[8] found PPI incidence of 1.4% in almost 5,000 cardiac surgery procedures; whereas Del Rizzo et al[9] observed this event in 1.3% of the patients. Higher rate of PPI (2.2%) is also described in another series of 6,268 patients[4].

PPI occurs more often after valvular surgery due to the close vicinity of the conduction system to the operated

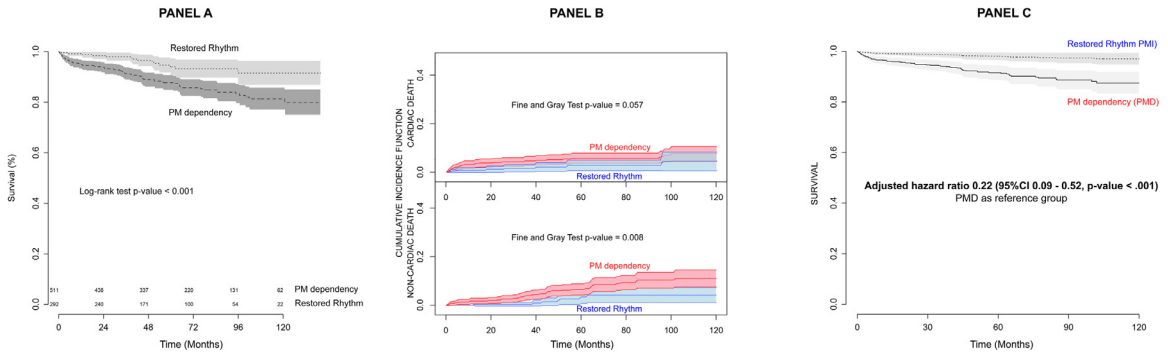

Figure 1. Panel A: Unadjusted KM estimates of long-term survival (up to 10 years). Panel B: Cumulative incidence function of cardiac death, with non-cardiac death as a competing risk, and vice-versa. Panel C: Predicted CIF estimates of all-cause mortality for the two groups (PMD and PMI) based on the adjusted model.

Table 2
Hazard ratios of the adjusted Cox semiparametric model for predicting long-term mortality

Variable	Hazard Ratio	95% CI of HR	p value
PMI	0,22	0,09−0,52	<0,001
Diabetes mellitus	2,46	1,48−4,08	<0,001
Active endocarditis	1,91	0,87−4,20	0,09
Chronic renal failure	2,75	1,43−5,27	0,006

Table 3
Hazard ratios of the adjusted Fine and Gray model for predicting restored PM-independency

Variable	Hazard Ratio	95% CI of HR	p value
Pre-operative SR	2,17	1,50−3,12	<0,001
Coronary artery bypass grafting	0,60	0,42−0,83	0,006
Aortic valve replacement	0,87	0,67−1,11	0,084

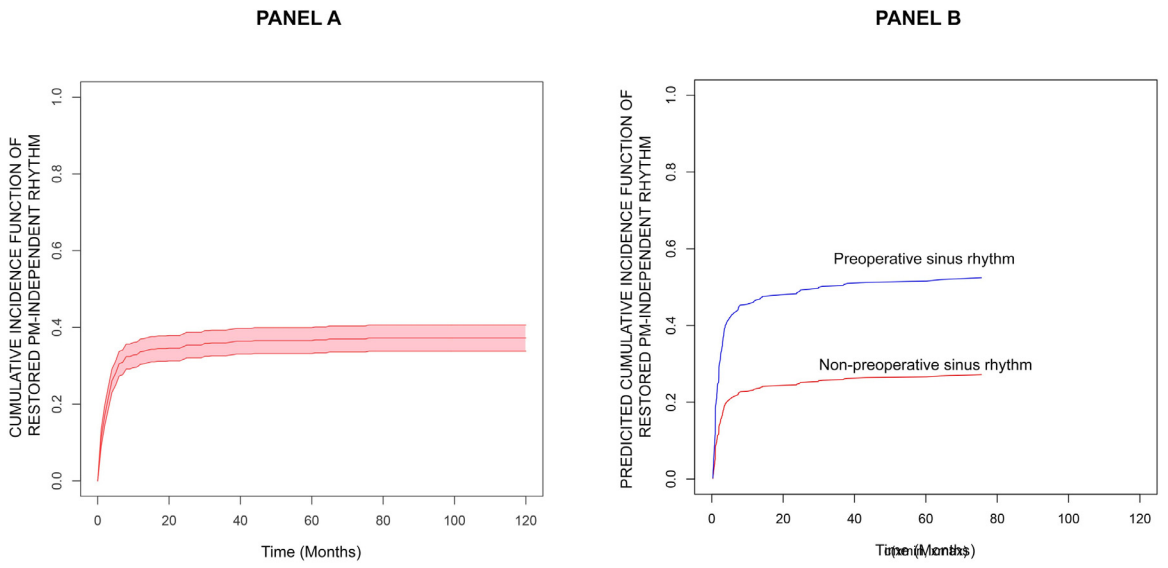

Figure 2. Panel A: CIFs of restored PM-independent rhythm at follow-up. More than 30% of patients with postoperative PPI recovered a PM-independent rhythm. Panel B: Adjusted cumulative incidence function of restored PM independent rhythm in patients with preoperative SR and non-preoperative SR.

cardiac structures,[10] and is reported in up to 16% in MVR.[11] Recently, Leyva and colleagues published the largest cohort of patients who underwent valvular surgery and focused on time to PPI after surgery during a follow-up of 10 years.[12] They found higher chances of PPI in AVR compared with MVR, with higher chances in multiple valve replacements.[12] Nevertheless, they did not look at PMD of the PPI patients at the long-term follow-up. In the current cohort, more than 30% of patients were PMI after 6 months follow-up. Interestingly, at 12-year follow-up, an additional 8% of patients were independent from pacemaker activity, suggesting that the rhythm recovery occurs mostly in the first 6 months rather than during the following years. Cumulative probabilities of PMI in patients with A/V block of 63% at 5 years and 30% at 10 years are described; also emphasizing a regression of PMD at long-term follow-up after surgery.[2] In our series, PPI occurred within the first months in almost 50% of patients. These data suggest that it should be possible to reduce rates of PPI by optimizing patient selection and by investigating predictors of PMD.

In our study, predictors of PMD in the long run were CABG and AVR. Although MVR may have higher

incidence of PPI in the early postoperative phase, SR recovery at the long run is more common in these groups. Indeed, PMI has been demonstrated in up to 40% of PPI patients after cardiac surgery at different time points.[5,8]

The pathophysiology of A/V conduction disturbances after cardiac surgery may be multifactorial, with direct injury of the conduction structures as the most frequent.[13] Interestingly, pathological examination of the conduction system in patients with A/V block after AVR showed "old" lesions which existed prior to the surgery and recent lesions attributed to mechanical compression of the conduction system.[14] In line with this, preexisting bundle branch block is an independent predictor of PPI in valvular surgery[15] as a result of high degree A/V block, further emphasizing the role of mechanical impact on the A/V conduction system.[16] Thus, in theory, preexisting lesions make patients prone to conduction disturbances, and the extent of accumulating lesions during surgery may (transiently) surpass the threshold above which A/V block persists postoperatively. This is further illustrated in the protective effect of normal SR prior to surgery in our study and in others[8] and the recovery of a large number of PPI patients during follow-up.

A novel finding in this study is the impact of PMD on survival. Although previous studies failed to show higher mortality in PPI patients, we demonstrate a survival benefit of restored rhythm in patients with PMI at follow-up. As well in general population, PPI patients with structural heart disease show greater mortality during follow-up compared with PPI patients without structural heart disease.[17] Also, as demonstrated by the DAVID trial, as the right ventricle pacing can increase morbidity and mortality at follow-up, absence of ventricular back-up pacing should be a potential explanation for the protective effect of the restored sinus rhythm in this study.[18] Furthermore, important predictors of long-term mortality in PPI patients in general population are age, cardiomyopathy and valvular heart disease[17] In our population, chronic renal failure and diabetes were important predictors of long-term mortality in PPI patients. Leyva et al[12] demonstrated higher chances of late PPI after valve surgery in patients with diabetes, renal impairment and heart failure. Notably, while PPI patients with sick sinus syndrome show better survival than those with high degree A/V block,[19] patients with atrial fibrillation at time of implant seem to have the worse outcomes.[20] These findings suggest that PMD may be a surrogate characteristic of specific underlying diseases such as cardiomyopathy and renal impairment, all of which may contribute to higher mortality.

Our study has several limitations. This is a multicenter retrospective study and, therefore, inherent limitation due to such data collection should be considered for result interpretation. No information was available on pacemaker indication, cardiac pacing or echocardiographics findings. The lack of pacemaker indication may have led to inclusion of some patients with paroxysmal atrial fibrillation and conversion pauses, making therefore the incidence and interpretation postoperative of A/V conduction recovery not fully appropriate. However, to our knowledge, this study represents the largest investigation assessing such a perioperative complication. PMD might also have been largely undetected based on different institutional policies for PPI-patient follow-up: however, all patients have been examined at the pacemaker outpatient clinic including reduced PM rate to disclose undergoing native heart rate. Post-discharge pharmacological therapy was also not completely available in the study population and, therefore, it might have impact on overall recovery and timing of reappearance of A/V conduction. Finally, complications related to PPI either at early or late stage were not completely collected, and, therefore, not available for data assessment and presentation

In conclusion, this study represents the largest data collection about PPI immediately after cardiac surgery and indicates that PPI incidence in such a setting is relatively low (around 1%). Our data confirmed that a high proportion of these patients (>40%) recover A/V conduction property, and this event occurs within months after PPI in most patients. PMD, however, was associated with higher mortality during prolonged follow-up. SR prior to surgery seems to have a protective effect on PMD after PPI.

Data availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Authors contribution

Roberto Lorusso: Conceptualization, Methodology, Investigation, Validation, Writing – original draft, Writing – Review and Editing, Visualization, Supervision. **Justine M. Ravaux**: Conceptualization, Methodology, Investigation, Validation, Writing – original draft, Writing – Review and Editing, Visualization, Supervision. **Elham Bidar**: Resources, Formal Analysis. **Fabio Barili**: Software, Formal Analysis, Data curation. **Kevin Vernooy**: Validation, Writing – Review and Editing. **Michele Di Mauro**: Software, Formal Analysis, Data curation. **Antonio Miceli**: Resources, Investigations. **Alessandro Parolari**: Resources, Investigations. **Andrea Daprati**: Resources, Investigations. **Veronika Myasoedova**: Resources, Investigations. **Francesco Alamanni**: Resources, Investigations. **Carlo De Vincentiis**: Resources, Investigations. **Ezio Aime'**: Resources, Investigations. **Francesco Nicolini**: Resources, Investigations. **GianLuca Gonzi**: Resources, Investigations. **Andrea Colli**: Resources, Investigations. **Gino Gerosa**: Resources, Investigations. **Michele De Bonis**: Resources, Investigations. **Gabriele Paglino**: Resources, Investigations. **Paolo Della Bella**: Resources, Investigations. **Guglielmo Actis Dato**: Resources, Investigations. **Egidio Varone**: Resources, Investigations. **Sandro Sponga**: Resources, Investigations. **Mauro Toniolo**: Resources, Investigations. **Alessandro Proclemer**: Resources, Investigations. **Ugolino Livi**: Resources, Investigations. **Giovanni Mariscalco**: Resources, Investigations. **Marzia Cottini**: Resources, Investigations. **Cesare Beghi**: Resources, Investigations. **Roberto Scrofani**: Resources, Investigations. **Davide Foresti**: Resources, Investigations. **Francesco Paolo Tritto**: Resources, Investigations. **Rosario Gregorio**: Resources, Investigations.**Emmanuel Villa**: Resources, Investigations. **Giovanni Troise**: Resources, Investigations. **Domenico Pecora**: Resources, Investigations. **Filiberto Serraino**: Resources, Investigations. **Federica Jiritano**: Resources, Investigations. **Francesco Rosato**: Resources,

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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