Significant mitral regurgitation after permanent right ventricular pacemaker implantation: prognostic implications

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Significant Mitral Regurgitation After Permanent Right Ventricular Pacemaker Implantation: Prognostic Implications

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The underlying mechanisms leading to the development of mitral regurgitation (MR) after right ventricular (RV) pacemaker (PM) implantation and its prognostic value have yet to be fully understood. The purpose of this study was to evaluate the prevalence and clinical variables associated with the development of MR after RV pacing and its association with outcomes. A total of 451 patients (mean age 69 ± 15 years, 61% male) who underwent de novo RV PM implantation were included. The development of significant MR, defined as ≥moderate from mild or none/trace at baseline, occurred in 131 (29%) patients at a median of 2.4 years (interquartile range: 1.0 to 3.8 years) after PM implantation. Multivariate logistic regression analysis demonstrated that implantation of a single-chamber PM, left ventricular end-systolic volume index, and the presence of mild MR (vs no MR) at baseline were independently associated with the development of significant MR post-implant. Cardiac events, defined as the composite of all-cause mortality or heart failure hospitalization, occurred in 143 patients (31.7%) during a median follow-up of 5.4 years (interquartile range: 3.0 to 8.1 years). Multivariate Cox regression analysis demonstrated that the development of significant MR was independently related to the occurrence of cardiac events. In conclusion, the development of significant MR after PM implantation is seen in about one-third of recipients and is independently associated with adverse cardiac events. **(Am J Cardiol 2024;222:78−86)**

Keywords: echocardiography, heart failure, mitral regurgitation, pacemaker, valvular disease

Right ventricular (RV) pacing is the standard of care for pathological bradycardia, with implantation rates of more than 1,000 per million population.[1,2] However, despite its symptomatic and survival benefits, left ventricular (LV) adverse remodeling and LV systolic dysfunction have been reported as unwanted effects of chronic RV pacing.[2,3] Furthermore, the development of severe mitral regurgitation (MR) is noted after permanent RV pacemaker (PM) implantation.[4,5] Loss of atrioventricular and interventricular synchrony and transient papillary muscle dysfunction secondary to ischemia caused by fast cardiac pacing, are believed to underlie the development of MR.[6] Not all recipients of RV pacemakers develop MR though, which raises the possibility that some patients are predisposed to this complication. A comprehensive assessment of the potential factors leading to the development of MR after PM implantation is required. In addition, the outcome implications of post-pacing MR are not well understood. Accordingly, the purpose of the present study was to evaluate the prevalence and clinical variables associated with the development of MR after permanent RV pacing, and the prognosis of patients who developed MR subsequent to permanent RV pacing.

Methods

Patients who underwent de novo RV PM implantation at the Leiden University Medical Centre, The Netherlands, between 2010 and 2020, were retrospectively included. Exclusion criteria were (1) previous mitral valve surgery or transcatheter edge-to-edge repair, (2) congenital heart disease, except for an atrial septal defect, (3) absence of transthoracic echocardiography within 1 year before or after PM implantation, (4) implantation of atrial or epicardial leads only, (5) conduction system pacing (His' bundle pacing, left bundle branch area pacing) or coronary sinus pacing, and (6) primary MR or MR severity ≥moderate before PM implantation. Indications for PM implantation were based on the European Society of Cardiology guidelines on cardiac pacing and resynchronization therapy.[1] Data on baseline patient clinical characteristics, PM characteristics, and settings were retrospectively collected from the departmental information system (EPD-vision; Leiden University Medical Center). The PM settings were individually tailored, based on the indication for and response to cardiac pacing. Patients were followed up and devices interrogated

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See page 85 for Declaration of Competing Interest.

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every 6 months or at the direction of the attending physician after implantation. The ventricular pacing rate documented within 6 months of implantation was used for the current analysis. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board. Because of the retrospective study design, the Medical Ethics Committee waived the requirement for written informed consent on a patient level.

All patients underwent transthoracic echocardiography with commercially available ultrasound equipment (Vivid 7, E9, or E95 GE-Vingmed, Horten, Norway) within 1 year before PM implantation and at least 1 echocardiogram during the first 5 years of follow-up. Electrocardiography-triggered echocardiographic data were digitally stored in cineloop format for offline analysis using EchoPAC version 204 (GE-Medical Systems, Horten, Norway). LV end-diastolic and end-systolic volumes, LV ejection fraction (EF), and left atrial (LA) volumes were measured using the Simpson's biplane method,[7] and LV and LA volumes were indexed to body surface area. LV global longitudinal strain was measured using the apical 4-chamber, 2-chamber, and long-axis views of the LV and expressed as absolute values.[8] RV function was quantified by tricuspid annular plane systolic excursion. Systolic pulmonary artery pressure was estimated as the sum of the right atrial pressure and the RV end-systolic pressure gradient. Right atrial pressure was estimated based on inferior vena cava diameter and collapse during inspiration.[9] The severity of MR and tricuspid regurgitation (TR) was assessed using a multiparametric approach according to the American Society of Echocardiography guidelines.[10] Significant MR and TR was defined as ≥moderate. Echocardiography was performed after PM implantation according to clinical indications, and we assessed all echocardiograms within 5 years of PM implantation. In patients with significant MR, follow-up echocardiography was defined as the first echocardiogram showing the development of ≥moderate MR, after having been documented to be mild or none/trace initially. In patients without development of significant MR within 5 years of follow-up, the last available echocardiogram was used for follow-up. We also assessed LV and LA volumes, LVEF, and right atrial area at follow-up echocardiography. Deterioration in LV systolic function was defined as a decrease in LVEF ≥10%[3] and LV adverse remodeling was defined as an increase in the LV end-diastolic volume index ≥20% from baseline. Furthermore, we assessed septal motion using 2-dimensional and M-mode images at follow-up echocardiography and defined septal flash as a pacing-induced abnormality of septal motion.

Study end points were defined as the composite of all-cause mortality or heart failure hospitalization after PM implantation. Survival data were collected from municipal civil registries linked to the medical records of the patient and were complete for all patients. Data on heart failure hospitalization were acquired from medical record review.

Categorical variables are expressed as numbers and percentages. Continuous data are presented as mean ± SD when normally distributed or as median and interquartile range (IQR) when non-normally distributed. Group differences were evaluated using Student *t* test or Mann-Whitney U for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Differences in echocardiographic variables between baseline and follow-up were evaluated using paired Student *t* tests between patients with and without the development of significant MR. Univariate and multivariate logistic regression analysis was performed to investigate the variables associated with the development of significant MR post-pacing. Cumulative, event-free survival rates were calculated using the Kaplan-Meier method, whereas the log-rank test was used to compare the risk of events between patients with and without the development of significant MR after pacing. Univariate and multivariate Cox regression analysis was used to identify variables associated with study end points. Variables with a p value <0.1 in the univariate analysis and a correlation factor <0.6 (to avoid multicollinearity) were included in the multivariate models. Incremental prognostic value of the development of significant MR was evaluated by the change in likelihood ratio chi-square value for nested models when added to models including LV systolic function deterioration or LV adverse remodeling for each clinical end point. All statistical analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, New York) and R software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). All p values were two-sided and values <0.05 were considered statistically significant.

Results

A total of 451 patients (mean age 69 ± 15 years, 61% male) were included (Figure 1). Baseline clinical characteristics of the total study population, stratified according to the development of significant MR, are listed in Table 1. High-degree atrioventricular block (76%) was the primary indication for PM implantation. Dual-chamber PMs were implanted in 370 (82%) patients and single-chamber PMs were implanted in 81 (18%) patients. Those with atrial fibrillation (AF) more often had single-chamber PM implantation performed. Baseline echocardiographic variables of the study population are listed in Table 2. The mean LVEF was 58 ± 11% and 370 (82%) patients had LVEF ≥50% at baseline.

The development of significant MR occurred in 131 (29%) patients at a median of 2.4 years (IQR: 1.0 to 3.8 years) after PM implantation (Table 2). Those who developed significant MR after pacing were older, and more often had AF and a history of aortic valve replacement, compared with patients without the development of significant MR. Implantation of single-chamber PMs was more common and the ventricular pacing rate was higher in patients who developed significant MR. Baseline LV and LA volumes were significantly greater in patients in whom significant MR developed, compared with those without. The prevalence of mild MR and significant TR before pacing was also higher in patients who developed significant MR, as compared with those who did not. Multivariate logistic regression analysis demonstrated that implantation of a single-chamber PM, LV end-systolic volume index, and the presence of mild MR at baseline, were independently associated with the development of significant MR after PM implantation (Table 3; Graphical Abstract).

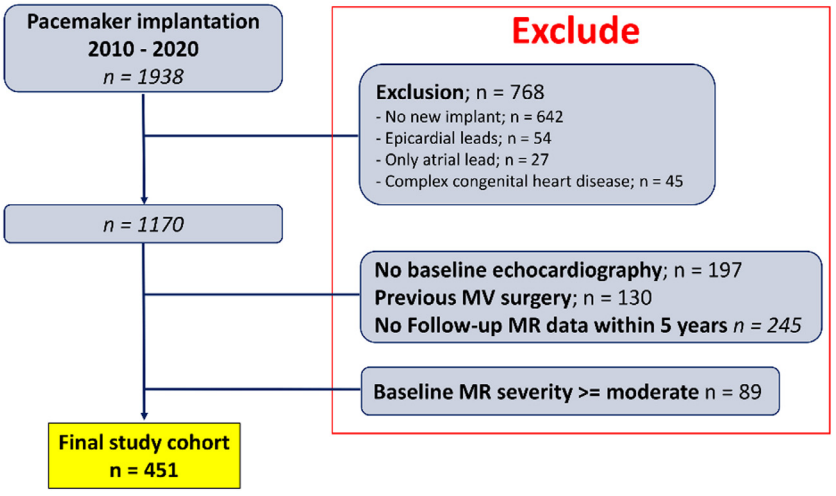

Figure 1. Patient flow.
MR = mitral regurgitation; MV = mitral valve, PM = pacemaker.

At follow-up echocardiography, the LV end-diastolic volume index, the LA volume index, and the right atrial area were greater, and the LVEF lower, after PM implantation in patients who developed significant MR, compared with those who did not (Figure 2). Regarding the change in echocardiographic parameters from baseline to follow-up, the LV end-diastolic volume index and the LA volume index were more increased and the LVEF was more decreased in patients who developed significant MR, as compared with those without. ($p < 0.001$, respectively) Septal flash was observed in 63 (14.1%) patients. Furthermore, septal flash was observed more frequently in patients who developed significant MR than in those who did not (28% vs 8.1%, $p < 0.001$).

Combined end points occurred in 143 (31.7%) patients and all-cause death occurred in 110 (24.3%) patients during a median follow-up of 5.4 years (IQR: 3.0 to 8.1 years) after PM implantation. Patients who developed significant MR after PM implantation had a significantly higher risk of death or heart failure hospitalization, compared with those who did not develop significant MR (Figure 3). Similarly, patients who developed significant MR after PM implantation had a significantly higher risk of all-cause death alone (Figure 3). Multivariate Cox regression analysis

Table 1
Baseline patient characteristics

Variables	Overall N = 451	Development significant MR (-) N = 320	Development significant MR (+) N = 131	p-value
Age, years	69 (15)	68 (15)	74 (12)	**<0.001**
Gender, male	276 (61%)	200 (62%)	76 (58%)	0.375
Diabetes mellitus	76 (17%)	51 (16%)	25 (19%)	0.418
Arterial hypertension	238 (53%)	159 (50%)	79 (60%)	0.040
Dyslipidemia	131 (29%)	92 (29%)	39 (30%)	0.828
Atrial fibrillation	193 (43%)	120 (38%)	73 (56%)	**<0.001**
Previous myocardial infarction	75 (17%)	46 (14%)	29 (22%)	**0.044**
History of aortic valve replacement	118 (26%)	66 (21%)	52 (40%)	**<0.001**
Beta-blocker	153 (34%)	87 (27%)	66 (50%)	**<0.001**
ACEI or ARB	206 (46%)	134 (42%)	72 (55%)	**0.011**
Loop diuretics	85 (19%)	46 (14%)	39 (30%)	**<0.001**
Pacemaker indication				0.215
Atrioventricular block	344 (76%)	239 (75%)	105 (80%)	
Sick sinus syndrome	107 (24%)	81 (25%)	26 (20%)	
Pacemaker type				**<0.001**
Single-chamber	81 (18%)	40 (12%)	41 (31%)	
Dual-chamber	370 (82%)	280 (88%)	90 (69%)	
Ventricular pacing rate (%)	22 [1, 98]	13 [0, 98]	34 [3, 98]	**0.021**
Groups stratified by pacing rate				0.056
<20%	219 (49%)	167 (52%)	52 (40%)	
20% - 79%	71 (16%)	48 (15%)	23 (18%)	
≥80%	159 (35%)	104 (33%)	55 (42%)	

Values are expressed as mean (SD) or median (25% to 75%).
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MR = mitral regurgitation.

Table 2
Baseline echocardiographic parameters

Variables	Overall N = 451	Development significant MR (-) N = 320	Development significant MR (+) N = 131	p-value
LVEDVI (mm/cm2)	43 (15)	42 (14)	46 (18)	0.064
LVESVI (mm/cm2)	19 (10)	18 (9)	21 (13)	**0.024**
LVEF (%)	58 (11)	59 (11)	57 (12)	0.074
LVEF ≥ 50%	370 (82%)	267 (83%)	103 (79%)	0.227
LAVI (ml/cm2)	35 (15)	33 (14)	39 (15)	**<0.001**
LVGLS (%)	14.9 (4.3)	15.2 (4.2)	14.2 (4.3)	**0.037**
MR grade				**<0.001**
None/trace	300 (67%)	240 (75%)	60 (46%)	
mild	151 (33%)	80 (25%)	71 (54%)	
E wave (cm)	79 (29)	77 (28)	84 (31)	**0.030**
A wave (cm)	78 (30)	75 (28)	85 (33)	**0.024**
E/e prime (cm)	11.3 (6.1)	10.8 (5.9)	12.3 (6.4)	0.055
RA area (mm)	18.4 (6.1)	17.8 (5.8)	19.7 (6.6)	**0.005**
TAPSE (mm)	18.9 (4.8)	19.3 (4.9)	17.9 (4.5)	**0.003**
Significant TR	67 (15%)	36 (11%)	31 (24%)	**<0.001**
PAP (mmHg)	27 (11)	26 (10)	30 (11)	**<0.001**
RAP (mmHg)	4.3 (3.1)	4.3 (3.1)	4.5 (3.2)	0.550

Values are expressed as mean (SD).

LAVI = left atrial volume index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; LVGLS = left ventricular global longitudinal strain; MR = mitral regurgitation; PAP = pulmonary artery pressure; RA = right atrial; RAP = right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

demonstrated that the development of significant MR, LV systolic dysfunction, age, male gender, and diabetes mellitus were independently associated with all-cause death or heart failure hospitalization (Table 4). Despite the development of significant MR after PM implantation was significantly associated with all-cause death alone on univariate analysis, it did not remain significantly associated with all-cause death on the multivariate analysis after correcting for significant covariates (Supplementary Table 1). The development of MR had significant incremental prognostic value over multivariate models (including a deterioration in LV systolic

Table 3
Logistic regression analysis for development of significant mitral regurgitation

	Univariable analysis			Multivariable analysis		
Variables	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Age, years	1.04	1.02, 1.05	<0.001	1.02	1.00, 1.05	0.088
Gender, male	0.83	0.55, 1.26	0.375	-	-	-
Diabetes mellitus	1.24	0.72, 2.09	0.418	-	-	-
Arterial hypertension	1.54	1.02, 2.33	0.041	1.45	0.86, 2.46	0.160
Dyslipidemia	1.05	0.67, 1.63	0.828	-	-	-
Atrial fibrillation	2.10	1.39, 3.18	<0.001	1.63	0.95, 2.79	0.075
Previous myocardial infarction	1.69	1.00, 2.83	0.046	1.44	0.75, 2.75	0.269
History of aortic valve replacement	2.53	1.63, 3.95	<0.001	1.76	0.97, 3.19	0.061
Single-chamber PM (vs dual-chamber PM)	3.19	1.94, 5.25	<0.001	2.30	1.19, 4.45	**0.013**
Baseline echo parameters						
LVEDVI (ml/cm2)	1.01	1.00, 1.03	0.040	-	-	-
LVESVI (ml/cm2)	1.03	1.01, 1.05	0.010	1.05	1.02, 1.08	**0.003**
LVEF (%)	0.98	0.96, 1.00	0.065	-	-	-
LAVI (ml/cm2)	1.03	1.01, 1.04	<0.001	1.01	0.99, 1.03	0.485
LVGLS (%)	0.95	0.90, 1.00	0.037	1.05	0.98, 1.13	0.203
MR grade mild (vs none/trace)	3.55	2.32, 5.46	<0.001	2.45	1.48, 4.05	**<0.001**
RA area (mm)	1.05	1.02, 1.09	0.003	-	-	-
TAPSE (mm)	0.94	0.90, 0.98	0.005	0.97	0.91, 1.02	0.245
Significant TR	2.44	1.43, 4.16	0.001	1.65	0.86, 3.16	0.129
RAP (mmHg)	1.02	0.95, 1.09	0.548	-	-	-
Ventricular pacing rate (%)	1.00	1.00, 1.01	0.064	1.07	1.00, 1.01	0.656

CI = confidence interval; LAVI = left atrial volume index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; LVGLS = left ventricular global longitudinal strain; MR = mitral regurgitation; PM = pacemaker; RA = right atrial; RAP = right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

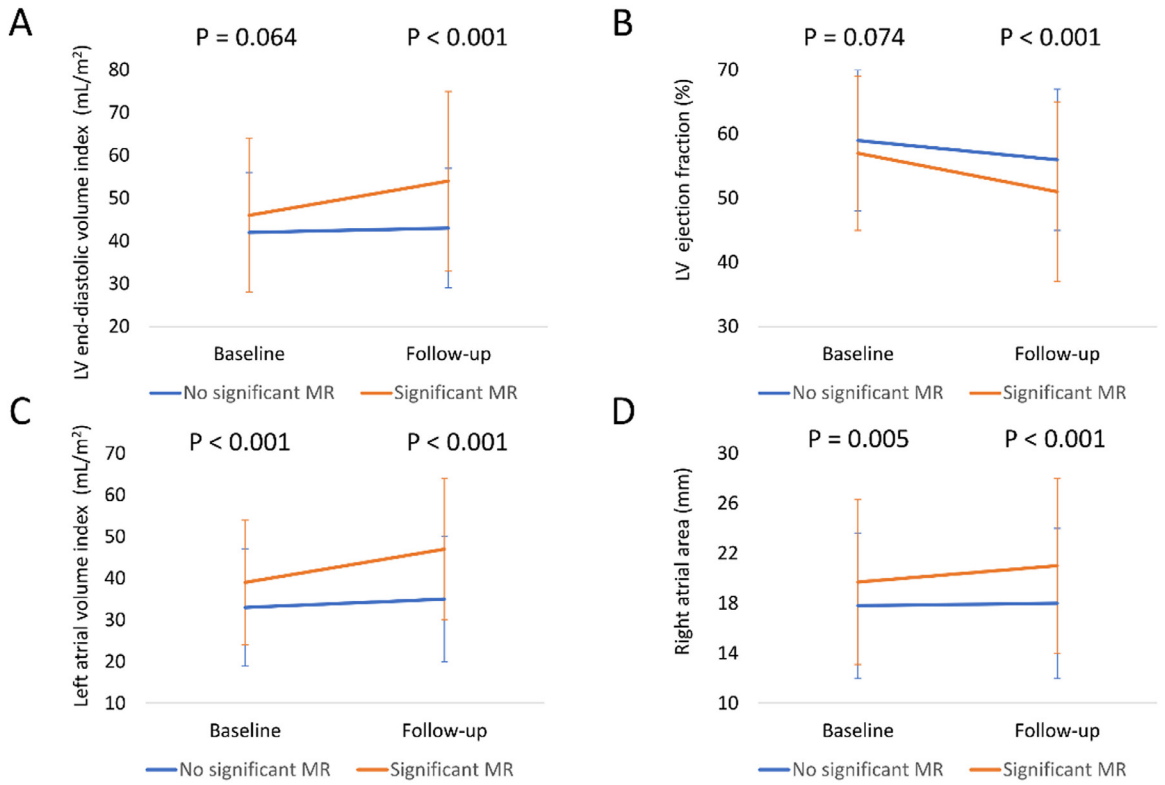

Figure 2. Change in echocardiographic parameters between baseline and follow-up.
Left ventricular (LV) end-diastolic volume index (*A*) and left atrial volume index (*C*) were more significantly increased and LV ejection fraction (*B*) was more significantly decreased after pacemaker implantation in patients with significant MR than in those without. No significant differences were shown in changes in right atrial area (*D*) between patients with and without significant MR.

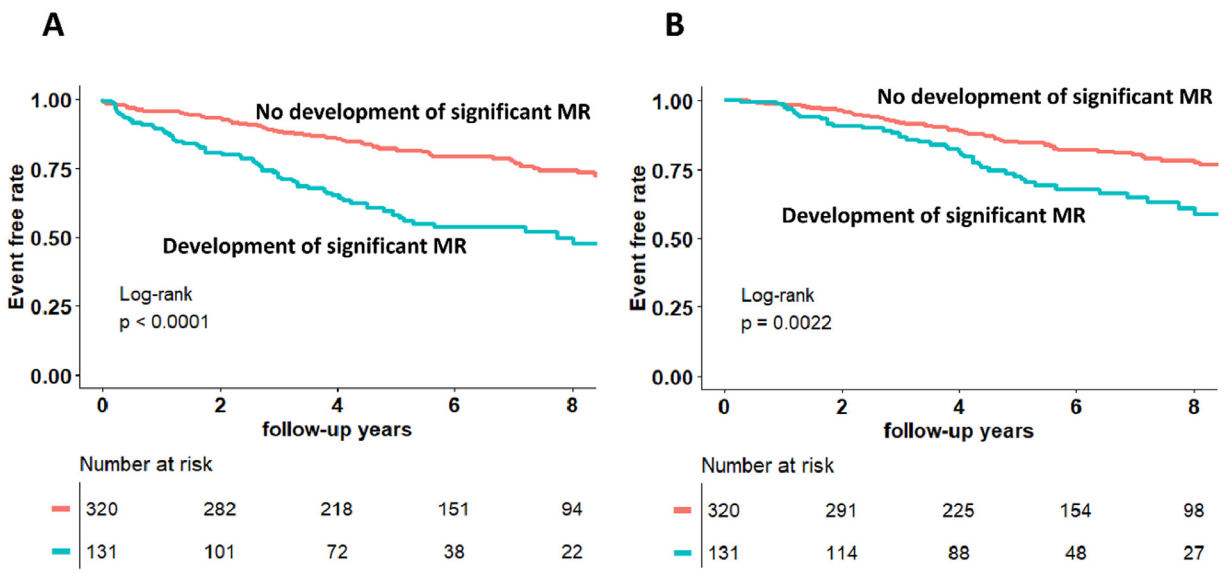

Figure 3. Kaplan-Meier curves.
Kaplan-Meier curves for the composite end point (*A*) and all-cause death (*B*).

function, p = 0.008 and adverse LV remodeling, p = 0.016) for all-cause death or heart failure hospitalization (Figure 4). Conversely, the development of significant MR showed no significant incremental value over the multivariate model for all-cause death alone (Figure 4).

Discussion

The main findings of the present study may be summarized as follows: (i) development of significant MR was seen in 131 (29%) patients after PM implantation, (ii) single-chamber PMs, greater LV end-systolic volume index

Table 4
Cox regression analysis for composite end points

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	p-value	HR	95% CI	p-value
Age, years	1.06	1.04, 1.08	<0.001	1.06	1.04, 1.08	**<0.001**
Gender, male	1.35	0.96, 1.92	0.088	1.55	1.02, 2.35	**0.039**
Diabetes mellitus	1.87	1.27, 2.77	0.002	1.65	1.05, 2.60	**0.029**
Arterial hypertension	1.39	1.00, 1.94	0.051	0.76	0.52, 1.10	0.146
Dyslipidemia	1.15	0.80, 1.65	0.457	-	-	-
Atrial fibrillation	1.74	1.25, 2.42	0.001	1.26	0.84, 1.91	0.262
Previous myocardial infarction	2.19	1.49, 3.23	0.000	1.50	0.97, 2.33	0.071
History of aortic valve replacement	1.42	0.99, 2.04	0.058	0.70	0.44, 1.10	0.123
Single-chamber PM (vs dual-chamber PM)	2.72	1.86, 3.97	<0.001	1.52	0.95, 2.44	0.081
Baseline echo parameters						
LVEDVI (ml/cm2)	1.00	0.99, 1.01	0.554	-	-	-
LVESVI (ml/cm2)	1.01	1.00, 1.03	0.064	1.00	0.98, 1.02	0.957
LVEF (%)	0.98	0.97, 1.00	0.019	-	-	-
LAVI (ml/mm2)	1.03	1.01, 1.04	0.000	1.01	0.99, 1.02	0.346
LVGLS (%)	0.90	0.86, 0.94	0.000	0.96	0.91, 1.01	0.099
MR grade mild (vs none)	1.31	0.93, 1.85	0.119	-	-	-
RA area (mm)	1.03	1.00, 1.06	0.028	-	-	-
TAPSE (mm)	0.94	0.91, 0.98	0.002	0.96	0.92, 1.01	0.100
Significant TR	1.39	0.90, 2.16	0.142	-	-	-
RAP (mmHg)	1.04	0.99, 1.09	0.105	-	-	-
Ventricular pacing rate (%)	1.01	1.00, 1.01	0.002	1.00	1.00, 1.01	0.275
Follow-up echo data						
Development significant MR	2.34	1.68, 3.27	0.000	1.57	1.04, 2.37	**0.031**
LV dysfunction (LVEF decrease ≥10%)	1.79	1.28, 2.51	0.001	1.62	1.12, 2.35	**0.011**

CI = confidence interval; HR = hazard ratio; LAVI = left atrial volume index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; LVGLS = left ventricular global longitudinal strain; MR = mitral regurgitation; PM = pacemaker; RA = right atrial; RAP = right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

and the presence of mild MR at PM implantation were independently associated with the development of significant MR after implantation, (iii) the development of significant MR was independently associated with all-cause death and heart failure hospitalization and (iv) the development of significant MR had incremental prognostic value over LV systolic dysfunction and adverse remodeling after PM implantation.

The development of significant MR after RV pacing occurred in almost a third (29%) of patients in the present study, which is consistent with two previous reports, where worsening MR was observed in 27.6% and 23.5% of patients with RV leads, respectively.[11,12] In the present study, greater LV end-systolic volume index and the presence of mild MR at PM implantation, and single-chamber PMs, were independently associated with the development of significant MR. Greater LV end-systolic volume index implies LV enlargement and systolic dysfunction. Impairment of leaflet coaptation and papillary muscle displacement through adverse LV remodeling are common mechanisms of secondary MR in general.[13] Reduced strength of the mitral valve closing force because of LV systolic dysfunction also contributes to the development of secondary MR.[13] These mechanisms could explain why greater LV end-systolic volume index portends the development of MR after PM implantation. The nature of the progression of secondary MR, and the factors influencing the process, are still incompletely understood. In a study of 257 patients with severe, secondary MR, Layoun et al[14] identified 2 clusters of progressive, secondary MR, namely: (1) with larger LV volumes and impaired systolic function, with a slower progression toward severe MR and (2) with smaller LV volumes, more preserved systolic function and a more rapid progression toward severe MR. MR was more proportionate in cluster 1, compared with cluster 2. Most patients in our study have a profile compatible with "cluster 2", that is, with smaller LV volumes and more preserved systolic function at baseline when RV pacing was instituted. Adaptive MV leaflet growth was found to be deficient in "cluster 2" in the study by Layoun and is likely to be deficient in PM recipients as well, because the insult causing MR progression is acute (i.e., PM implantation), which will not allow chronic leaflet area adaptation. Severe MR in the presence of single-chamber RV pacing has been documented to improve after upgrading to a dual-chamber device and/or adjustment of the atrioventricular interval.[6] Atrioventricular dyssynchrony or an inappropriate atrioventricular interval which is related to single-chamber pacing, may serve as a mechanism for the development of MR.[5,6] Single-chamber pacing was independently associated with the development of MR in the present study, which could serve as a surrogate marker for atrioventricular dyssynchrony. An additional mechanism that could link single-chamber PMs with the development of MR, is AF. AF contributes to atrial functional MR by adverse LA remodeling.[15] Single-chamber PMs have been associated with a higher frequency of new-onset AF, compared with dual-chamber PMs, making the pathophysiological link between

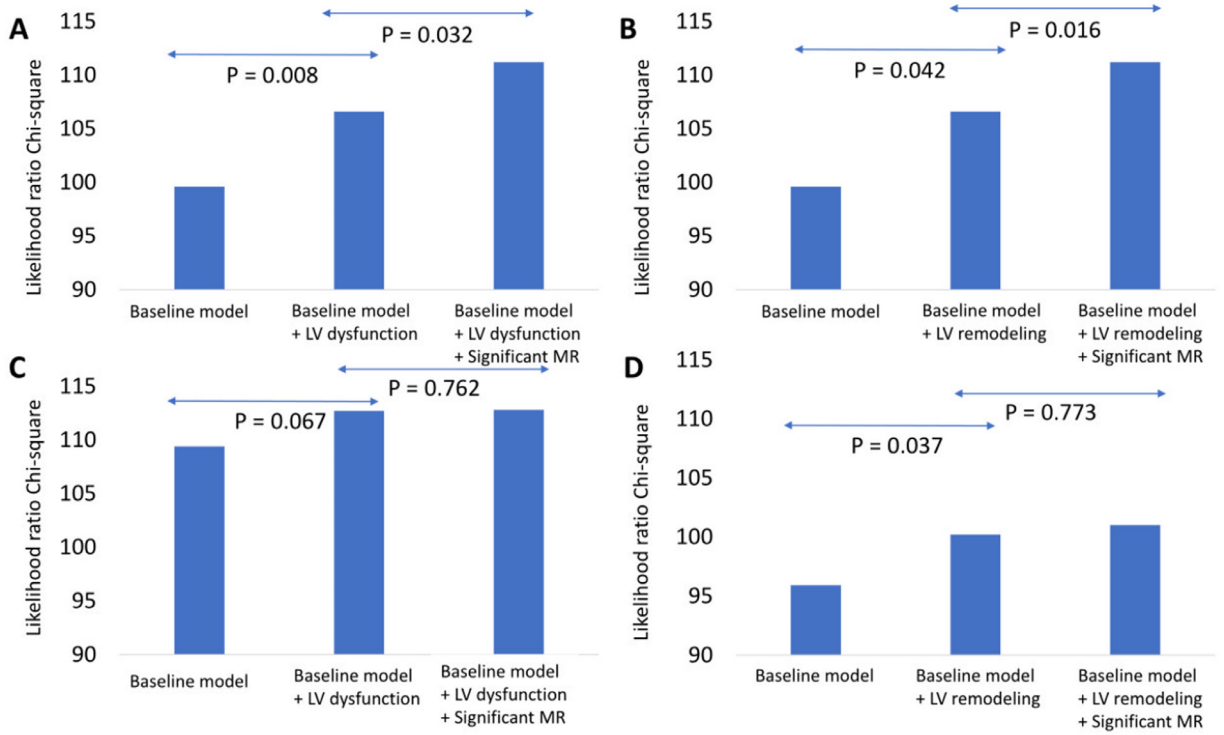

Figure 4. Incremental prognostic value of development of significant mitral regurgitation Development of significant mitral regurgitation (MR) had incremental prognostic value over multivariate model including left ventricular (LV) dysfunction (a decrease in LV ejection fraction ≥10%) (*A*) or LV remodeling (an increase in the LV end-diastolic volume index ≥20%) from baseline (*B*) for composite end points. However, no significant incremental prognostic value of the development of significant MR was demonstrated over LV dysfunction (*C*) or LV remodeling (*D*) for all-cause death. Baseline model for each end point included the variables were p value <0.1 in univariate Cox regression analysis.

single-chamber pacing and AF bidirectional.[1] LV dyssynchrony is often accepted as a mechanism for development after implantation. This concept was experimentally demonstrated by Maurer et al,[4] who showed that the degree of MR was more severe with RV apical pacing than with coronary sinus pacing in a canine model. Clinical evidence linking LV dyssynchrony to the development of MR, however, is limited. Only one study has reported worsening MR in patients with a higher percentage of RV pacing than in those with lower percentage of RV pacing,[11] but this association was not verified to be independent. In the present analysis, the ventricular pacing rate was higher in patients who developed MR but was not independently associated with the development of MR. It therefore appears that LV dyssynchrony, of which ventricular pacing rate is a surrogate, is of less importance for the development of MR when compared with the LV end-systolic volume index, preexisting MR, and atrioventricular dyssynchrony.

The present study is the first to demonstrate that the development of MR after PM implantation is independently associated with heart failure hospitalization and all-cause mortality. Secondary MR in general, is a well-established risk factor for heart failure hospitalization and all-cause mortality, irrespective of LV systolic function.[13,16] Therefore, it is not surprising that the development of MR translates into a worse prognosis in patients with permanent RV pacing. Notably, significant post-pacing MR has incremental prognostic value over LV systolic dysfunction and adverse LV remodeling, both of which have been individually related to adverse cardiac events.[17–19] On the other hand, although the development of MR was associated with all-cause death on univariate analysis, this association did not persist in multivariate analysis in the present study. In a study of >1400 patients who underwent PM implantation, Cho et al[19] found that pacing-induced cardiomyopathy was independently associated with cardiovascular death and heart failure hospitalization, but not with all-cause death. Non-cardiovascular deaths have become more common in patients with heart failure over the past two decades, primarily because of improved survival with modern heart failure therapy. The development of significant MR after PM implantation therefore also likely does not represent a prominent cause of all-cause mortality in heart failure patients.[20]

Cardiac resynchronization therapy or conduction pacing system, such as His' bundle or left bundle area pacing, has demonstrated superiority over conventional PMs in patients with preexisting LV systolic dysfunction.[21,22] Conduction system pacing or biventricular pacing may therefore prove to be the first choice in patients with baseline LV enlargement or the presence of mild MR, which are variables associated with the development of significant post-pacing MR, although prospective data are still required. Careful, periodic assessment may be indicated in patients who receive RV PMs and are at high risk of developing pacing-induced MR, that is, with mild MR or an enlarged LV at baseline. Single-chamber pacing is probably best avoided in its entirety in most patients. Since MR due to PM is potentially

reversible, consideration should be given to upgrading to cardiac resynchronization therapy or conduction system pacing in patients who have developed significant MR after PM implantation.[23,24] As a last resort, mitral valve transcatheter edge-to-edge repair may be effective in mitigating the impact of MR in patients who are unresponsive to resynchronization.[25]

The present study had a retrospective, single-center, observational design. Because echocardiographic follow-up was performed at the discretion of the attending physician, selection bias cannot be excluded. No distinction could be made between cardiac and noncardiac mortality because the specific cause of death is not systematically recorded in the database used.

In conclusion, the development of significant MR was observed in 131 (29%) patients after permanent RV PM implantation. The development of significant post-pacing MR was independently associated with the composite of all-cause death and heart failure hospitalization. Single-chamber PM implantation, and baseline LV end-systolic volume index, and mild MR before PM implantation, were independently associated with the development of significant MR. Single-chamber PM is probably best avoided altogether, whereas alternative pacing strategies, for example, conduction system pacing, rather than RV pacing, may be warranted in patients with increased LV size and mild MR at baseline.

Declaration of competing interest

Nina Ajmone Marsan received speaker fees from Abbott Vascular and GE Healthcare. Jeroen J. Bax received speaker fees from Abbott Vascular, Edwards Lifesciences, and Omron. The remaining authors have no competing interests to declare.

CRediT authorship contribution statement

Takeru Nabeta: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xavier Galloo:** Methodology, Data curation, Conceptualization. **Laurens Tops:** Writing – review & editing, Supervision. **Jan Stassen:** Methodology, Data curation. **Nina Ajmone Marsan:** Writing – review & editing, Supervision. **Pieter van der Bijl:** Writing – review & editing, Supervision. **Jeroen J Bax:** Writing – review & editing, Supervision, Resources, Conceptualization.

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Supplementary materials

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