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ORIGINAL ARTICLE

Significant mitral regurgitation as a predictor of long-term prognosis in patients receiving cardiac resynchronisation therapy

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Abstract

Background: Cardiac resynchronisation therapy (CRT) has been shown to reduce functional mitral regurgitation, although the relationship between significant mitral regurgitation (SMR) and the clinical prognosis of CRT remains uncertain.

Aim: We sought to investigate the association of baseline SMR with long-term outcomes in patients undergoing CRT.

Methods: A total of 296 consecutive patients undergoing CRT were enrolled. SMR was quantified by colour Doppler in all patients at baseline and defined as level ≥ 3 on the severity scale. The primary endpoints included all-cause death, heart failure hospitalisation (HFH), and heart transplantation, and the secondary endpoints were response to CRT and New York Heart Association (NYHA) class III or IV six months after CRT implantation.

Results: The mean age was 59 ± 11 years, and 202 (68.2%) patients were male. Among all patients, 124 (41.9%) presented with baseline SMR. Over a mean follow-up of 4.17 ± 3.16 years, there were 53 (17.9%) cases of all-cause death, 41 (13.8%) cases of HFH, and four (1.4%) cases of heart transplantation. SMR was positively associated with primary endpoint events (hazard ratio [HR] 1.602, 95% confidence interval [CI] 1.083–2.371, $p = 0.019$), HFH (HR 3.567, 95% CI 1.763–7.219, $p < 0.001$) and NYHA class III or IV (HR 2.101, 95% CI 1.313–3.363, $p = 0.002$). After adjusting for multiple factors, we found that SMR (HR 1.785, 95% CI 1.091–2.920, $p = 0.021$), ischaemic heart disease (HR 1.628, 95% CI 1.062–2.494, $p = 0.025$), and the lack of use of spironolactone (HR 2.044, 95% CI 1.040–4.017, $p = 0.038$) were independent predictors of primary endpoints, and SMR remained an independent predictor of HFH (HR 4.622, 95% CI 1.955–10.923, $p < 0.001$).

Conclusions: Significant mitral regurgitation before CRT implantation was strongly associated with long-term poor prognosis. SMR was positively associated with HFH rather than all-cause death and CRT response.

Key words: cardiac resynchronisation therapy, significant mitral regurgitation, heart failure

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INTRODUCTION

Heart failure (HF) is a progressive disease with high morbidity and prevalence [1]. Functional mitral regurgitation (FMR) is the most common valvular heart disorder among HF patients [2, 3]. A quarter of hospitalised patients with HF present at least a minimal amount of significant mitral regurgitation (SMR), and more than half of them suffer from moderate to severe FMR at baseline [4, 5]. Left ventricular remodelling and ventricular systolic dyssynchrony have been shown to be the pathophysiological processes in HF patients with FMR [6].

Cardiac resynchronisation therapy (CRT) improves life quality and survival rate among advanced HF patients with ventricular dyssynchrony [7, 8]. It has been shown that CRT efficiently reduces SMR in HF patients [9–11]. However, whether SMR can effectively predict the long-term quality of life and mortality in CRT candidates remains inconclusive and requires further study.

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METHODS

A total of 316 consecutive participants with CRT pacemaker (CRT-P) or defibrillator (CRT-D) were enrolled in our study from March 2001 to January 2016 in the Arrhythmia Centre of Fuwai Hospital. Inclusion criteria were in accordance with guidelines for CRT-P/D implantation [12]. Before device implantation, all patients had already been on maximum optimal medical therapy for at least three months. Seven patients were excluded due to age < 18 years old, primary mitral regurgitation, or pregnancy. Thirteen patients were lost during the follow-up period. Overall, a total of 296 patients were enrolled. Ischaemic heart disease (IHD) was defined as cardiomyopathy with impaired contractile performance and a history of myocardial infarction. Intervention treatments included percutaneous coronary intervention, coronary artery bypass grafting, or clear evidence of coronary stenosis (more than 75%) [13].

The study was approved by the Institutional Review Board of Fuwai Hospital and complied with the Declaration of Helsinki. Informed consent was obtained from all participants.

Device therapy

Technical aspects of lead and device implantation are briefly described. The coronary sinus was cannulated from the left subclavian and/or cephalic entry site using a commercially available long, peelable guiding sheath. The left ventricular (LV) lead was positioned preferably in the lateral or posterolateral vein. The right atrial and right ventricular (RV) leads were placed regularly at the right atrial appendage and the RV apex, respectively. For patients with permanent atrial fibrillation, only RV and LV leads were implanted, plugging the atrial port and programming the generator to a ventricular-triggered mode. Ablation of atrioventricular junction was not performed in any patient. All procedures were performed under local anaesthesia.

Echocardiography, biochemistry, and programming

Fasting venous blood samples and the test results of N-terminal pro-B-type natriuretic peptide (NT-proBNP) were collected from each patient on the day before CRT device implantation. Two independent certificated sonographers performed two-dimensional echocardiography (Vivid 7 Dimension/Pro System, GE Healthcare, Chalfont St. Giles, Bucks, UK) to assess the level of FMR, LV end-systolic diameter (LVESD), LV end-diastolic diameter (LVEDD), LV end-systolic volume (LVESV), and LV ejection fraction (LVEF) according to modified Simpson's rule on the day before device implantation. The severity of FMR was classified into four levels: mild — grade 1 (jet area/left atrial area < 20%), moderate — grade 2 (jet area/left atrial area 20%–30%), moderately severe — grade 3 (jet area/left atrial area 30%–40%), and severe — grade 4 (jet area/left atrial area > 40%) [14]. SMR was defined as level ≥ 3 according to colour Doppler in all the patients at baseline.

For optimisation, patients in sinus rhythm underwent transmitral Doppler-derived optimisation of atrioventricular delay using an iterative technique [15] prior to discharge and at every scheduled visit thereafter. V-V delay ranged from 0 to 40 ms, according to the standard of the shortest biventricular paced QRS duration.

Follow-up and assessment of endpoints

Baseline electrocardiography and clinical assessment were collected via Hospital Information System. All patients underwent regular follow-up via outpatient clinical visits or telephone interviews. Physicians from Fuwai Hospital assessed the events. All the physicians were blinded to the results of FMR levels and patients' clinical data, and independently judged the clinical events.

Primary endpoints were all-cause death, heart transplantation, and HF hospitalisation (HFH). If episodes of HFH occurred more than once, only the first hospitalisation was recorded.

Secondary endpoints included: response to CRT and New York Heart Association (NYHA) functional class III or IV six months after CRT implantation; response to CRT was defined as > 15% decrease of LVESV after six months [16]. Patients who died or underwent heart transplantation within six months after implantation were regarded as non-responders.

Statistical analysis

All data were processed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD) and compared using the independent samples t test. Categorical data were summarised as frequencies and percentages and were compared using the χ^2 test. The Kaplan-Meier method with log-rank test was used to analyse the survival of patients free from endpoint events. Univariable binary logistic and Cox regression analyses were used to determine predictors of the primary and secondary endpoints, respectively. Multivariate regression analysis with stepwise selection method was performed to control potentially confounding demographic, echocardiographic and clinical variables. A two-sided p value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The participants were divided into an SMR group and a non-SMR group. The mean age of study cohort was 59 ± 11 years. Of the enlisted patients, 202 (68.2%) were male, 43 (14.5%) had atrial fibrillation, 251 (84.8%) had left bundle branch block, 143 (48.3%) had CRT-D, and 63 (21.3%) patients had IHD. Overall, 69 (23.3%) patients were NYHA class II, 174 (58.8%) were NYHA class III, and 50 (16.9%) were NYHA class IV. The mean LVEDD was 70.39 ± 9.40 mm, LVESD was 60.43 ± 24.96 mm, and LVEF was 29.02% ± 7.88%. Patients in the SMR

Table 1. Baseline characteristics of patients with and without significant mitral regurgitation (SMR)

Variables	Overall	Non-SMR	SMR	p
Number of patients	296	172	124	
Age [years]	59 ± 11	59 ± 11	58 ± 11	0.784
Male sex	202 (68.2%)	121 (70.3%)	81 (65.3%)	0.359
CRT-D	143 (48.3%)	76 (44.2%)	67 (54%)	0.094
IHD	63 (21.3%)	41 (23.8%)	22 (17.7%)	0.206
AF	43 (14.5%)	23 (13.4%)	20 (16.1%)	0.507
LBBB	251 (84.8%)	143 (83.1%)	108 (87.1%)	0.350
NYHA class:				
II	69 (23.3%)	57 (33.1%)	12 (9.7%)	< 0.001
III	174 (58.8%)	90 (52.3%)	84 (67.7%)	0.008
IV	50 (16.9%)	23 (13.4%)	27 (21.8%)	0.057
Initial QRS width [ms]	160.76 ± 19.44	159.27 ± 19.25	162.84 ± 19.58	0.119
LVEDD [mm]	70.39 ± 9.40	68.79 ± 9.30	72.60 ± 9.12	0.001
LVESD [mm]	62.43 ± 24.96	60.69 ± 28.35	64.82 ± 19.28	0.308
LVEF [%]	29.02 ± 7.88	30.30 ± 7.77	27.25 ± 7.71	0.001
LVESV [mL]	189.72 ± 65.24	167.43 ± 71.25	194.64 ± 60.37	0.210
NT-proBNP [pg/mL]	1893.72 ± 1555.59	1537.48 ± 1384.11	2382.62 ± 1649.87	< 0.001
ACEI/ARB	231 (78.0%)	147 (85.5%)	84 (67.7%)	< 0.001
β-blockers	265 (89.5%)	153 (89.0%)	112 (90.3%)	0.704
Amiodarone	68 (23.0%)	39 (22.7%)	29 (23.4%)	0.886
Spironolactone	274 (92.6%)	162 (94.2%)	112 (90.3%)	0.211

Data presented as number (percentage) or mean ± standard deviation. NT-proBNP was measured in 223 patients. ACEI — angiotensin converting enzyme inhibitor; AF — atrial fibrillation; ARB — angiotensin receptor blockers; CRT-D — cardiac resynchronisation therapy with a defibrillator; IHD — ischaemic heart disease; LBBB — left bundle branch block; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; LVESD — left ventricular end-systolic diameter; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association functional classification

group tended to have worse cardiac function, larger LVEDD, higher NT-proBNP, and less often used angiotensin converting enzyme inhibitor/angiotensin receptor blockers (ACEI/ARB) (Table 1).

Clinical outcomes

Mean follow-up period was 4.17 ± 3.16 years, and it was completed by 296 patients. There were 53 (17.9%) cases of all-cause death, 41 (13.8%) cases of HFH, and four (1.4%) cases of heart transplantation. Among deceased patients, 29 (9.8%) died of HF, sudden death occurred in 12 (4.1%) patients, and 12 (4.1%) patients died of non-cardiac causes, such as car accident and fatal stroke (Fig. 1).

At the six-month follow-up, a total of 129 patients had a decrease of at least one FMR level from the baseline, 91 (70.5%) were in the SMR group, and 38 (29.5%) were in the non-SMR group. Response to CRT was observed in 63 (58.8%) patients in the SMR group and 98 (56.9%) patients in the non-SMR group. However, neither improvement in FMR nor response to CRT were statistically significant in either group.

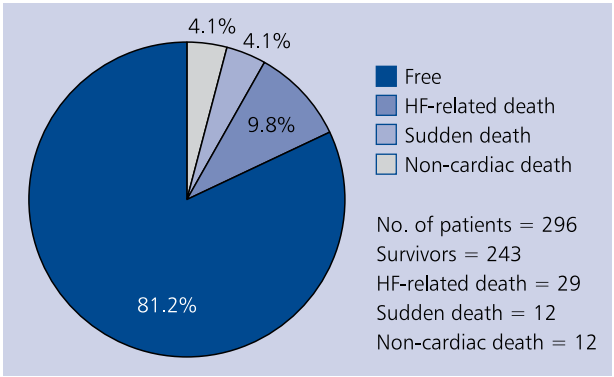

Figure 1. Percentage of survivors and deceased patients with specified cause of death; HF — heart failure

Survival analysis of primary endpoints

Kaplan-Meier survival analysis was performed to compare the survival conditions between the SMR group and the non-SMR group (Fig. 2). The results showed that the risk of primary

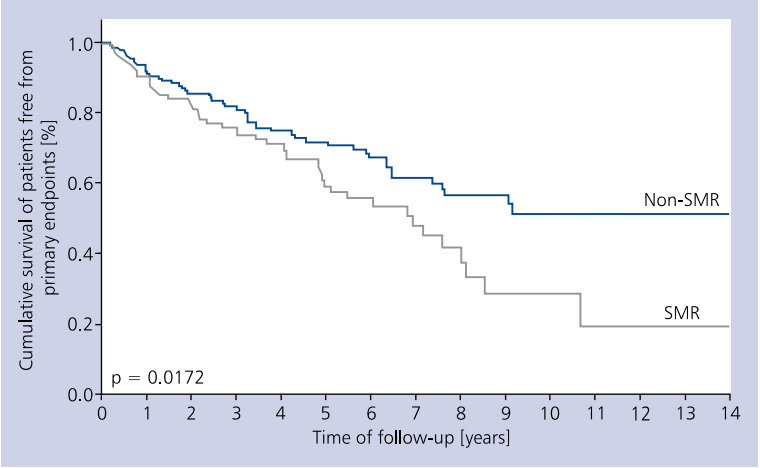

Figure 2. Kaplan-Meier plot estimating survival of patients free from primary endpoints according to severity of functional mitral regurgitation; SMR — significant mitral regurgitation

Table 2. Predictors of primary endpoints in uni- and multivariate Cox proportional hazards models

Variable	Univariate model HR (95% CI)	p	Multivariate model HR (95% CI)	p
SMR	1.602 (1.083–2.371)	0.019	1.785 (1.091– 2.920)	0.021
IHD	1.628 (1.062–2.494)	0.025	1.682 (1.062–2.494)	0.025
AF	1.787 (1.083–2.948)	0.033	–	–
CRT-D	1.033 (0.696–1.534)	0.026	–	–
NYHA class IV	1.960 (1.268–3.029)	0.002	–	–
NT-proBNP	1.000 (1.000–1.000)	0.031	–	–
LVEDD	1.015 (0.995–1.036)	0.140		
LVESD	1.003 (0.996–1.009)	0.430		
ACEI/ARB	0.625 (0.404–0.967)	0.035	–	–
β-blockers	0.647 (0.374–1.119)	0.647		
Lack of spironolactone	2.368 (1.387–4.042)	0.002	2.044 (1.040–4.017)	0.038

Only variables with $p < 0.05$ in univariate analyses were included in multivariate model; CI — confidence interval; HR — hazard ratio; SMR — significant mitral regurgitation; other abbreviations — see Table 1

endpoints was increased with SMR before CRT implantation (log-rank test, $p = 0.0172$, $\chi^2 = 5.678$).

Predictors of primary endpoints

In the multivariate Cox proportional hazard regression model, SMR (hazard ratio [HR] 1.785, 95% confidence interval [CI] 1.091–2.920, $p = 0.021$), IHD (HR 1.628, 95% CI 1.062––2.494, $p = 0.025$), and the lack of use of spironolactone (HR 2.044, 95% CI 1.040–4.017, $p = 0.038$) were independent predictors of primary endpoints (Table 2).

Finally, SMR remained an independent predictor of HFH (HR 4.622, 95% CI 1.955–10.923, $p < 0.001$) (Table 3).

DISCUSSION

In our study, the proportion of CRT candidates with FMR was 78.0%, with the proportion of SMR patients up to 41.8%. We demonstrated that SMR constituted a risk factor for long-term poor prognosis in patients receiving CRT. The survival analysis proved the independent prognostic value of SMR for primary endpoints. Specifically, SMR was positively associated with HFH rather than HF-related death, sudden death, and response to CRT, according to logistic regression analysis. Finally, we also found that IHD and the lack of use of spironolactone were positively associated with primary endpoints after adjusting for multiple factors.

With a high morbidity and mortality, HF has become a major health problem in the ageing society, placing a huge economic burden on patients. LV dyssynchrony contributes to the imbalance of closing force and stretch stress of the mitral valve, and results in FMR. Previous studies have shown that a quarter of patients with HF demonstrate at least mild FMR, and more than 50% demonstrate moderate or severe FMR at baseline [2, 5].

Table 3. Association between significant mitral regurgitation and different events

Events	Univariate logistic analysis		Multivariate logistic analysis	
	HR (95% CI)	p	HR (95% CI)	p
HF-related death	1.332 (0.618–2.871)	0.464	–	–
Sudden death	0.990 (0.307–3.196)	0.987	–	–
HFH	3.567 (1.763–7.219)	< 0.001	4.622 (1.955-10.923)	< 0.001
CRT response	0.657 (0.376–1.150)	0.141	–	–
NYHA class III or IV	2.101 (1.313–3.363)	0.002	–	–

Only variables with $p < 0.05$ in univariate analyses were included in multivariate model. CRT — cardiac resynchronisation therapy; HF — heart failure; HFH — heart failure hospitalisation; other abbreviations — see Tables 1 and 2

The occurrence of FMR was generally regarded as a powerful predictor for poor prognosis of systolic HF patients. As for CRT candidates, some previous studies have shown that preoperative FMR indicates a weak response and worse long-term clinical outcome in patients with CRT [17], while other studies indicated that the baseline level of FMR was not associated with long-term clinical prognosis [18, 19]. This may be due to the relatively short follow-up period and the small number of samples with different FMR group criteria in those studies. Our study concentrated on SMR (jet area/left atrial area > 30%) during a follow-up of 4.17 ± 3.16 years. We found that when comparing the relationship between SMR and different outcomes, SMR was strongly associated with HFH, indicating that the level of FMR may be more related to HF symptoms rather than mortality and CRT response.

In our population, the proportion of non-ischaemic HF patients was relatively large compared to the other studies. In the study of Yamamoto et al. [20], the proportion of IHD patients is 22.2% (26/117). A similar percentage (18%) of IHD patients was enrolled in our study. Non-ischaemic aetiology was more frequent in patients with improving FMR and better prognosis after CRT. This observation was consistent with previous findings [21, 22]. People with IHD had a lower echocardiographic response to CRT, and it may have resulted from the presence of scarring at the site of the papillary muscle or from progressive regional loss of viable myocardium due to ischaemia, both of which may have limited the efficacy of CRT [23, 24].

For a single-centre, observational study, the number of patients was relatively small. Results from the current study should be confirmed in further, large-scale clinical trials. Moreover, the method of FMR quantification based on the jet area/left atrial area ratio was only a semi-quantitative method compared with integration of various echocardiographic measures of FMR severity [25]. Moreover, because it was a non-controlled study, no conclusions can be made regarding the possible benefits of CRT. However, to ensure the effects of CRT, strict heart rate control with medication was performed and a percentage of biventricular pacing > 90% was achieved in all subjects during follow-up.

In conclusion, SMR before CRT implantation was strongly related to long-term poor prognosis in HF patients. SMR was positively associated with HF hospitalisation rather than mortality and CRT response.

Conflict of interest: *none declared*

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