Assessing mitral regurgitation in the prediction of clinical outcome after cardiac resynchronization therapy

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BACKGROUND Cardiac resynchronization therapy (CRT) has been shown to reduce mitral regurgitation (MR), although the clinical impact of this improvement remains uncertain.

OBJECTIVES We sought to evaluate the impact of MR improvement on clinical outcome after CRT and to assess predictors and mechanism for change in MR.

METHODS This was a cohort study of patients undergoing CRT for conventional indications with baseline and follow-up echocardiography (at 6 months). MR severity was classified into 4 grades. The primary end point was time to all-cause death or time to first heart failure (HF) hospitalization assessed at 3 years.

RESULTS A total of 439 patients were included: median age was 70.2 years, 90 (20.5%) were women, 255 (58.1%) with ischemic cardiomyopathy, and mean QRS width was 162 ms. Worsening severity of baseline MR was independently predictive of HF or all-cause mortality (hazard ratio 1.33; 95% confidence interval 1.01–1.75; $P = .042$). Reduction in MR after CRT was significantly associated with lower HF hospitalization and improved survival (hazard ratio 0.65; 95% confidence interval 0.49–0.85; $P = .002$). Degree of baseline MR and longer surface QRS to left ventricular lead time were significant predictors of MR change. Patients with MR reduction exhibited lower mitral valve tenting area ($P < .001$) and coaptation height ($P < .001$) than those with stable or worsening MR, suggestive of improved ventricular geometry as a mechanism for change in MR.

CONCLUSION Degree of baseline MR and change in MR after CRT predicted all-cause mortality and HF hospitalization at 3 years. Longer surface QRS to left ventricular lead time at implant may be a means to target MR improvement.

KEYWORDS Cardiac resynchronization therapy (CRT); Biventricular pacing; LV lead electrical delay; QLV; Mitral regurgitation; Heart failure

ABBREVIATIONS CI = confidence interval; **HF** = heart failure; **HR** = hazard ratio; **LA** = left atrial; **LBBB** = left bundle branch block; **LV** = left ventricular; **LVEDD** = left ventricular end-diastolic diameter; **LVEF** = left ventricular ejection fraction; **LVESD** = left ventricular end-systolic diameter; **LVLED** = left ventricular lead electrical delay; **MR** = mitral regurgitation; **PM** = papillary muscle; **QLV** = surface QRS to left ventricular lead time

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Introduction

Among drivers of hospitalization and morbidity in heart failure (HF), mitral regurgitation (MR) is common: a quarter of patients with HF demonstrate at least mild MR, and more than half demonstrate moderate or greater MR at baseline.[1,2] Furthermore, increasing severity of MR is independently associated with adverse ventricular remodeling and increased mortality in patients with systolic dysfunction.[3]

For patients with HF secondary to intraventricular conduction delay and systolic dysfunction, cardiac resynchronization therapy (CRT) is now an accepted device-based therapy that reduces hospitalization, improves survival, and has a well-recognized impact on acute and long-term reduction in MR.[4–7] Given that medical therapy for MR with vasodilators is of limited benefit and surgical intervention for patients with HF and severe MR carries high operative risk, CRT has been advocated as a treatment option for selected patients.[8] Furthermore, there is growing awareness that addressing valve incompetence through surgery alone may not be enough to address ventricular remodeling or overall clinical outcome in patients with moderate or severe MR.[9]

Notably, however, up to one-third of patients treated with CRT do not derive any detectable clinical or echocardiographic benefit from therapy, including reduction in MR.[10] Similarly, even when CRT is effective at reducing MR, the impact of MR improvement after CRT on clinical outcome is not well characterized, nor are the electrical or echocardiographic features that predict MR improvement. Furthermore,

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the mechanistic basis for change in MR after CRT remains debated.

We sought to evaluate the role of MR assessment in predicting clinical outcome after CRT as well as to identify predictors of MR change. Finally, we examined tethering forces acting on the mitral valve in order to elucidate a possible mechanism for MR improvement after CRT.

Methods

Study population

All patients with medically refractory systolic HF who received CRT or CRT with defibrillator devices at the Massachusetts General Hospital for conventional indications (left ventricular [LV] ejection fraction [LVEF] $< 35\%$, QRS duration > 120 ms, and New York Heart Association class III or IV) were reviewed. Patients were selected for inclusion in this study if they were implanted with CRT or CRT with defibrillator devices during the enrollment period (2003–2012), had baseline and 6-month postimplant transthoracic echocardiograms, and were followed for postimplantation care at our clinic. Clinical care of these patients was standardized for all patients implanted after November 2005, with the creation of a multidisciplinary clinic providing prospective patient evaluation and device optimization at regular intervals as has been previously described.[11] The project was approved by the Massachusetts General Hospital Institutional Review Board and Ethics Committee.

Baseline characteristics and echocardiography

Baseline demographic data, clinical characteristics (ie, medical comorbidities and medication use), and electrophysiological data (ie, QRS duration and bundle branch block morphology) were obtained for all patients. Baseline bundle branch block morphology was defined using the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society consensus criteria.[12] Echocardiography was performed using a commercial system (Vingmed Vivid 7, GE, Milwaukee, Wisconsin) using a 2.5–5.0-MHz transducer. All images were recorded digitally, with offline analysis performed using commercial software (EchoPAC 6.0, GE-Vingmed, Horten, Norway). Images were obtained at baseline (before implant) and follow-up (target of 6 months postimplant). Left atrial (LA) size, LV end-diastolic diameter (LVEDD), and LV end-systolic diameter (LVESD) were measured from the parasternal long-axis view. LVEF was calculated using the biplane method of discs from the apical 4- and 2-chamber views or from the modified Quinones equation using diameters obtained from the parasternal long-axis view. An *LVEF responder* was defined as a patient with an LVEF improvement of 5% or greater after CRT.

The degree of systolic MR was determined through integrative assessment as recommended by the American Society of Echocardiography.[13] Parameters assessed were as follows: mitral jet area as a percentage of LA area, pulse wave Doppler patterns of mitral and pulmonary venous inflow, vena contracta width, and calculation of effective regurgitant orifice area using the proximal isovelocity surface area method (in patients with moderate or severe MR). Integrative assessment included a final determination of MR into 1 of 4 grades (1 = none or trace; 2 = mild; 3 = moderate; 4 = severe). An *MR responder* was defined as a patient with a reduction in at least 1 grade of MR after CRT with at least mild MR at baseline (ie, ≥ 1 grade reduction in MR after CRT).

Mechanistic MR analysis

Exploratory analysis of mechanism for MR improvement was performed in a sample of patients demonstrating all degrees of MR (from trace to severe) and in whom all clinical, electrocardiographic, and LV lead electrical delay (LVLED) data were available. Echocardiographic images were retrospectively rereviewed to assess LV volumes (assessed in 2- and 4-chamber apical views). Measures of increased tethering force acting on the mitral valve included enlarged apical mid-systolic mitral valve tenting area (in cm^2), heightened apical leaflet coaptation height (in cm), and increased sphericity index of the LV chamber (Figure 1). Mitral valve systolic tenting area and coaptation height were measured at mid-systole. Sphericity index was measured at end-diastole (where sphericity index closer to 1 indicates a more globular LV cavity).[14–16]

LV lead location and LVLED

LV leads were placed in regions with acceptable capture without diaphragmatic stimulation. LV lead anatomical location was classified within the long and short axes of the left ventricle adjudicated through review of posterior-anterior and lateral chest radiographs or venous angiograms. Surface QRS to LV lead time (QLV) was measured electronically using Cardio Calipers version 3.3 (Iconico Software, New York, NY) from the onset of the surface QRS complex to the first sensed peak of the LV lead electrogram (to obtain the QLV). This value was standardized for QRS width to obtain the LVLED, as described previously.[17–19]

End points

The primary end point of this study was a composite of time to all-cause death or time to first HF hospitalization assessed at 3 years. Medical records were retrospectively reviewed to ascertain clinical outcome, supplemented with a search of the Social Security Death Index, where appropriate. Hospitalizations for HF were adjudicated by a blinded reviewer. Echocardiographic evaluation, as described in detail above, was evaluated with attention to change in LVEF, change in LVEDD or LVESD, and change in the degree of MR.

Statistical analysis

Categorical variables were expressed as a percentage and were compared using the Fisher exact test. Continuous variables were expressed as mean $\pm$ SD and were compared using the unpaired 2-tailed Student *t* test. The Kaplan-Meier