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Indexed maximal left atrial volume predicts response to cardiac resynchronization therapy

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ABSTRACT

Aims: Cardiac resynchronization therapy (CRT) has shown morbidity and mortality benefits in patients with advanced congestive heart failure (HF). Since about one-third of the patients did not appear to respond to CRT, it would seem reasonable to try to identify patients more accurately before implantation. Left atrial (LA) dimension has been proposed as a powerful outcome predictor in patients with heart disease. Accordingly, the aim of this study is to prospectively assess the predictive value of LA for selecting CRT responders.

Methods: Fifty two consecutive patients with refractory HF, sinus rhythm and left bundle branch block were enrolled in the study and planned for CRT implantation. Clinical and echocardiographic evaluations were performed before CRT implantation and after 6 months. Three LA volumes indexed to body surface area (iLAV) were computed to evaluate the LA complexity: maximal LAV (iLAVmax), LAV just before atrial systole (iLAVpre), and minimal LAV (iLAVpost). CRT responders were defined as those who presented a reduction of >10% in LVESVi at 6-month follow-up.

Results: Responders (63%) and nonresponders (37%) had similar baseline clinical characteristics and pre-implantation LV volumes. However, baseline LA volumes were significantly associated with the extent of LV reverse remodeling: in particular, baseline iLAVmax was remarkably lower in responders than in nonresponders (50.2 ± 14.1 ml/m^2 vs 65.8 ± 15.7 ml/m^2, $p = 0.001$) resulting predictive for CRT response.

Conclusion: Patients with small iLAV result as better responders to CRT than larger one. iLAVmax is an independent predictor of LV reverse remodeling and allows to indentify the best candidates for CRT.

1. Introduction

Cardiac resynchronization therapy (CRT) has become an effective treatment modality in patients with advanced congestive heart failure (HF) and prolongs survival compared to optimal medical therapy alone [1,2]. However, about 30% of patients fail to respond to this therapy, realizing a growing interest toward the identification of potential responders to CRT before implantation [3]. Recently, several echocardiographic measurements of ventricular dyssynchrony have been tested for prediction of CRT response with mixed results.

To date the role of left atrium (LA) to predict response to CRT has not yet been evaluated, although LA size has been suggested as a powerful outcome predictor in patients with heart disease [4–6]. Moreover, LA size expresses the chronicity of exposure to abnormal filling pressures and has been proposed in a retrospective analysis as a predictor of mortality after CRT in patients with advanced HF [7]. Accordingly, the purpose of the present study was to prospectively assess the predictive value of LA for selecting CRT responders.

2. Methods

2.1. Patient selection and study protocol

From the Cardiology Department of Piacenza Hospital and Modena University Hospital fifty two consecutive patients with refractory HF, left bundle branch block and sinus rhythm were prospectively enrolled in the study before CRT implantation. Patients were classified as having HF of ischemic or nonischemic etiology based on a history of myocardial infarction or based on objective evidence of coronary artery disease as assessed with coronary angiography. The criteria for CRT implantation were based according to the established international guidelines: symptomatic patients (NYHA functional class II or more), left ventricular ejection fraction (LVEF) less than 35%, QRS duration > 120 ms (>150 ms if NYHA functional class II) although on optimal pharmacologic therapy, including diuretics, β-blockers, and angiotensin converting enzyme inhibitors or angiotensin receptor

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blockers for at least 30 days prior to enrollment in the study. Exclusion criteria were symptomatic bradyarrhythmias, previous history of atrial arrhythmias, pregnancy, myocardial infarction or coronary intervention within 3 months of enrollment, or a significant comorbid illness defined as severe obstructive pulmonary disease requiring chronic supplementation of oxygen, severe renal failure (creatinine clearance < 30 ml/min), malignancy, or medically refractory anginal symptoms.

Patients meeting inclusion criteria underwent a baseline evaluation prior to CRT that included NYHA functional classification, quality-of-life (QOL) assessment with the Minnesota Living with Heart Failure Questionnaire and resting two-dimensional Doppler echocardiographic study. At 6-month follow-up the same echocardiographic and clinical parameters were reassessed. The study complies with the Declaration of Helsinki, the study protocol was approved by the regional ethics committee of our institutions, and informed consent was obtained from each patient.

2.2. Device implantation

All fifty two patients underwent successful implantation of a biventricular device. The LV pacing lead was inserted by a transvenous approach through the coronary sinus to target lateral or posterolateral cardiac vein; in one patient the target vein was unavailable, so anterior vein was used. One day after implantation, the LV lead position was assessed from a chest X-ray using the lateral views. The right atrial and ventricular leads were positioned conventionally in right atrial appendage and in right ventricular apex respectively. Choices of CRT devices included biventricular defibrillators in 42 patients (Concerto II from Medtronic Inc.; Contak Renewal 4 from Boston scientific; Atlas II HF from St. Jude Medicals) and biventricular pacemakers in 10 patients (InSync III from Medtronic Inc.; Contak Renewal TR2 from Boston scientific; Frontier II from St. Jude Medicals). No AVD dynamic mode was set and no AV delay optimization guided by echocardiography was performed after device implantation.

2.3. Echocardiography

Transthoracic echocardiography was performed with the subjects at rest in the left lateral position with commercially available ultrasound equipment (Vivid 7, General Electric and Acuson Sequoia c512, Siemens Medical). Images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis, two-chamber and four-chamber images) and measurements were performed after a 10-minute run-in period for stabilization and equilibration.

2.3.1. LV and mitral valve evaluation

The LV volumes and the LVEF were calculated from the apical two- and four-chamber images using the biplane Simpson's rule. Values were indexed to body surface area calculated using the Du Bois and Du Bois Formula [8]. LV reverse remodeling was computed as LV end-systolic volume (LVESVi) change between baseline and 6-month follow-up values (ΔLVESVi). Inter-ventricular mechanical delay (IVMD) was calculated as the absolute difference in the LV and right ventricular pre-ejection times, with ≥40 ms IVMD regarded as a significant delay. LV dyssynchrony was assessed by septal-to-lateral delay (Ts-LS) defined as described previously [9]. The ratio between peak early (E) and late (A) diastolic LV filling velocities was used as standard indices of LV diastolic function [10]. LV longitudinal function was explored by pulsed Tissue Doppler imaging, placing the sample volume at the level of mitral septal annulus from the apical fourchamber view [11]. Mean peak early diastolic (E′) annular velocities were measured for 3 consecutive beats and averaged. Mean E/E′ ratio was also calculated as load-independent marker of ventricular diastolic relaxation [12]. Mitral regurgitation (MR) severity was graded according to the current guidelines [13]. LV responders to CRT were defined as those patients who presented a reduction of >10% in LVESVi at 6-month follow-up, whereas those with a lesser degree of reduction of 10% were defined as nonresponders [14].

2.3.2. LA evaluation

Anteroposterior LA diameter (iLAd) was assessed by M-mode scan in parasternal long axis view. LA volumes and LA emptying fraction were calculated from the apical two- and four-chamber images using the biplane Simpson's rule and were indexed to body surface area [8].

In order to evaluate the complexity of LA function we specified three atrial phases. The first is the reservoir phase: during ventricular systole and isovolumic relaxation blood arrive into LA from pulmonary venous return; in this phase LA stores energy in the form of pressure. The second is the passive phase: after mitral valve opening, in the early phase of ventricular diastole, the LA transfers blood into the LV because of pressure gradient, so blood flows passively from the pulmonary veins into the left ventricle. Finally in the contractile phase the LA systole serves to augment the LV stroke volume.

The following left atrial volume (LAV) parameters were recorded in order to completely describe the LA contribution:

- Maximal LAV at ventricular end-systole where LA size is maximal (iLAVmax),
- LAV just before atrial systole (iLAVpre),
- Minimal LAV after atrial systole (iLAVpost).

Moreover, left atrial emptying fractions (LAEF) were derived from LA volumes and calculated as follows:

- Total LA emptying volume (LAEFtot): [(iLAVmax − iLAVpost) / iLAVmax] × 100,
- LA passive emptying volume (LAEFpas): [(iLAVmax − iLAVpre) / iLAVmax] × 100,
- LA active emptying volume (LAEFcon): [(iLAVpre − iLAVpost) / iLAVpre] × 100.

2.4. Statistical analysis

Statistical analysis was conducted using Package for Social Sciences version 17.0 for Windows (SPSS Inc., Chicago, IL, USA) and Medcalc 7.3. Comparison of the continuous parametric variables between baseline and 6-month follow-up was performed using a paired sample t test or the χ^2 test for the ordinal variables. Unpaired t test was used to compare the echocardiographic parameters between responders and nonresponders. Logistic regression analysis was used to identify univariate and multivariable predictors of CRT response. For the univariable models, p-value ≤ 0.10 was considered significant and the corresponding variable was included in the multivariable model. The odds ratio (OR) and 95% confidence interval (CI) are shown. All parametric data were expressed as mean ± SD. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Repeatability and reproducibility of measurements

Reproducibility of our laboratories has been published previously [15]. Briefly, for iLAVmax assessment intra-observer variability was 4.8 ± 1.6% and inter-observer was 6.7 ± 3.2%; for LVEDVi, intra-observer variability was 5.7 ± 4.4% and inter-observer was 8.3 ± 4.6% both indicating outstanding reliability.

3.2. Study population

Baseline characteristics of the overall population are presented in Table 1. Ischemic heart disease was present in 44% of patients; 46% of patients were in NYHA class II, 50% in class III and 4% in class IV. Almost all patients were treated with a beta-blocker (92%) and with ACE-inhibitor or ARB (97%), 79% of patients had a diuretics. All patients had severe LV dilation and eleven patients (21%) presented severe MR.

3.3. Clinical and echocardiographic improvement after CRT

At 6-month follow-up, there was an improvement of clinical status for the overall population, namely NYHA functional class and Minnesota Living With Heart Failure QOL score. CRT resulted in a significant LA (mean iLAVmax from 55 ± 16.4 ml/m^2 to 50.3 ± 19 ml/m^2, p 0.006) and LV reverse remodeling (mean LVESVi from 94.7 ± 52.1 ml/m^2 to 72.9 ± 54.1 ml/m^2, $p < 0.001$) leading to an increase in both systolic function. Moreover, a significant reduction of MR and QRS duration was observed (Table 2). Biventricular pacing percentage was accurately assessed through device counters' analysis performed at the 6-month visit: a percentage of biventricular pacing > 85% was observed in all patients and no atrial or ventricular arrhythmias were recorded. During follow-up no patient died or was hospitalized for worsening heart failure as well for device-related problems.

Table 1
Demographic and baseline criteria (n = 52).

Age (yrs)		67.1 ± 10.2
Gender (M/F)		38/14
Systemic hypertension		15 (29%)
Diabetes mellitus		14 (27%)
GFR (ml/min/1.73 m^2)		68 ± 21
PR interval (ms)		202 ± 30
Ischemic etiology		23 (44%)
NYHA functional class:		
	II	24 (46%)
	III	26 (50%)
	IV	2 (4%)
Medications:		
	Beta-blockers	48 (92%)
	ACE inhibitors/ARBs	50 (97%)
	Diuretics	41 (79%)