# Left atrial function, a new predictor of response to cardiac resynchronization therapy?

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**BACKGROUND** Cardiac resynchronization therapy (CRT) improves left ventricular (LV) function and induces LV remodeling, and it is an established therapy for advanced heart failure with prolonged QRS duration. One third of patients will not benefit from this invasive therapy.

**OBJECTIVE** The purpose of this study was to evaluate whether left atrial (LA) strain imaging (ε) parameters could help in predicting the response in terms of LV reverse remodeling after CRT.

**METHODS** A total of 79 patients who underwent CRT were evaluated with echography before implantation. LA function and LV function were assessed with M-mode, 2-dimensional echocardiography, Doppler, tissue Doppler velocity, and ε. LV reverse remodeling was defined as a >15% reduction in LV end-systolic volume.

**RESULTS** At 6 months, 54 patients (68%) were responders to CRT. In multivariable logistic regression, LA systolic peak of strain rate (SRA) (odds ratio [OR} 10.5, 95% confidence interval [CI] 1.76–62.1, $P = .01$), left bundle branch block (OR 6.8, 95% CI 1.06–43.9, $P = .04$), ischemic cardiomyopathy (OR 3.93, 95% CI 1.07–14.4, $P = .04$), and LV preejection index (OR 1.03, 95% CI 1.01–1.05, $P = .01$) were associated with CRT response. With an SRA cutoff of –0.75%, the negative predictive value for predicting CRT response was 0.62.

**CONCLUSION** This study demonstrated the possible relevance of assessing LA function before CRT. SRA appeared to be a good predictor of CRT response. Integrating this LA function analysis into the multivariable assessment of patient candidates for CRT should be considered.

**KEYWORDS** Cardiac resynchronization therapy; Left atrial function; Strain imaging; Echocardiography

**ABBREVIATIONS AV** = atrioventricular; **CI** = confidence interval; **CRT** = cardiac resynchronization therapy; **EF** = ejection fraction; **LA** = left atrium; **LV** = left ventricle; **LVPEI** = left ventricular preejection interval; **NPV** = negative predictive value; **OR** = odds ratio; **PPV** = positive predictive value; **SRA** = left atrial systolic peak of strain rate

(Heart Rhythm 2015;12:1800–1806) 

## Introduction

Echocardiography plays an important role in patient assessment before cardiac resynchronization therapy (CRT), and it can monitor many of the mechanical effects of CRT in heart failure patients.[1–3] Encouraged by the highly variable individual response observed in the major CRT trials, echocardiography-based measurements of mechanical dyssynchrony have been extensively investigated, with the aim of improving the prediction of response to CRT.[2,4–7] There has been no consensus on mechanical dyssynchrony analysis before CRT implantation because results of larger studies have been somewhat disappointing.[1,8,9] According to the current literature, it seems that one can still hope to predict the response to CRT with mechanical dyssynchrony analysis, but the negative predictive value of all of the proposed approaches remains low.[10]

Apart from mechanical dyssynchrony, other morphologic parameters to predict CRT response have been tested. Leyva et al[11] considered left ventricular (LV) fibrosis assessed by cardiac magnetic resonance. Damy et al[12] showed the prognostic value of right ventricular function.

A few studies have examined the relationship of the left atrium (LA) with CRT.[13,14] Until now, diastolic function, with the exception of atrioventricular (AV) dyssynchrony,[15] has not been expected to be reported when assessing a patient before CRT implantation. Nevertheless, the value of LA volume as a strong prognostic marker has largely been demonstrated in many fields, including systolic heart failure.[16] Furthermore, the size of the LA as well as its function, to some extent, can be easily assessed. Promising observations have been made in the field of CRT,[17] including a study performed in our institution,[14] and even more observations

Drs. Feneon and Behaghel contributed equally to this work. This study was supported by a grant from "La Fondation de L'Avenir." **Address reprint requests and correspondence:** Dr. Erwan Donal, Service de Cardiologie, Hôpital Pontchaillou, CHU Rennes, F-35033 Rennes, France. E-mail address: erwan.donal@chu-rennes.fr.

1547-5271/$-see front matter  http://dx.doi.org/10.1016/j.hrthm.2015.04.021

have been made in the field of valvular heart disease,[18] Speckle tracking echocardiography is a novel method for angle-independent, objective quantification of myocardial deformation from standard bidimensional datasets. Speckle tracking has the advantages of being angle independent and being weakly affected by reverberations, side lobes, and dropout artifacts. Speckle tracking echocardiography has evolved and, by enabling the quantification of longitudinal myocardial LA deformation dynamics, was recently proposed as an alternative approach for the estimation of LV filling pressure. In fact, the LA is exposed to the cumulative effects of filling pressures over time and, therefore, could provide a more sensitive and likely more relevant expression of the severity of LV (and heart as a whole) dysfunction than measurement of the characteristics of the LV.

Therefore, we sought to examine the ability of LA function characteristics to predict response to treatment in a typical population of patients referred for CRT.

## Methods

### Patient population

Between April 2007 and February 2012, consecutive patients scheduled to undergo implantation of CRT systems at the Rennes University Medical Center were prospectively included in the study. The goal was to assess the feasibility and value of using LA strain (as a relevant manner for assessing LA function) in terms of predicting LV-reverse remodeling. Inclusion criteria were (1) New York Heart Association functional class II–IV, despite optimal medical therapy; (2) LV EF $\leq$35%; (3) stable sinus rhythm; (4) QRS duration $\geq$120 ms on 12-lead electrocardiography; and (5) no previous pacemaker or cardioverter-defibrillator implantation. Patients with atrial fibrillation were excluded. Heart disease was considered ischemic if a 50% stenosis was observed in $\geq$1 major epicardial coronary artery or if the patient had a history of myocardial infarction or prior coronary revascularization. Patients were followed-up 6 months after device implantation. No patients were lost to follow-up, and all patients returned to the laboratory to meet the requirements of the study.

Responders were defined as having a $\geq$15% decrease in LV end-systolic volume at the 6-month follow-up compared with baseline. This measurement was chosen because it was the end-point chosen in most of the studies in this field.[19]

The study was performed in accordance with the principles outlined in the Declaration of Helsinki on research in human subjects and with the procedures of the Rennes University Hospital Medical Ethics Committee (usual care). The study was approved by a national review committee (no. CNIL 0507317b). Patients provided informed consent.

### Transthoracic echocardiography

Each patient was placed in the left lateral decubitus position and assessed using echocardiography with either the Vivid 7 or Vivid e 9 ultrasound system (GE Medical Systems, Horten, Norway), equipped with 2.5-MHz transducers. LV volume and LA volume were quantified according to the recommendations of the American Society of Echocardiography.[20] LA volumes were calculated using the apical 4- and 2-chamber area–length method and subsequently indexed to body surface area (LA volume index]) as described previously.[21]

Transmitral flow (E wave and deceleration time) and mitral annular tissue Doppler (E′ and S′) velocities were measured. The Doppler value recorded was the mean of 3 beats. All of the measurements were obtained according to recommendations of chamber quantification[20] and diastolic function assessment.[22] The ratio of diastolic filling time to RR interval was used to characterize AV dyssynchrony in the left heart. AV dyssynchrony was defined as ratio of diastolic filling time to RR interval $<$40%.[15] LV preejection interval (LVPEI) and interventricular mechanical delay were used to characterize interventricular dyssynchrony.[15]

### LA deformation imaging indices

Three consecutive cardiac cycles were recorded and averaged, and the frame rate was set to 60 to 80 frames per second. The analysis was performed offline using customized software (EchoPAC PC BT12; GE Healthcare, Horten, Norway). The LA endocardial border was manually traced on the apical 4-chamber view. After manual adjustment of a region of interest covering the full thickness of the myocardium, the software divided the LA into 6 segments and automatically scored the segmental tracking quality. The software rejected segments with inadequate image quality and excluded them from the analysis. Longitudinal strain curves were generated for each of the 6 LA segments in the 4 chambers. Global peak LA longitudinal strain during ventricular systole (εs) was then measured by averaging the values obtained from the 6 LA segments. The same tracing method was used to calculate the strain rate and to analyze the LA systolic peak of strain rate (SRA).[23] A cardiologist with a level 3 in echocardiography, who was unaware of the patients' information, analyzed all of the echocardiographic values (Figure 1).

### Observer variability

Twenty studies were randomly selected for interobserver and intraobserver variability. Systolic strain and SRA from the LA apical 4-chamber view were remeasured by the same observer and by a second independent observer based on the digital data, using an offline system.

### Statistical analysis

Continuous variables are presented as mean (SD) or median (interquartile range) in cases of skewness. Categorical data are summarized as frequency and percentage. Differences in baseline characteristics between the 2 groups (responders and nonresponders) were analyzed with the Student *t* test, the Mann–Whitney test, $\chi^2$ test, or Fisher exact test, as appropriate. Correlations between variables were determined with Pearson product moment correlation analysis. Multivariate logistic regression analysis was used to assess relationships between the different variables and CRT response.