



## Original Research Article

## Low-dose dobutamine stress echo for reverse remodeling prediction after cardiac resynchronization



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## ABSTRACT

**Purpose:** Cardiac resynchronization therapy (CRT) is a valuable option for patients with heart failure and wide QRS to reduce electromechanical dyssynchrony (DYS). High non-responders rate (30%) urges the need to improve selection of candidates for CRT. We hypothesized that low-dose dobutamine stress echocardiography (DSE) can help unmask dyssynchronous motion. The aim of this study is comparison between dyssynchrony index at rest and during low-dose dobutamine stress to predict left ventricular reverse remodeling after CRT.

**Patients and methods:** Prospectively, 57 consecutive patients (37 male) aged  $61.8 \pm 9$  who qualified for CRT according to current guidelines were enrolled. Two dimensional echocardiography and tissue Doppler imaging (TDI) were performed before and 6 month after CRT to assess reverse remodeling (rLV). Additionally DSE was performed before CRT. DYS was assessed at rest (DYSr) and peak DSE (DYSd) separately, as a difference between time to peak systolic velocity (Ts) of septum and lateral wall. Ts was corrected for heart rate.

**Results:** rLV defined as decrease  $\geq 15\%$  of LVESV at follow-up was found in 38 (67%) patients. DYSr and DYSd were independent predictors of rLV (OR = 1.04, CI  $\pm 1.02$ –1.06,  $p < 0.02$  and OR = 1.05, CI  $\pm 1.03$ –1.08,  $p < 0.0002$  respectively). ROC analysis found that  $DYSr > 42$  ms and  $DYSd > 59$  ms had sensitivity of 70% and 87%, specificity of 61% and 78%, and accuracy of 70% and 84% respectively for prediction of reverse remodeling LV. Area under Receiver Operating Characteristic Curve for DYSd was higher than for DYSr (0.89 vs 0.71,  $p < 0.007$ ).

**Conclusion:** Exercise intraventricular dyssynchrony assessed by dobutamine stress echo is a strong independent predictor of cardiac resynchronization therapy response.

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## 1. Introduction

Cardiac resynchronization therapy (CRT) is firmly established as a valuable additive treatment for symptomatic patients with systolic heart failure regardless of optimal medical treatment.

CRT improves clinical status, quality of life and exercise capacity, prolongs survival and promotes structural ventricular changes [1]. Left ventricle (LV) reverse remodeling was also observed in large, multicenter clinical trials. Reduction of left ventricular volume signifying LV reverse remodeling was first shown in case series. In those studies, LV end-systolic volume (LVESV) was the strongest predictor of survival among clinical and echocardiographic parameters. However, one-third of the patients fail to respond to CRT thus underlining the need for better selection of patients [2,3].

A number of parameters have already been suggested which may modify response to cardiac CRT, including viability, contractile

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reserve, LV lead position or LV dyssynchrony of left ventricle. Observational studies using echocardiography demonstrated that the mechanism leading to clinical improvement is the resynchronization of pre-existing left ventricular dyssynchrony. Unfortunately, the first multicenter study (PROSPECT) recently reported that any echocardiographic parameter of mechanical dyssynchrony at rest was useless in identifying patients likely to respond to CRT [4]. However, all echocardiographic parameters in this study and most of other studies were estimated at rest, though typical clinical and pathophysiological manifestations of heart failure are particularly apparent during exercise.

We hypothesized that low-dose dobutamine stress echo (LDSE) can help unmask dyssynchronous motion and the aim of the present study was comparison value of index of dyssynchrony at rest and during LDSE for prediction for LV reverse remodeling. The verification of this hypothesis was available by performing the Myocardial Viability in Cardiac Resynchronization Therapy (ViaCRT) trial that was dedicated to investigate the potential impact of myocardial viability on CRT efficacy in different clinical settings.

## 2. Patients and methods

### 2.1. Study patients

We assessed prospective 57 consecutive patients (38 men and 19 women) aged  $61.9 \pm 8.7$ , who were enrolled into the multicenter, prospective, observational VIACRT trial. Patients underwent the CRT implantation as part of their clinical management in line with the current international guidelines. The initial indications for CRT were drug-refractory NYHA class III or IV heart failure with wide QRS complexes ( $\geq 130$  ms), ejection fraction LV  $\leq 35\%$  and optimal pharmacotherapy [2].

Serial echocardiographic studies with tissue Doppler imaging (TDI) were performed before and 6 months after CRT to assess rLV. Additionally, before CRT was implanted a LDSE had been done. Clinical assessment was also performed at the same time, including New York Heart Association (NYHA) class, 6-min walk test, and Canadian Cardiovascular Society (CCS) class. The study was approved by the Local Ethics Committees and informed consent was obtained from each participant.

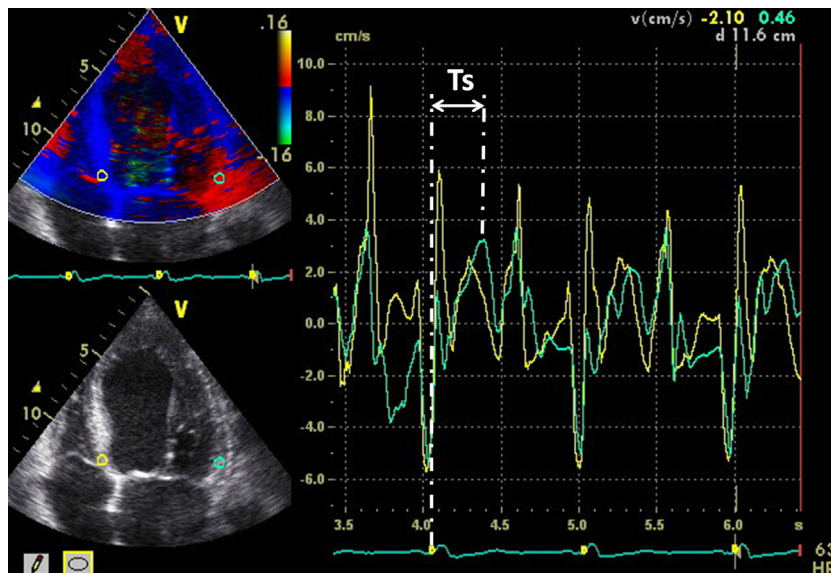
Exclusion criteria were technically poor acoustic window, hemodynamic instability, atrial fibrillation, significant co-morbidity reduction of life expectancy to less than 1 year and unwillingness to give informed consent.

All patients underwent coronary angiograms before implantation. Etiology was considered ischemic in the presence of significant coronary artery disease ( $\geq 50\%$  stenosis in one of the major coronary arteries) and/or history of myocardial infarction or prior revascularization.

### 2.2. Echocardiography

All investigators have been working in referenced medical centers and took part in the dedicated workshops twice a year. The results obtained were verified by the main center experienced in managing of multicenter studies.

Standard Echocardiography, including TDI studies, was performed with commercial equipment. The LV end-diastolic and end-systolic volumes (LVEDV, LVESV) and LVEF were assessed by the biplane Simpson's equation in apical 4-chamber and 2-chamber views. The severity of mitral regurgitation was assessed by measurement of vena contracta (Vc). Absence of the systolic backflow to the left atrium or its small significance was considered as absence of regurgitation. At least 3 consecutive beats of sinus rhythm were measured and the mean was calculated. TDI images were performed at rest and the peak of LDSE. Images were optimized for pulse repetition frequency, color saturation, sector size and depth to allow high frame rates. The loops were stored on magneto-optical discs and analyzed offline using software. The myocardial velocity curves were constructed offline and the septal-to-lateral delay at the basal segments was measured as an index of systolic dyssynchrony. The time to peak systolic velocity (Ts) was measured from the onset of the QRS complex to the peak of the myocardial systolic velocity during ejection at rest and at peak stress (Fig. 1). Ts was corrected for heart rate ( $T_{\text{scorR}} = T_{\text{s}} \text{ corrected rest}$ ,  $T_{\text{scorD}} = T_{\text{s}} \text{ corrected peak of LDSE}$ ,  $T_{\text{scor}} = T_{\text{s}} / (R - R)$ ) using the Bazett's formula to allow comparison between the Ts of segment at rest and at peak stress. All timings were calculated as the average of 3 consecutive cardiac cycles and were analyzed by single investigator blinded to the clinical characteristics of the patient. Intraventricular dyssynchrony (at rest and at dobutamine)



**Fig. 1.** The example of evaluation time to peak systolic velocity. The yellow line indicates the velocity of basal segment of interventricular septum and green line relates to basal segment of lateral wall. Ts is the time to peak systolic velocity of basal segment of lateral wall.

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