Value of Myocardial Work Estimation in the Prediction of Response to Cardiac Resynchronization Therapy

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Background: Cardiac resynchronization therapy (CRT) in heart failure is plagued by too many nonresponders. The aim of the present study is to evaluate whether the estimation of myocardial performance by pressure-strain loops (PSLs) is useful for the selection of CRT candidates.

Methods: Ninety-seven patients undergoing CRT were included in the study. Bidimensional and speckle-tracking echocardiography were performed before CRT and at the 6-month follow-up (FU). Conventional dyssynchrony parameters were evaluated. Left ventricular (LV) constructive work (CW) and wasted work (WW) were estimated by PSLs. Positive response to CRT (CRT+) was defined as ≥15% reduction in LV end-systolic volume at FU and was observed in 63 (65%) patients.

Results: The addition of CW > 1,057 mm Hg% (area under the curve, 0.72, $P < .0001$) and WW > 384 mm Hg% (area under the curve, 0.67, $P = .005$) to a baseline model including clinical, echocardiographic, and conventional dyssynchrony parameters significantly increased the model power (χ^2, 25.11 vs 47.5, $P < .0001$). In this model, septal flash (odds ratio [OR] = 2.78; $P = .001$), CW > 1,057 mm Hg% (OR = 9.49; $P = .002$), and WW > 384 mm Hg% (OR = 16.24, $P < .006$) remained the only parameters associated with CRT+. The combination of CW > 1,057 mm Hg% and WW > 384 mm Hg% showed a good specificity (100%) and positive predictive value (100%) but a low sensitivity (22%), negative predictive value (41%), and accuracy (49%) for the identification of CRT+.

Conclusions: The estimation of CW and WW by PSLs is a novel tool for the assessment of CRT patients. Although these parameters cannot be used by their own to select CRT candidates, they can provide further insights into the comprehension of dyssynchrony mechanisms and contribute to improving the identification of CRT responders. (J Am Soc Echocardiogr 2017;■:■-■.)

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Cardiac resynchronization therapy (CRT) has shown a major favorable impact on the care of symptomatic patients with heart failure (HF), left ventricular (LV) systolic dysfunction, and mechanical dyssynchrony.[1] Despite the great success of randomized clinical trials, 25%-35% of patients undergoing CRT do not respond favorably.[1,2] It has been suggested that electrocardiographic (ECG) widened QRS is a suboptimal marker for LV dyssynchrony, and various echocardiographic parameters have therefore been proposed to predict CRT response (CRT+).[3] Despite this, none of these parameters have been proven to be a good CRT predictor in large multicenter studies.[4] Therefore, current guidelines do not recommend the assessment of dyssynchrony by echocardiography or by any other imaging modality in the diagnostic workup of CRT candidates.[1]

In a normal heart, all LV segments contract in a relatively synchronized fashion and contribute to blood ejection into the aorta. When there is electrical conduction delay, however, early and late activated segments contract at different times and energy might be wasted in stretching opposing segments.[5-9] As observed typically in case of left bundle branch block (LBBB), the early activated septum contracts prior to aortic valve opening and stretches the LV lateral wall. The delayed contraction of the lateral wall causes a variable degree of systolic lengthening of the septum, which makes no contribution to LV ejection and therefore represents a waste.[8,10,11] It has been suggested that the amount of effective (constructive) work remaining in the dyssynchronous ventricle reflects the potential for recovery of function after CRT.[8,9,12] LV pressure-strain loops (PSLs)

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Abbreviations

2D = Two-dimensional

CRT = Cardiac resynchronization therapy

CW = Constructive work

ECG = Electrocardiographic

ESV = End-systolic volume

FU = Follow-up

GLS = Global longitudinal strain

HF = Heart failure

ICC = Interclass coefficient

LBBB = Left bundle branch block

LV = Left ventricular

NPV = Negative predictive value

NYHA = New York Heart Association

PPV = Positive predictive value

PSL = Pressure-strain loop

ROC = Receiver operator characteristic

Se = Sensitivity

SF = Septal flash

Sp = Specificity

STE = Speckle-tracking echocardiography

WW = Wasted work

are a novel and reliable tool for the noninvasive assessment of myocardial work.[8,13]

The aim of the study was to evaluate the role of myocardial constructive work (CW) and wasted work (WW) assessed by PSLs in the prediction of CRT response.

METHODS

Population

Ninety-seven patients with ischemic or dilated cardiomyopathy undergoing CRT implantation according to current guidelines[1] at the University Hospital of Rennes were retrospectively included in the study.

All patients were in sinus rhythm and had a good acoustic window, allowing acquisition of bidimensional echocardiography and speckle-tracking echocardiography (STE) with an excellent image quality. At the time of CRT implantation, all patients were receiving optimized medical therapy. CRT response was indicated by a decrease in LV end-systolic volume (ESV) > 15% at follow-up (FU).[4,14] Clinical data including age, gender, and treatments were collected for each patient. The functional status was assessed by the estimation of the New York Heart Association (NYHA) functional class. An ischemic etiology for LV was claimed in cases with history of myocardial infarction, coronary revascularization, or angiographic evidence of multiple vessel disease or single-vessel disease with ≥75% stenosis of the left main or proximal left anterior descending artery.[15] The study was conducted in accordance with the *Good Clinical Practice Guidelines* as laid down in the Declaration of Helsinki and reviewed by an independent ethics committee (Regional Ethic Committee validation number: 35RC14-9767). All patients gave their written informed consent.

ECG Data

The 12-lead surface ECG were recorded at 25 and 50 mm/sec during spontaneous rhythm before implantation of the CRT device. The method used for QRS duration analysis has been already reported.[16] LBBB was defined as a QRS duration of ≥120 msec with the following characteristics: QS or rS in lead V1, broad R waves in leads I, aVL, V5, or V6, and absent q waves in leads V5 and V6.

Echocardiography

All patients underwent standard transthoracic echocardiography using a Vivid 7 or Vivid E9 ultrasound system (GE Healthcare, Horten, Norway) equipped with a 3S or M5S 3.5-mHz transducer. Two-dimensional (2D), color Doppler, pulsed wave and continuous wave Doppler data were stored on a dedicated workstation for the offline analysis (EchoPAC, GE Healthcare). LV volumes and function were measured by the biplane method as recommended.[17]

Two-Dimensional Speckle-Tracking Echocardiography

Two-dimensional grayscale images were acquired in the standard apical four-, three- and two-chamber views at a frame rate ≥60 frames/sec. The recordings were processed using an acoustic-tracking dedicated software (EchoPAC version 112.99, Research Release, GE Healthcare), which allowed for an offline semiautomated analysis of speckle-based strain.

To calculate the LV global longitudinal strain (GLS), a line was traced along the LV endocardium's inner border in each of the three apical views on an end-systolic frame, and a region of interest was automatically identified by the software (EchoPAC, GE Healthcare) between the endocardial and epicardial borders. The sampling of the region of interest was then adjusted to ensure that the wall thickness was incorporated in the analysis, avoiding the pericardium and following myocardial motion, as recommended.[18,19] The results of segmental and global LV longitudinal strain were then provided by the software. Image quality for the enrolled patients was optimal, and no LV segments were excluded from analysis.

Assessment of Dyssynchrony

Mechanical dyssynchrony was quantified using a multiparametric approach.

1. Atrioventricular delay was calculated as the ratio between LV filling time and the RR interval. Atrioventricular dyssynchrony was considered significant when the duration of LV filling time was <40% of the RR interval.[3]
2. Interventricular delay was calculated as the time difference between right ventricular to LV ejection. Right ventricular and LV preejection intervals were calculated as the time spans between QRS onset and pulmonary or aortic valve opening determined using Doppler profiles. An interventricular mechanical delay >40 msec was considered an index of interventricular mechanical dyssynchrony.[3]
3. Intraventricular dyssynchrony was defined by the presence of septal flash (SF)[20] or by the quantification of septolateral or anterior and inferior wall delays measured by STE. A maximal delay >65 msec was indicative of intraventricular dyssynchrony.[3]

Quantification of Myocardial Work

Myocardial work and related indices were estimated using custom software. Myocardial work was estimated as a function of time throughout the cardiac cycle by the combination of LV strain data obtained by STE and a noninvasively estimated LV pressure curve, as previously described by Russell *et al.*[13] A 17-segment model was used for the estimation of segmental myocardial work.

Estimation of LV Pressure. Peak systolic LV pressure was assumed to be equal to peak arterial pressure measured with a cuff manometer and assumed to be uniform throughout the ventricle. The noninvasive LV pressure curve was then obtained using an empiric, normalized reference curve that was adjusted according to the duration of the isovolumetric and ejection phases defined by the timing of aortic and mitral valve events by echocardiography (Figure 1A). Variation in systolic blood pressure as far as variation in valvular events may influence