Detecting Volume Responders prior to Implantation of a Cardiac Resynchronization Therapy Device via Minithoracotomy: The Septal Flash as a Predictor of Immediate Left Ventricular Reverse Remodeling

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ABSTRACT

Background: Although cardiac resynchronization therapy (CRT) is well established as an adjunctive heart failure treatment, a 30% rate of nonresponders poses a challenge to improve the detection of potential responders prior to device implantation. A previously proposed mechanism-based approach to patient selection suggests in part that the septal flash is a sign of intraventricular dyssynchrony, which is predictive of CRT responsiveness.

Methods: In this pilot study, data from 5 consecutive patients (2 women and 3 men; mean ± SD age, 62 ± 9 years) referred for CRT device implantation via a minithoracotomy were analyzed. Intraoperative transthoracic and/or transesophageal echocardiography data, as well as Doppler myocardial imaging data, were acquired before and after CRT device activation. The septal flash was defined as an early ventricular inward and outward septal motion within the isovolumic contraction period and was imaged with grayscale imaging or tissue Doppler color M-mode. Reverse remodeling was defined as a reduction in the left ventricular end-systolic volume (LVESV) of ≥10%. The right atrial and right ventricular leads were placed transvenously, and the LV screw-in lead was positioned epicardially on the lateral wall.

Results: The septal flash was detected preoperatively in all patients and resolved immediately after the onset of biventricular pacing. Immediately following pacemaker activation, we measured a significant reduction in the LVESV (248 ± 99 mL versus 190 ± 100 mL, P = .01) and an increase in the ejection fraction (19% ± 5% versus 28% ± 5%, P = .01) in all patients. Likewise, a significant increase in the postactivation dP/dt (rate of LV pressure change) measured noninvasively from the mitral regurgitation trace was noted in all patients (298.6 ± 58.0 mm Hg/s versus 601.7 ± 111.2 mm Hg/s, P = .001).

Conclusion: The preoperative presence of the septal flash is a valid predictor of the response to CRT. Immediately after CRT device activation, the septal flash disappears, and LV reverse remodeling and an increase in contractility are observed.

INTRODUCTION

Although cardiac resynchronization therapy (CRT) is well established as an adjunctive heart failure treatment, the 30% rate of nonresponders poses a challenge to better define potential candidates before device implantation [Cleland 2005]. Several echocardiographic parameters for predicting CRT responders have been proposed. Most of these parameters are based on measurements of time intervals between velocities of the segments of the left ventricular (LV) walls, but they have been shown to add no further benefit for predicting the response to CRT [Chung 2008]. A recently proposed mechanism-based approach to patient selection is based on multiple independent mechanisms, the correction of which leads to CRT response [Parsai 2009a, 2009b]. Along with atrioventricular (AV) and interventricular dyssynchrony, the septal flash has been defined as an echocardiographic sign of LV intraventricular dyssynchrony that occurs as a mechanical consequence of left bundle branch block (LBBB)-induced activation of the LV. Furthermore, the disappearance of the septal flash after CRT implantation, which occurs in almost 90% of patients at a median follow-up of 6 months, has been shown to provide high sensitivity and specificity in detecting the response to CRT.

We hypothesized that the immediate response to CRT implantation observed from the point of LV intraventricular dyssynchrony can be detected/predicted by resolution of the septal flash (immediately following device activation), thus demonstrating that the presence of a septal flash prior to CRT pacing is a direct consequence of early septal activation in LBBB, which is correctable by biventricular pacing.

METHODS

Patients

In this pilot study, we studied 5 consecutive patents referred for CRT pacemaker implantation by means of a left anterior minithoracotomy. These patients underwent a preoperative echocardiographic dyssynchrony-screening study,
which is routinely performed in our center, that identified them as potential CRT responders on the basis of the presence of the septal flash. The group consisted of 3 male and 2 female patients (mean ± SD age, 62 ± 9 years). All patients fulfilled the current guideline criteria for CRT device implantation (ejection fraction [EF] <35%, QRS duration >120 milliseconds, New York Heart Association class III-IV, undergoing optimal pharmacotherapy) [Hunt 2005]. All patients underwent coronary angiography evaluation prior to CRT device implantation to exclude significant obstructive coronary artery disease.

Informed, signed consent was obtained from all patients, and the study was conducted in accordance with the ethics guidelines of the hospital.

**Echocardiographic Imaging**

Standard cardiac ultrasound data were acquired intraoperatively before and after CRT device implantation by means of a Vivid 7 ultrasound scanner equipped with a 2.5-MHz phased-array transducer (GE Healthcare, Horten, Norway). The postactivation echocardiography sequences were obtained after AV interval optimization was performed, as described below.

Standard 2-dimensional data, spectral Doppler flows, and myocardial velocity data were obtained from the parasternal and apical views. The echocardiographic data were obtained for 3 complete cardiac cycles. In patients with lower-quality transthoracic views, the intraoperative study was extended with a transesophageal echocardiography (TEE) study (6-MHz transducer; GE Healthcare) with the mid-esophageal and transgastric views.

Offline analysis was performed with dedicated software (EchoPAC; GE Healthcare). LV size was measured from the M-mode images [Devereux 1986; Schiller 1989]. The LVEF and LV volumes were measured by the Simpson biplane method from the apical 4- and 2-chamber views [Schiller 1989]. Pulse wave Doppler traces of the LV outflow acquired from the 4-chamber view were analyzed by planimetry of the Doppler envelope to obtain the stroke volume, which was calculated by multiplying the LV outflow tract (LVOT) velocity time integral by the LVOT area (the LVOT diameter was measured from the 2-dimensional image of the parasternal long axis). In addition, cardiac output was calculated as the product of the stroke volume and heart rate. Transmitial flow velocities were obtained by positioning the pulse wave sample volume at the tips of the mitral leaflets in the 4-chamber view. dP/dt (the rate of change in LV pressure) was measured from the continuous wave traces of mitral regurgitation, from which the presystolic mitral regurgitation was assessed as well (when available) [Bargiggia 1989; Chung 1992].

Velocity data were acquired by Doppler myocardial imaging (DMI) as data superimposed on the underlying 2-dimensional gray-scale image. The necessary high frame rate was obtained by optimizing the angle of insonation and the depth of imaging, as previously described [Weidemann 2001]. Special attention was paid to avoid aliasing within the image by adjusting the values of the pulse-repetition frequency (between 2.0 and 2.5 kHz).

Figure 1. The septal flash, ie, early septal thickening/thinning (occurring within the duration of the QRS complex), visualized on the parasternal long-axis view with gray scale (top left) or by tissue Doppler color M-mode (bottom left), in which the flash is imaged as a rapid change in color during the isovolumic contraction time. Resolution of the septal flash is seen immediately after implantation of the cardiac resynchronization therapy (CRT) device (top and bottom, right).

The early septal fast inward/outward motion (thickening/thinning), ie, the septal flash, was visualized on the parasternal short- or long-axis view with either gray scale or tissue Doppler color M-mode, in which the septal flash was imaged as a rapid change in color during the isovolumic contraction time (IVCT) (Figure 1, left). The amplitude of this septal motion was measured as the maximal excursion in the parasternal (or transgastric, in cases of TEE imaging) short- or long-axis view or as a transverse M-mode in an apical 4-chamber view. Furthermore, the septal flash was identified on the DMI radial velocity data as an early, fast, and short-lived negative declination shortly after the QRS onset, where its peak velocity was measured [Parsai 2009a, 2009b].

**Minithoracotomy and CRT Device Optimization**

The right atrial and ventricular leads were placed tranvenously. Actual placement of the LV lead was performed through a left anterior minithoracotomy, with the LV screw-in lead positioned epicardially on the LV lateral wall.
Immediately after CRT device activation, a simplified AV-delay screening was performed. In cases of a truncated or absent transmitral A wave (indicating too short of an AV delay) or a merged E and A wave (indicating too long of an AV delay), the initial AV optimization was performed with the iterative method.

**Statistical Analysis**

The data for continuous variables are expressed as the mean ± SD, and the data for pre- and postimplantation groups were compared with a paired t-test. Categorical variables are expressed as percentages. For categorical variables, group comparisons were made with the chi-square test. Results with P values <.05 were considered statistically significant.

**RESULTS**

**Patient Characteristics**

During an extensive diagnostic investigation of the etiology of heart failure, significant coronary artery disease was detected by coronary angiography in only 1 of 5 patients. This patient underwent a percutaneous coronary intervention. Therefore, coronary artery disease was absent or resolved in all patients at least 1 year prior to CRT. The diagnosis for the remaining patients (80%) was idiopathic dilated cardiomyopathy. Neither the values for systolic and diastolic blood pressures nor those for the heart rate before CRT device implantation differed significantly from the values after device implantation (Table). All patients were in sinus rhythm before and after the procedure. The duration of the QRS interval decreased significantly after CRT (182 ± 36 milliseconds versus 136 ± 22 milliseconds, P = .05). The mean duration of the PR interval was reduced by biventricular pacing as well (184 ± 43 milliseconds versus 138 ± 17 milliseconds, not statistically significant).

**Echocardiographic Imaging**

The Table summarizes the echocardiographic measurements. Significant reductions in the LV end-diastolic...
In this study, we have shown that patients who fulfilled the guideline criteria for CRT device implantation and who presented with a septal flash as a marker of intraventricular dyssynchrony showed an acute volume response as well as contractility recruitment immediately after activation of the CRT device.

Ventricular remodeling is in the first instance a response to an inherent problem within either the myocardium or the environment in which it has to work and is a compensatory attempt to preserve the heart’s function. In the long term, imminent mechanical disadvantages within this abnormal situation will lead to irreversible myocardial damage and then to ventricular dysfunction and heart failure [Bijnens 2009]. With the new approaches to treatment available for heart failure patients, reverse remodeling is emerging as a new entity for patients for whom progressive LV dilatation and deterioration in contractile function show a partial reversibility instead of stagnation [Sutton 2007].

A substantial number of studies that assessed survival and clinical response (change in New York Heart Association class, exercise capacity, and quality of life) have acknowledged the benefits of CRT, whereas the current knowledge on the mechanisms and effects of the volume response is far less evident.
Generally, CRT leads to a significant decrease in LV size (optimally assessed by measuring LV volumes), as well as an increase in the LVEF [Linde 2002; Yu 2002; Molhoek 2004; Cleland 2005]. Various time periods have been chosen for patient follow-up for documenting signs of reverse remodeling. These periods range from as early as 1 month to 18 months, when LV reverse remodeling and associated clinical improvement are sustained [Linde 2002; Abraham 2003; Molhoek 2004; Cleland 2005]. Recently published long-term results from the Cardiac Resynchronization in Heart Failure (CARE-HF) trial reported on the long-term effects of CRT on LV reverse remodeling [Ghio 2009]. After a mean study period of 29 months after CRT device implantation, CRT was demonstrated to induce sustained LV reverse remodeling, with the most marked effects occurring within the first 3 to 9 months (the earliest follow-up being 3 months after device implantation) and further improvement occurring at subsequent assessments.

The onset of reverse remodeling induced by CRT is not well documented, however. In the present study, we have demonstrated that in patients with true LBBB-induced intraventricular dysynchrony (as defined by the septal flash), reverse remodeling occurs immediately after the activation of biventricular pacing. All patients within this group had preoperative evidence of the septal flash (a marker of intraventricular dysynchrony) that was promptly abolished by biventricular pacing. The preoperative presence of the septal flash was thought to be a direct mechanical consequence of LBBB-induced early septal activation that develops force and shortens against the opposite lateral wall, which is still latent. Because the septum is contracting against a reduced load, it will move faster than normally, resulting in the septal flash. The septum thus pulls the lateral wall until the latter becomes electrically activated, at which point the lateral wall starts to contract and then begins to influence the septum, resulting in a “rocking” apical motion in the ejection phase [Bijnens 2009; Parsai 2009b].

Besides a prompt, significant decrease in LV volumes and a concomitant increase in the EF, we also observed a marked increase in the noninvasively obtained dP/dt in this study. This increase reflects a direct, positive influence of CRT on LV contractility.

CONCLUSION

In this group of patients with overt heart failure and LBBB, immediate reverse remodeling (volume response) to biventricular pacing occurred in all patients after CRT device activation. The reverse remodeling appears to be a direct effect of correcting the underlying conduction abnormality and its mechanical consequence, which can readily be imaged by echocardiography as the septal flash.

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REFERENCES


