Impact of septal flash and left ventricle contractile reserve on positive remodeling during 1 year cardiac resynchronization therapy: the multicenter ViaCRT study

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Abstract

Introduction: Cardiac resynchronization therapy (CRT) has been shown to improve outcomes in patients with systolic heart failure (HFREF). However, the relatively high non-responder rate results in a need for more precise qualification for CRT. The ViaCRT study was designed to determine the role of contractile reserve and dyssynchrony parameters in predicting CRT response. The purpose of this analysis was to determine the effect of baseline septal flash and contractile reserve (CR) on clinical and echocardiographic parameters of response to CRT in 12-month follow-up.
Material and methods: One hundred thirty-three guideline-selected CRT candidates (both ischemic and non-ischemic heart failure with reduced ejection fraction) were enrolled in the study. Baseline study population characteristics were: left ventricle ejection fraction (LVEF) 25 ±6%, QRS 165 ±25 ms, NYHA class III (90%) and IV (10%).
Results: In subjects with septal flash (SF) registered before CRT implantation improvement in LVEF (14 ±2% vs. 8 ±1%, $p < 0.05$) and left ventricle (LV) systolic (63 ±10 ml vs. 36 ±6 ml, $p < 0.05$) and diastolic (46 ±10 ml vs. 32 ±7, $p < 0.05$) volumes was more pronounced than in patients without SF. In patients with CR (defined as LVEF increase by 20% or 4 viable segments) improvement in echo parameters was not significantly different then in the CR– group. Neither SF nor CR was associated with improvement in NYHA class. Subgroup analysis revealed that only in non-ischemic HF patients is presence of septal flash associated with LV function improvement after CRT.
Conclusions: In non-ischemic HF patients septal flash is a helpful parameter in prediction of LV remodeling after 12 months of resynchronization therapy.

Key words: septal flash, dyssynchrony, contractile reserve, cardiac resynchronization therapy.

Introduction

Cardiac resynchronization therapy (CRT) has been shown to improve quality of life and survival in a significant number of patients with systolic heart failure (HF). However, the relatively high non-responder rate [1] and lack of tools for effective selection of responders remain a challenge. Cardiac resynchronization therapy implantation aims to restore synchrony and improve myocardium contractility, thus improving global function of the left ventricle (LV). Assessing the presence of an easily measurable phenomenon reflecting LV dyssynchrony along with evaluating myocardial viability may help in better identification of responders to CRT.

A portion of patients with severe heart failure present with a particular depolarization and LV constriction pattern that involves early constriction and inward motion of the interventricular septum (IVS) with lateral wall (LW) stretching followed by IVS lengthening and LW constriction. This inward and outward motion of the IVS within the isovolumetric contraction time (IVCT) is referred to as a *septal flash* (SF) and can be recorded in echo. According to the literature SF is considered one of the pathophysiological mechanisms of heart failure [2] and an electro-mechanical link in HF in patients with left bundle branch block (LBBB).

Myocardial viability is another key issue in LV function improvement. Low-dose dobutamine stress echo (LDSE) is a readily accessible examination to reveal contractile reserve (CR) in heart failure with reduced ejection fraction (HFREF). There are several reports evaluating the role of LDSE in prediction of various HF therapies, but the data on its significance in CRT patients are somewhat confusing [3, 4].

The multicentre myocardial Viability in Cardiac Resynchronization Therapy (ViaCRT) trial was designed to investigate the potential impact of myocardial viability on CRT efficacy as well as the role of selected echocardiography parameters in prediction of response to CRT. The purpose of this analysis was to determine the role of: (1) septal flash presence in M-Mode Echo before CRT implantation, and (2) myocardial contractile reserve determined in LDSE in prediction of clinical and echocardiographic response to CRT during 12-month follow-up in ischemic and non-ischemic LV dysfunction.

Material and methods

We analyzed 133 subjects (102 males, aged 63 ±10 years, Caucasian) enrolled in the ViaCRT Study with severe HFREF who met standard indications for CRT. ViaCRT was a prospective multicenter study conducted in 11 centers in Poland in 2009–2012. Key inclusion criteria were: sinus rhythm, LV ejection fraction (LVEF) ≤ 35%, QRS complex width ≥ 120 ms and NYHA class III or IV despite optimal medical treatment.

At baseline study population characteristics were as follows: LVEF 25 ±6%, QRS 165 ±25 ms, NYHA class III (90%) and IV (10%). Sixty-eight (51%) patients were diagnosed with HFREF of ischemic etiology (61 patients with history of myocardial infarction, 30 patients after coronary bypass) and 65 (49%) of non-ischemic origin of heart failure (post-inflammatory and primary dilative cardiomyopathy).

Main clinical parameters (NYHA class, age, sex distribution, medical treatment, comorbidities) and echocardiographic data (including standard echo parameters and asynchrony indices) were similar in both the ischemic and non-ischemic group.

Prior to CRT implantation all patients had standard transthoracic echocardiography performed and the presence or absence of septal flash was recorded (n = 87). Ninety-nine patients underwent low-dose dobutamine stress echo (up to 20 μg/kg/min) before CRT. Preserved contractile reserve was defined as LVEF increase by 20% or improved contractility in ≥ 4 segments during LDSE. Patients had clinical and echocardiographic follow-up visits scheduled for 6 weeks, 6 months and 12 months after CRT.

Baseline and 1-year follow-up data were analyzed in all study groups and in HF etiology subgroups separately.

The investigation conforms to the Declaration of Helsinki, and the local ethics committee approved the research. Written informed consent for non-standard procedures was obtained from patients prior to CRT implantation.

Statistical analysis

Statistical analysis was performed with Statistica 10.0 (StatSoft, Poland). All values were expressed as means ± standard error (average ± SEM). Differences were considered to be significant at $p < 0.05$. In order to check normality of the distribution, the Shapiro-Wilk test was performed. In case of a normal distribution the Student t-test was performed, otherwise the Mann-Whitney U test was used.

Results

Positive CR was observed in 46% of the general HF population (49% in ischemic HF, 44% in non-ischemic HF). Septal flash in baseline examination was observed in 24 of 87 (28%) (24% in ischemic HF, 31% in non-ischemic HF).

Patients with contractile reserve on LDSE experienced improvement in LVEF, end-systolic volume

Parameter Δ 1 year follow-up	CR+, *n* = 46	CR–, *n* = 53	*P*-value	SF+, *n* = 24	SF–, *n* = 63	*P*-value
Δ LVEDV [ml]	–46 ±7.7	–30 ±7.6	0.16	–46 ±10	–32 ±7	< 0.05
Δ LVESV [ml]	–49 ±7	–35 ±7.7	0.18	–63 ±10	–36 ±6	< 0.05
Δ LVEF (%)	11 ±1.5	9 ±1.5	0.2	14 ±2	8 ±1	< 0.05
Δ NYHA (%)	–0.96	–0.86	0.44	–1.1	–0.8	0.06

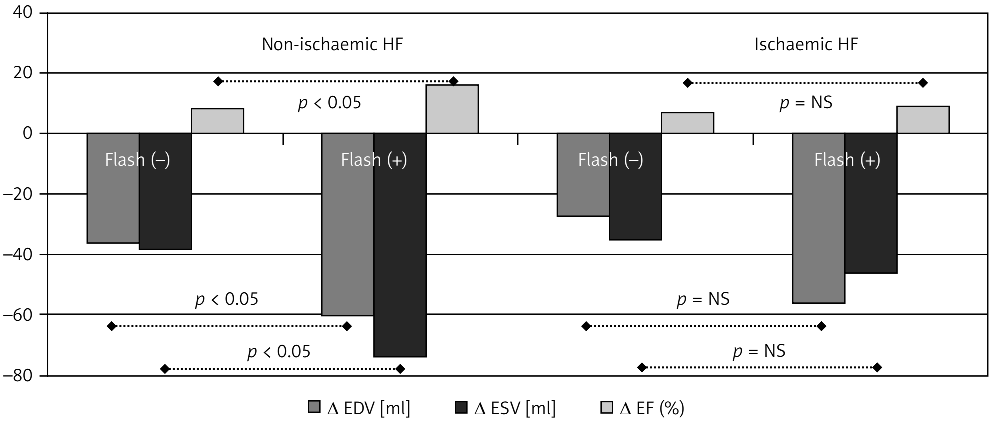

Figure 1. Top: table presenting changes of echocardiographic parameters and NYHA class after 1 year CRT vs. baseline (before CRT implantation) in patients with baseline contractile reserve (CR+) vs. patients without CR (CR–) and in subjects with septal flash before CRT (SF+) and without (SF–). Bottom: graph representing changes of LV parameters separately in ischemic and non-ischemic group

LVEDV – left ventricular end-diastolic volume, LVESV – LV end-systolic volume, LVEF – LV ejection fraction.

(ESV) and end-diastolic volume (EDV), but the difference did not reach statistical significance.

In subjects with septal flash registered before CRT implantation significant improvement in LVEF and LV systolic and diastolic volumes was observed (Figure 1 – top). Neither SF nor CR was associated with improvement in NYHA class.

Analysis in subgroups revealed that only in non-ischemic HF patients is presence of septal flash associated with LV function improvement after CRT (Figure 1 – bottom).

During the observation period 15 (11%) patients died and 5 (3.8%) patients were lost to follow-up.

Discussion

The growing number of CRT implants, high cost of the procedure and limited health care resources underline the importance of careful and accurate selection of candidates for the therapy. Apart from commonly used guideline criteria there is a need for a reproducible and easy to perform test to improve selection of responders for CRT.

Septal flash has recently been a subject of thorough research in patients with heart failure, as it has been reported to be a mechanism to link conduction abnormalities and IVS dyssynchrony in HF [5]. According to the most recently published data, SF predicts CRT response in patients with permanent atrial fibrillation [6]. Sohal *et al.* proved that SF presence in cardiac magnetic resonance is also an independent predictor of good response to CRT [7]. Recently Brunet-Bernard *et al.* suggested a multiparameter model for prediction of response to CRT, where presence of septal flash is an independent and strong predictor [8]. The model however does not distinguish etiology of HF. In our study both septal flash positive and negative groups showed improved in LVESV, EDV and EF, but the improvement was significantly more pronounced in patients with SF compared to subjects without SF. Moreover, subgroup analysis revealed that only in non-ischemic patients was SF related to better echocardiographic response, while in ischemic patients changes in echo parameters were similar in SF+ and SF– patients. One possible explanation is a specific pattern of conduction abnormalities seen in non-ischemic dilated cardiomyopathy, where the LV dyssynchrony pattern seems similar in most patients and is commonly associated with persistent or inducible LBBB.

In the ischemic group dyssynchrony patterns are more heterogeneous because various segments are involved depending on the ischemic region. This might explain why septal flash is less often found in this group and does not reflect synchrony abnormalities in all the subgroups.

Myocardial viability is another factor closely associated with HF prognosis and success of therapy. Although multiple studies suggest the role of CR in patient selection for CRT, it has not been reflected in guidelines to date. Several studies confirm the importance of viability in the region of LV pacing lead implantation [9, 10]. The criteria of CR, however, vary from study to study, making the conclusions confusing. In our study CR was defined as a relative increase of EF by 20% or in ≥ 4 viable segments on LDSE. We observed improvement in echo parameters in both CR+ and CR– groups, but the improvement in CR+ was not significantly better than in patients without CR. Further analysis is required to select a myocardial viability related parameter and/or cutoff point that would help to predict response to CRT.

To our knowledge this is the first study to date to analyze the effect of SF presence on CRT results in a large number of patients and with regard to etiology of HF. The results suggest that septal flash – an easy to obtain parameter in standard transthoracic echo – may be a useful parameter in prediction of response to CRT, particularly in non-ischemic HF patients. Further analysis is however required to evaluate the prognostic power of septal flash in CRT patients, and other parameters need to be considered to build an effective complex prognostic tool for identification of CRT responders.

In conclusion, in non-ischemic HF patients septal flash is a helpful parameter in prediction of LV remodeling after 12 months of resynchronisation therapy.

Conflict of interest

The authors declare no conflict of interest.

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