ORIGINAL ARTICLE

Role of low-dose dobutamine echocardiography in predicting response to biventricular pacing

Results from the multicenter Viability in Cardiac Resynchronisation Therapy (ViaCRT) study

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KEY WORDS

cardiac resynchronization therapy, dyssynchrony, myocardial viability

ABSTRACT

INTRODUCTION Response to cardiac resynchronization therapy (CRT) varies significantly among individuals, resulting in the lack of improvement in a substantial proportion of patients.

OBJECTIVES The study aimed to identify mechanical dyssynchrony indices in combination with myocardial viability characteristics for predicting long-term response to CRT.

PATIENTS AND METHODS ViaCRT was a prospective multicenter study involving 127 patients with heart failure. Cardiac dyssynchrony indices and low-dose dobutamine response were determined by echocardiography prior to CRT. Preserved contractile reserve was defined as improvement in the wall motion score index (WMSI) or left ventricular ejection fraction (LVEF) exceeding 20% at peak stress.

RESULTS A 12-month follow-up showed a significant difference in survival between the subgroups with and without viability assessed on the basis of a decrease in the WMSI, corresponding to 1 (4.4%) and 20 (19.4%) fatal events, respectively ($P = 0.048$). The predictive value of LVEF gain on dobutamine stress echocardiography (DSE) was only significant at 6 months, with all-cause death occurring in 1 (1.6%) and 7 (12.1%) patients with viable and nonviable myocardium, respectively ($P = 0.029$). A multivariate regression analysis identified the presence of septal flash and interventricular dyssynchrony as independent indices able to predict echocardiographic response alone at 12 months.

CONCLUSIONS The study demonstrated a significant relationship between left ventricular contractile reserve on DSE and long-term all-cause mortality following CRT device implantation. The presence of septal flash and interventricular dyssynchrony but not myocardial viability was predictive of the response to resynchronization. The results indicate that interference of multiple different mechanisms may be responsible for the general effect of CRT.

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Received: September 16, 2016.
Revision accepted: December 9, 2016.
Published online: December 12, 2016.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2016; 126 (12): 989-994
doi:10.20452/pamw.3715

INTRODUCTION Cardiac resynchronization therapy (CRT) has become a beneficial treatment option in patients with systolic heart failure and wide QRS complexes, as recommended with the highest level of evidence by clinical guidelines.[1-3] The beneficial effects of CRT are reduction of overall mortality, decreased hospitalization rate, functional capacity gain, and reversal of left ventricular (LV) remodeling. The response to CRT, however, varies significantly among

individuals, resulting in a lack of improvement among the substantial proportion of patients. To reduce the rate of such nonresponders, different predictors of beneficial outcome have been proposed, including numerous echocardiographic dyssynchrony indices and myocardial viability.[4-7] Although believed to be promising, their role remains controversial and there is no general acceptance to use them in clinical management of patients. This study sought to identify mechanical dyssynchrony indices with combination of myocardial viability assessment with low-dose dobutamine for predicting a long-term response to CRT, with both clinical and echocardiographic follow-up.

PATIENTS AND METHODS ViaCRT was an investigator-initiated multicenter study under the coordination of the Working Group on Echocardiography of the Polish Cardiac Society. Patients were enrolled across 12 centers in Poland between January 2009 and May 2012. The detailed list of participating institutions and investigators is given in the **APPENDIX**. The study was approved by local ethics committees, and patients provided written informed consent to participate in the study.

Patient population Patients with heart failure symptoms referred for CRT in line with the 2007 and 2008 guidelines of the European Society of Cardiology (ESC) were assessed prospectively.[8,9] The following inclusion criteria were applied: New York Heart Association (NYHA) functional class III or IV under optimal pharmacotherapy, QRS duration of 120 ms or higher, and LV ejection fraction (LVEF) of 35% or lower. Clinical assessment (NYHA functional class, 6-minute walk test, medical therapy, electrocardiography [ECG], and echocardiography) were performed at baseline and following CRT after 6 weeks, 6 months, and 12 months. All participating centers collected the data for an integrated database.

Echocardiographic imaging A standard transthoracic cardiac ultrasound examination was performed both at rest and during dobutamine infusion. This included the acquisition of optimized grey scale imaging data sets and spectral Doppler flows as well as myocardial velocity data. Vivid 7 and 9 (GE Vingmed, Horten, Norway) scanners were mainly used, while Philips IE 33 (Philips Healthcare, Best, The Netherlands) was used occasionally. The images were stored digitally for subsequent reading (EchoPac, GE Vingmed, Horten, Norway).

The following parameters were included into the analysis: LV internal dimensions in end-diastolic and end-systolic phases that were measured from parasternal long-axis 2-dimensional (2D) images; LV volumes and ejection fraction that were measured using the 2D Simpson method; peak E wave, its deceleration time, and A-wave velocities that were measured using transmitral flow velocities obtained from the apical 4-chamber view with pulsed-wave Doppler sample volume positioned at the tip of the leaflets; and stroke volume that was obtained at rest and at stress by the LV outflow (LVOT) Doppler method (outflow tract area × LVOT time velocity integral).

Mitral regurgitation (MR) severity was evaluated by an integrative approach, including the measurements of vena contracta at color Doppler images and the ratio of the MR jet to the left atrial area. Also, diastolic regurgitant flow was reported if present.

The conventional 16-segment LV model was used to characterize contraction by the echocardiographic wall motion score index (WMSI). Each of the segments was analyzed individually in multiple echocardiographic views on the basis of systolic thickening and motion. The segment function was scored as follows: normal = 1, hypokinetic = 2, akinetic = 3, and dyskinetic (or aneurysmatic) = 4. The WMSI was derived as the sum of all scores divided by the number of segments visualized.

Doppler myocardial imaging velocity data were recorded using a color-coded technique with a sector adjusted to include 2 opposing LV walls at optimal width and depth in apical views.. The longitudinal velocity profiles were also recorded using spectral images with the sample volume placed over the color-coded myocardial area at the septal and lateral mitral annulus and lateral tricuspid annulus in the apical 4-chamber view. This allowed us to calculate the E/E' ratio as well as to evaluate right ventricular (RV) systolic function.

Timing of diastole, systole, and isovolumic contraction (ICT) and relaxation times were determined using transmitral and aortic Doppler profiles.

Assessment of left ventricular mechanical dyssynchrony Several indices of intraventricular dyssynchrony were included into the study: 1) LV filling time (LVFT) in relation to cardiac cycle length (RR) as measured by transmitral pulsed-wave Doppler and expressed as percentage LVFT/RR[10]; 2) maximum difference of time to onset of systolic velocity for 6 segments at basal level[11]; and 3) septal flash, defined as the presence of an early septal wall thickening/thinning within the ICT at rest and/or during dobutamine stress echocardiography (DSE). The septal flash occurrence was determined on the short-axis or parasternal long-axis view either using grey scale or tissue Doppler color M-mode (rapid change of color related to the early and fast motion of the septum occurring during the ICT), as described previously.[12]

Interventricular delay was calculated as the difference between the LV and RV preejection periods from pulsed-wave Doppler velocity images of the corresponding outflow tracts.

Dobutamine stress echocardiography protocol β-blocker therapy was either temporarily discontinued 24 hours prior to the study, or the most

TABLE 1 Baseline characteristics of the study group (n = 127)

Parameter		Value
age, y, mean ± SD		62.7 ±9.3
sex, male, n (%)		100 (78.7)
QRS complex width, ms, mean ± SD		163 ±23
height, cm, mean ± SD		171 ±9.2
body mass, kg, mean ± SD		82 ±13.7
BMI, kg/m^2, mean ± SD		28.0 ±3.9
nonischemic etiology of HF, n (%)		67 (52.8)
previous MI, n (%)		61 (48.0)
previous CABG, n (%)		30 (23.8)
previous PTCA, n (%)		37 (29.4)
NYHA class, n (%)	I	1 (0.8)
	II	16 (12.6)
	II/III	2 (1.6)
	III	95 (74.8)
	III/IV	2 (1.6)
	IV	11 (8.7)
previous pulmonary edema, n (%)		15 (11.8)
diabetes, n (%)		40 (31.5)
arterial hypertension, n (%)		67 (52.8)
dyslipidaemia, n (%)		72 (57.6)
treatment with β-blockers		122 (96)
treatment with ACEIs		111 (88)
treatment with ARBs		11 (9)
CRT with defibrillating function		117 (92.9)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; HF, heart failure; MI, myocardial infarction; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angioplasty

recent dose of the medication was postponed and administered after completion of imaging. A standard low-dose DSE using the 16-segment LV model was performed by a graded dobutamine intravenous infusion, starting at a dose of 5 mg/kg/min, and increasing at 5-minute intervals to 10 mg/kg/min, 15 mg/kg/min, and a maximum of 20 mg/kg/min. Blood pressure and ECG recordings were obtained at rest and at the end of every stage of the protocol. The infusion was terminated if completion of the protocol or 85% of the maximum age-predicted heart rate was achieved. Also, dobutamine was discontinued if any of the following events occurred: arrhythmia, angina, hemodynamic decompensation, as well as new ECG abnormalities or new wall motion abnormalities in at least 2 LV segments. Improvement in the WMSI or in LVEF exceeding 20% from baseline to peak stress was considered significant for detection of preserved contractile reserve.

Definition of response Response to CRT was defined as a relative change in LV end-systolic volume leading to a reduction of more than 10% compared with baseline (paired LV end-systolic volume measurements). This approach is in agreement with a previous report.[13] Additionally, LVEF measurements were included into the analysis of the CRT effect on myocardial contraction from baseline through follow-up. Clinical improvement was also assessed, corresponding to an increase in the 6-minute walk test of 10% or higher or a reduction in NYHA functional class of 1 or more.

Statistical analysis Normally distributed continuous variables were expressed as mean ± SD, unless otherwise indicated. Dichotomous data were expressed as percentages. Continuous variables within and between groups were compared using 2-tailed paired and unpaired *t* test. Categorical data were compared using the Fisher exact test or the χ^2 test. Continuous variables were correlated using a simple regression test. The following parameters were planned to be tested a priori for significance: contractile reserve during low-dose DSE, correlation between contractile reserve and degree of reverse remodeling, and correlation between contractile reserve and clinical improvement. A *P* value of less than 0.05 was considered statistically significant. The analyses were performed with the use of SAS/STAT software (SAS Institute Inc, Cary, North Carolina, United States). A multivariate analysis was performerd using stepwise multiple regression and including standard error of coefficient.

RESULTS A total of 127 patients were studied. Their baseline characteristics are presented in TABLE 1. Heart failure with reduced LVEF included ischemic as well as nonischemic etiology. Sinus rhythm was seen on ECG in all patients. On DSE, preserved LV contractile reserve was detected in 23 patients (18%) with regards to an increase in the WMSI increase and in 62 patients (48.0%) with regards to an improvement in LVEF.

Responders and nonresponders in echocardiographic and clinical follow-up Death from all-cause occurred in 21 patients (16.5%) at 12 months. There was a significant difference in mortality between the subgroups with and without preserved LV contractile reserve detected by an increase in the WMSI, corresponding to 1 (4.4%) and 20 (19.4%) fatal events, respectively (*P* = 0.048). The predictive value of an increase in LVEF on DSE was only significant at 6 months, with all--cause death occurring in 1 patient (1.6%) with viabile myocardium and 7 patients (12.1%) with nonviable myocardium (*P* = 0.029). No significant differences in both clinical and echocardographic responder rates were observed at 12 months between surviving patients with and without LV contractile reserve, determined by a reduction in the WMSI as well as an increase in LVEF (TABLE 2). There was a weak but significant correlation between the echocardiographic response to CRT at 12 months and improvement of LV contractility during DSE, baseline interventricular dyssynchrony, as well as intraventricular dyssynchrony expressed by the maximum difference of time to onset of systolic velocity for 6 segments at basal

TABLE 2 Responder rates at 12 months of follow-up in the subgroups of patients with and without left ventricular contractile reserve identified during dobutamine study prior to cardiac resynchronization therapy device implantation

Parameter	No contractile reserve by LVEF improvement	Contractile reserve by LVEF improvement	*P* value
responders at 12 months based on:			
ESV reduction	24 (54.6)	35 (72.9)	0.1856
LVEF increase	32 (72.7)	40 (83.3)	0.2179
NYHA class reduction	34 (75.6)	33 (68.7)	0.4649
6MWT prolongation	24 (64.9)	25 (64.1)	0.9447
parameter	no contractile reserve by WMSI improvement	contractile reserve by WMSI improvement	
responders at 12 months based on:			
ESV reduction	44 (58.7)	15 (79.0)	0.1027
LVEF increase	59 (78.7)	14 (73.7)	0.7584
NYHA class reduction	60 (76.0)	13 (68.4)	0.5609
6MWT prolongation	43 (65.1)	9 (60)	0.7072

Data are presented as number (percentage) of patients.

Abbreviations: 6MWT, 6-minute walk test; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; others, see TABLE 1

TABLE 3 Correlations between echocardiographic response by reduction in end--systolic volume at 12 months of follow-up, contractile reserve during dobutamine study, and dyssynchrony indices

Parameter	ESV reduction at 12 months
contractile reserve by WMSI improvement	$r = 0.37$ $P = 0.0003$
contractile reserve by LVEF improvement	$r = 0.25$; $P = 0.0171$
interventricular dyssynchrony	$r = 0.28$ $P = 0.0067$
maximum difference of time to onset of systolic velocity for 6 segments at basal level	$r = 0.21$ $P = 0.049$

Abbreviations: WMSI, wall motion score index; others, see TABLE 2

TABLE 4 Independent predictors of echocardiographic response at 12 months of follow-up by multivariate analysis

ESV reduction at 12 months	Regression coefficient ±SE	*P* value
septal flash	27.5 ±13.04	0.04
interventricular dyssynchrony	0.36 ±0.15	0.04
matching	$P = 0.0018$	$R^2 = 0.17$

Abbreviations: SE, standard error; others, see TABLE 2

level (TABLE 3). No such correlation was observed for clinical response. Regarding the identification of potential echocardiographic predictors, patients with septal flash before the device therapy were more likely to present with beneficial echocardiographic response at 12 months (22 of 24 patients, 91.7% vs 42 of 62 patients, 67.7%; $P = 0.0226$, odds ratio, 3.78 [confidence interval, 0.97–14.79]). Apart from that, other indices of dyssynchrony did not show any significant predictive value for echocardiographic or clinical improvement.

Multivariate analysis In a stepwise regression analysis, the presence of septal flash and interventricular dyssynchrony were identified as independent indices with the ability to predict echocardiographic response at 12 months (TABLE 4). Septal flash and myocardial viability determined by an increase in LVEF during DSE were predictors of beneficial LV remodeling only at 6 weeks and 6 months.

DISCUSSION

Survival at follow-up The present ViaCRT study demonstrated a significant relationship between LV contractile reserve at baseline DSE and all-cause mortality in patients with a subsequent implantation of CRT device. The detection of viability determined by the decrease of the WMSI was a predictor of improved survival at long term, whereas the increase of LVEF had a beneficial effect on the risk of fatal events at 6 weeks and 6 months. These findings provide an important additional insight into the concept of management efficacy in patients considered for biventricular pacing and are in agreement with the previously published prospective follow--up.[14] Another multicenter trial, LODO,[6] demonstrated a significant difference between patients with and without LV contractile reserve, but the clinical benefit was only reported evaluating a composite endpoint of cardiac survival/hospitalization. A number of studies on the role of dobutamine in the assessment of candidates for CRT did not include all-cause mortality for the follow-up analysis.[7,12] However, the most recent report has found no association between contractile reserve on low-dose DSE with a threshold of 5% change in LVEF and long-term survival.[15] In the ViaCRT cohort, the underlying mechanism of fatal events was not studied. Furthermore, the assessment did not include prognostic significance of biomarkers.[16]

Echocardiographic and clinical parameters reflecting response to cardiac resynchronization therapy Unlike in the LODO trial and some other reports, detection of LV viability with a dobutamine test in the ViaCRT study was not predictive of the response to CRT at long-term follow-up. This is also contrary to a 6-week follow-up of the ViaCRT study group, which was published before.[17] The potential explanation is the difference in mortality between the subgroups with and without contractile reserve: it was demonstrated to be significant at 12 months but not at 6 weeks of follow-up. Furthermore, in the LODO trial,[6] the absence of cardiovascular death or heart failure hospitalization was defined as clinical response, while the 6-minute walk test and NYHA class were not assessed.

As septal flash was the echocardiographic parameter predicting response to CRT in our study, these results are consistent with a previous publication by other group.[12] From a different

perspective, the analysis of the CARE-HF trial[18] data showed that patients with more severe interventricular dyssynchrony derived greater benefit from CRT. Taking these data together with discrepant findings on the role of contractile reserve, it appears likely that there are multiple different mechanisms behind the response to CRT, as was suggested previously.[4] Therefore, according to the latest ESC guidelines on cardiac pacing and CRT, LV dyssynchrony assessment with imaging techniques is unreliable and should not be used as a selection criterion for CRT.[1] Furthermore, there is a spectrum of responses to biventricular pacing.[1] The choice of criteria for echocardiographic and clinical improvement varies between studies, complicating a direct comparison.

In conclusion, the ViaCRT study demonstrated a significant relationship between LV contractile reserve detected by low-dose dobutamine echocardiography and all-cause mortality during long-term follow-up in patients with an implantation of CRT device. On the contrary, the presence of septal flash and interventricular dyssynchrony but not detection of LV viability was predictive of the response to CRT. The results indicate that the interference of multiple different mechanisms may be responsible for the general effect of CRT.

Contribution statement EP-G conceived the idea for the study and coordinated the project. All authors were involved in data collection. EP-G, JD-K, and LC analyzed the data. All authors revised the manuscript critically for important intellectual content and provided final approval of the version to be submitted.

Appendix Institutions and investigators participating in ViaCRT study: Chair and Department of Cardiology, Medical University of Lodz, Lódź, Poland: Łukasz Chrzanowski, Jarosław D. Kasprzak; Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Center for Heart Disease, Medical University of Silesia, Zabrze, Poland: Tomasz Kukulski; I Chair and Department of Cardiology, Medical University of Silesia, Upper Silesia Medical Centre, Katowice, Poland: Katarzyna Mizia-Stec, Krystian Wita; Department of Cardiology, Medical University of Silesia, Zabrze, Poland: Ewa Nowalany-Kozielska; II Chair and Department of Cardiology, Medical University of Silesia, Upper Silesia Medical Centre, Katowice, Poland: Zbigniew Gąsior; II Chair and Department of Cardiology, Nicolas Copernicus University, Bydgoszcz, Poland: Władysław Sinkiewicz, Wojciech Gilewski; 2nd Department of Coronary Artery Disease, Institute of Cardiology, Warsaw, Poland: Hanna Szwed; Department of Cardiology, Provincial Hospital, Szczecin, Poland: Piotr Gosciniak; Department of Cardiology, Pomeranian Medical University, Szczecin, Poland: Edyta Płońska-Gościniak; Lower Silesia Specialist Hospital: Tadeusz Marciniak Centre For Emergency Medicine, Wrocław, Poland: Krystyna Łoboz-Grudzień; Department of Coronary Artery Disease, Institute of Cardiology, Jagiellonian University Medical College in John Paul II Hospital, Kraków, Poland: Andrzej Gackowski; Chair and Department of Cardiology, Medical University of Lublin, Lublin, Poland: Andrzej Tomaszewski.

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ARTYKUŁ ORYGINALNY

Znaczenie echokardiografii obciążeniowej z niską dawką dobutaminy w przewidywaniu odpowiedzi na stymulację dwukomorową

Wyniki badania wieloośrodkowego Viability in Cardiac Resynchronisation Therapy (ViaCRT)

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SŁOWA KLUCZOWE

dyssynchronia, terapia resynchronizująca, żywotność mięśnia sercowego

STRESZCZENIE

WPROWADZENIE Odpowiedź na terapię resynchronizującą (*cardiac resynchronization therapy* – CRT) jest wysoce zróżnicowana u różnych pacjentów i u znacznego ich odsetka wiąże się z brakiem poprawy.

CELE Celem badania była ocena przydatności wskaźników dyssynchronii mechanicznej w połączeniu z charakterystyką żywotności mięśnia sercowego w przewidywaniu długoterminowej odpowiedzi na CRT.

PACJENCI I METODY W wieloośrodkowym prospektywnym badaniu ViaCRT oceniono 127 pacjentów z niewydolnością serca. Przed zastosowaniem CRT określano echokardiograficznie wskaźniki dyssynchronii i reakcję na obciążenie niską dawką dobutaminy. Zachowaną rezerwę kurczliwości stwierdzano na podstawie poprawy wskaźnika kurczliwości odcinkowej ścian lewej komory (*wall motion score index* – WMSI) lub frakcji wyrzutowej lewej komory (*left ventricular ejection fraction* – LVEF) przekraczającej 20% podczas szczytowego obciążenia.

WYNIKI W obserwacji 12-miesięcznej wykazano istotną różnicę w przeżywalności między grupami z zachowaną żywotnością i jej brakiem na podstawie oceny zmniejszenia WMSI, obejmującą wystąpienie odpowiednio 1 (4,4%) i 20 (19,4%) zgonów ($p = 0,048$). Wartość predykcyjna wzrostu LVEF podczas próby dobutaminowej okazała się istotna jedynie w okresie 6-miesięcznym – stwierdzona śmiertelność całkowita wynosiła 1 (1,6%) w grupie z zachowaną kurczliwością i 7 (12,1%) w grupie bez rezerwy kurczliwości ($p = 0,029$). Analiza wieloczynnikowa wykazała wczesnoskurczową czynność mechaniczną przegrody międzykomorowej (*septal flash*) i dyssynchronię międzykomorą jako niezależne czynniki pozwalające przewidzieć odpowiedź – wyłącznie echokardiograficzną – na CRT po 12 miesiącach.

WNIOSKI Badanie wykazało istotną zależność pomiędzy rezerwą kurczliwości lewej komory w próbie dobutaminowej a całkowitą śmiertelnością w obserwacji długoterminowej u pacjentów po implantacji układu CRT. Obecność wczesnoskurczowej czynności mechanicznej przegrody międzykomorowej i dyssynchronii międzykomorowej miała znaczenie predykcyjne w zakresie odpowiedzi na resynchronizację, bez związku z żywotnością. Wyniki wskazują na potencjalne nakładanie się wielu zróżnicowanych mechanizmów warunkujących ogólny efekt terapeutyczny CRT.

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Praca wpłynęła: 16.09.2016.
Przyjęta do druku: 09.12.2016.
Publikacja *online*: 12.12.2016.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2016; 126 (12): 989-994
doi:10.20452/pamw.3715