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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Are changes in heart rate, observed during dobutamine stress echocardiography, associated with a response to cardiac resynchronisation therapy in patients with severe heart failure? Results of a multicentre ViaCRT study

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Abstract

Background: According to current European Society of Cardiology guidelines for the diagnosis and treatment of heart failure (HF), cardiac resynchronisation therapy (CRT) is indicated in patients suffering from HF with reduced ejection fraction (EF) with significantly widened QRS complexes. The presence of vital myocardium proven by dobutamine stress echocardiography (DSE) is considered as a good prognostic factor for responsiveness to this treatment. Chronotropic incompetence is, on the other hand, a known factor of unfavourable outcome in HF.

Aim: The aim of this study was to analyse the relationship between heart rate (HR) response during DSE and resultant changes in echocardiographic parameters determined prior to CRT and six weeks post-implantation of the CRT system.

Methods: The study included 72 men and 25 women with chronic HF and markedly deteriorated left ventricular (LV) systolic function (EF < 35%). Low-dose DSE was performed prior to the CRT system implantation. Baseline echocardiographic parameters determined before CRT were compared to those measured six weeks after implantation.

Results: Implantation of the CRT system resulted in an improvement of LV systolic function. DSE showed a significant increase in HR, by 16.3 bpm on average. Patients with the least prominent increase in HR during DSE (< 7 bpm) presented with significantly greater end-diastolic LV dimension and volume, as well as with significantly lower EF than the subjects with the most evident increase in HR (> 24 bpm). Improvement in EF at six weeks was associated with lower baseline HR and its greater absolute and relative increase during DSE. Greater absolute increase in HR during DSE was also associated with more prominent decrease in systolic/diastolic LV volumes.

Conclusions: Patients with better chronotropic response during DSE show significant improvement in LV parameters determined by echocardiography within six weeks of CRT. Chronotropic response to pharmacologic stress test may serve as a predictive factor in patients qualified for CRT.

Key words: dobutamine stress echocardiography, chronotropic incompetence, cardiac resynchronisation therapy, chronic heart failure

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INTRODUCTION

European Society of Cardiology (ESC) defines heart failure (HF) as a syndrome in which patients present with typical symptoms (e.g. breathlessness, fatigue, ankle swelling) and signs (e.g. elevated jugular venous pressure, pulmonary crackles) resulting from abnormal structure and function of the heart [1]. Ejection fraction (EF) is an established parameter used to determine the severity of global left ventricular (LV) systolic dysfunction. In order to maintain forward stroke volume in spite of contractile dysfunction, LV dilation develops, resulting in a larger end-systolic LV volume and declined EF. HF with reduced EF (HFrEF) is diagnosed whenever EF decreases below 40%. Due to severe clinical manifestations, patients with HFrEF are subjected to many trials assessing treatment efficacy and prognosis in this group.

Management of HF is based on pharmacotherapy, aimed at the inhibition of unfavourable neurohormonal and haemodynamic processes leading to further deterioration of cardiac function. Both preliminary trials of beta-adrenolytics (e.g. CIBIS II) [2] and recent research on ivabradine (an inhibitor of I_f channel in the sinoatrial myocytes) (e.g. SHIFT) [3] point to an important role of heart rate (HR) as a marker of HF progression.

In line with the guidelines on HF management [1], cardiac pacing, and resynchronisation [4], most patients with severe LV systolic dysfunction (i.e. with EF < 35%) should be qualified to treatment with implanted cardioverter-defibrillator (ICD) in order to prevent sudden cardiac death. Selected patients from this group may benefit from cardiac resynchronisation therapy (CRT). A large body of evidence suggests that CRT may decrease mortality and hospitalisation rates, and it improves LV systolic function in most patients with significantly reduced EF (< 35%), sinus rhythm, and left bundle branch block (LBBB) with QRS complexes exceeding 130 ms. CRT was shown to provide additional benefits aside from those resulting from optimal pharmacotherapy and ICD. CRT is also justified in patients with widened QRS complexes of a non-LBBB morphology, no smaller than 150 ms [1, 4].

The principal aim of the prospective multicentre Viability in Cardiac Resynchronisation Therapy (ViaCRT) trial was to determine LV myocardial viability during dobutamine stress echocardiography (DSE) in patients scheduled for CRT due to severe HF. In our previous contributions, we examined a relationship between the presence of viable myocardium and response to CRT [5]. The aim of this study is to analyse retrospectively the association between HR response during DSE and resultant changes in echocardiographic parameters determined prior to CRT and six weeks post-implantation.

METHODS

The protocol of the study was approved by the Local Bioethics Committee at L. Rydygier Collegium Medicum in Bydgoszcz and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study included 97 patients (72 men and 25 women) with HF. The inclusion criteria of the study were: markedly deteriorated LV systolic function (EF < 35%), stable clinical status, at least one-month history of optimal pharmacotherapy, and qualification for CRT at one of the clinical centres participating in the ViaCRT project. Mean age of the study participants was 61.9 years (range 31–83 years). The majority of patients represented New York Heart Association (NYHA) functional class III (n = 74, 76.3% of the study group); NYHA class II and ambulatory NYHA class IV were represented by 14 (14.4%) and 9 (9.2%) subjects, respectively. Detailed characteristics of the study participants are summarised in Table 1. During recruitment, aside from routine clinical evaluation and laboratory testing, all patients were subjected to resting echocardiography with determination of selected LV systolic and diastolic parameters

Table 1. Characteristics of the study participants

Study group	N = 97	100%	Baseline parameters	Mean ± SD
Men	72	74.2%	Body height [cm]	170.33 ± 9.39
Women	25	25.8%		
Ischaemic aetiology	42	43.3%	Body weight [kg]	81.46 ± 13.52
Non-ischaemic aetiology	55	56.7%		
NYHA functional class:			Ejection fraction [%]	24.73 ± 6.3
II	14	14.4%		
III	74	76.3%		
IV	9	9.2%		
Comorbidities:			Heart rate [bpm]	71.15 ± 11.80
Arterial hypertension	47	48.5%		
Diabetes mellitus	29	29.9%		

Data are shown as mean ± standard deviation (SD) or number and percentage. NYHA — New York Heart Association

Table 2. Echocardiographic parameters determined prior to the cardiac resynchronisation therapy system implantation (at the baseline) and after a six-week follow-up

Parameter	Baseline	After six weeks	p
VTI LVOT [cm]	18.38 ± 11.97	18.76 ± 5.26	0.001
LA area [cm^2]	26.18 ± 7.85	23.16 ± 6.95	0.001
LVDd [mm]	70.89 ± 9.16	66.65 ± 11.23	< 0.001
LVDs [mm]	61.18 ± 9.76	56.97 ± 10.92	< 0.001
LVEDV [mL]	247.60 ± 99.38	218.20 ± 98.47	< 0.001
LVESV [mL]	187.99 ± 88.54	151.80 ± 86.54	< 0.001
LVEF [%]	24.73 ± 6.32	32.78 ± 9.50	< 0.001
E/e'	16.56 ± 8.59	12.56 ± 6.07	< 0.001
Heart rate [bpm]	71.15 ± 11.80	70.18 ± 10.71	< 0.001

Data are shown as mean ± standard deviation. VTI LVOT — left ventricular outflow tract velocity time integral; LA area — left atrial area; LVDd/s — left ventricular systolic/diastolic diameter; LVEDV/LVESV — left ventricular systolic/diastolic volume; LVEF — left ventricular ejection fraction; E/e' — the ratio of mitral annular velocity to early diastolic velocity of the mitral annulus

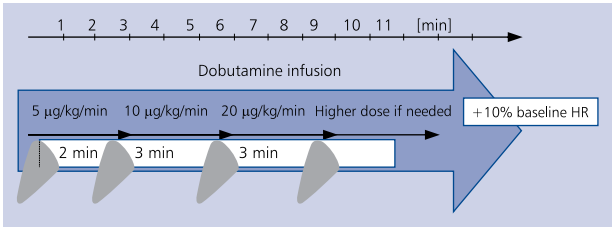

Figure 1. Protocol of dobutamine infusion during low-dose dobutamine stress testing. Increasing doses of dobutamine infused every 3 min with the intention to augment heart rate (HR) at approximately 10% of its baseline value. Grey beams represent timing of echocardiography images acquisition: 2 min after an increase in dobutamine dose

(Table 2). Subsequently, a low-dose DSE was performed to determine the degree of myocardial viability. Increasing doses of dobutamine (5–10–20 µg/kg/min) were meant to augment HR to at least 110% of its baseline count (Fig. 1).

Heart rate was determined at rest (DOB HR 0) and at peak load (DOB HR S). Subsequently, a CRT device was implanted in line with current guidelines. Six weeks after the implantation, another resting echocardiography was performed along with HR determination. Due to different pathophysiology and likely problems with interpretation of the echocardiograms, the data of patients who showed the evidence of atrial fibrillation during the test were excluded from further analysis.

Statistical analysis

Statistical analysis was performed with the Statistica 10.0 package (StatSoft, USA). Normal distribution of continuous variables was verified with Kolmogorov-Smirnov test. Depending on the distribution type, continuous variables were presented as means, standard deviations, medians, and lower and upper quartiles. Intergroup comparisons were conducted with Student t-test for independent variables and Mann-Whitney U-test or, whenever the number of subgroups was greater than two, using ANOVA with Tukey post-hoc test and Kruskal-Wallis test with Dunn's post-hoc test. The significance of intragroup differences was verified with Friedman ANOVA. Correlations between the pairs of variables were determined using Pearson's linear correlation coefficients (r) and Spearman's rank correlation coefficients (R). The threshold of statistical significance for all the tests was set at $p \leq 0.05$.

RESULTS

Echocardiography performed six weeks post-implantation of the CRT system documented an improvement of LV systolic function, manifesting as a significant increase in EF ($p < 0.001$), as well as a significant decrease in systolic and diastolic LV dimensions/volumes. Moreover, a significant decrease in E/e' value and left atrial area, corresponding to a drop off in LV filling pressure, was observed, along with a significant reduction of HR (Table 2).

A low-dose DSE conducted prior to the CRT system implantation resulted in a significant increase in HR, by 16.3 bpm on average (range 14.0–67.0 bpm) or by 23.7% (range 17.1–103.3%) of the baseline value. Mean dose of dobutamine was 21.6 ± 4.2 µg/kg/min, and the test lasted on average 11 ± 4.6 min. Maximum HR did not differ significantly, irrespective of the dobutamine dose and duration of the test. No significant association was found between HR at rest and the relative increase in this parameter (a difference between HR at baseline and at peak load). A number of statistically significant correlations were found between the HR indices and echocardiographic parameters at baseline and after a six-week follow-up (Table 3).

Stratification of the study group according to the quartile values of HR at rest and at peak load, and according to the absolute and relative increase in HR, enabled more comprehensive analysis of these relationships (Table 4). The subgroups of patients with extremely low and extremely high HR at baseline (< 62 bpm and ≥ 78 bpm, respectively) differed significantly in terms of their LV outflow tract velocity time integral values determined at baseline and after a six-week follow-up. Comparative analysis of the subgroups identified on the basis of HR at peak load (< 100 bpm vs. ≥ 100 bpm) revealed significant differences in end-systolic LV volume at the baseline and after a six-week follow-up. Patients with the most prominent increase in HR during DSE (> 24 bpm) were characterised by a significantly smaller left atrial area, both at baseline and after a six-week follow-up.

The most interesting relationships were associations between the increase in HR during DSE and LV dimension or EF

Table 3. Coefficients of correlation between heart rate indices and echocardiographic parameters

Variables	n	R	p
Significant correlations at the baseline (0 w)			
DOB HR 0 w & VTI LVOT 0 w	81	–0.304	0.006
ΔDOB HR & LA area 0 w	95	–0.240	0.019
ΔDOB HR% & LA area 0 w	95	–0.226	0.027
ΔVTI*HR & LA are 0 w	66	–0.246	0.047
ΔVTI*HR (%) & VTI LVOT 0 w	68	–0.287	0.018
Significant correlations at 6 weeks (6 w)			
DOB HR 0 w & VTI LVOT 6 w	70	–0.247	0.039
DOB HR 0 w & LVEF 6 w	79	–0.239	0.034
ΔDOB HR & LVEF 6 w	79	0.244	0.030
ΔDOB HR & LVDs 6 w	76	–0.234	0.042
ΔDOB HR% & LVEF 6 w	79	0.280	0.012
ΔVTI*HR & LA area 6 w	57	–0.280	0.035

DOB HR 0 — heart rate prior to dobutamine stress echocardiography; ΔDOB HR — absolute increase in heart rate during dobutamine stress echocardiography; ΔDOB HR% — relative (%) increase in heart rate during dobutamine stress echocardiography; ΔVTI*HR — increase of the product of multiplication of VTI LVOT and heart rate during dobutamine stress echocardiography; 0 w — measurement at baseline; 6 w — measurement at six weeks; other abbreviations as in Table 2

at six weeks. Patients with the least prominent increase in HR (< 7 bpm) presented with significantly greater end-diastolic LV dimension and volume, as well as with significantly lower EF than the subjects with the most evident increase in HR (> 24 bpm). Comparative analysis of EF values at baseline and at six weeks showed that the improvement in this parameter was associated both with lower HR at the baseline and with its greater relative increase. Furthermore, the greater absolute increase in HR during DSE turned out to be associated with a more prominent decrease in systolic/diastolic LV volume and an increase in EF at six weeks (Table 5).

Owing to improvement in mean values of many echocardiographic parameters observed over a six-week follow-up (Table 2), we verified whether these changes were associated with HR indices measured during DSE (Table 5). None of the analysed parameters showed correlation with the peak dobutamine dose.

Interestingly, HR at six weeks did not correlate significantly with the improvement in any of the analysed echocardiographic parameters. Patients in whom the biventricular stimulation rate exceeded 95% of all stimuli presented with a significantly more prominent decrease in LV diastolic dimension ($p = 0.05$) and LV end-diastolic volume ($p = 0.032$), as well as with less prominent decrease in E/e' ($p = 0.006$) than individuals with biventricular stimulation rate ≤ 95%. In contrast, we did not observe statistically significant associations between the biventricular stimulation rate and EF dynamics.

DISCUSSION

Resting HR is an established prognostic factor in HF. The CIBIS II trial showed that low HR at baseline (prior to administration of bisoprolol) was associated with the lowest mortality and lowest hospitalisation rates due to chronic HF [2]. Medical therapy, leading to a decrease in HR of patients with severe LV dysfunction, exerts beneficial effects on both the incidence of HF exacerbation (BEAUTIFUL) [6] and mortality (CIBIS II, SHIFT) [2, 3]. HR above 70 bpm was shown to be associated with more frequent exacerbations and hospitalisations due to HF.

Also, a change in HR during physical exercise reflects cardiovascular capacity and may have prognostic value. Jouven et al. [7] conducted a 23-year follow-up of nearly 6000 males without clinical evidence of cardiovascular disease, and showed that the risk of sudden cardiac death was increased in subjects with resting HR > 75 bpm (relative risk [RR] 3.95, 95% confidence interval [CI] 1.91–8.00), lesser (< 89 bpm) increase in HR during exercise (RR 6.18, 95% CI 2.37–16.11), and a post-exercise decrease in HR of < 25 bpm (RR 2.20, 95% CI 1.02–4.74). These findings point to an important role of so-called chronotropic incompetence of the heart (CI), i.e. an inability to adequately increase HR in response to physical exercise. Usually, CI is defined as an inability to achieve 80% of maximum predicted HR (calculated from the Astrand formula: $HR_{max} = 220 - age$). As early as in 1996, Lauer et al. [8] reported a significant association between all-cause mortality, incidence of coronary episodes, and presence of CI in healthy subjects. Another study conducted by these authors [9], including a similar group of subjects, showed that CI is associated with increased LV mass and cavity size. Jorde et al. [10] demonstrated that nearly a half (46%) of patients with decreased EF (< 40%) may present with the signs of CI. While CI occurred irrespective of beta-blocker use, it was associated with impaired exercise capacity expressed as peak oxygen uptake (VO_2peak) during cardiopulmonary exercise testing. Up to 70% of patients with VO_2peak < 14 mL/kg/min presented with CI. The effect of beta-blockers on the incidence of CI in patients with chronic HF was in turn reported by Witte et al. [11]. However, CI due to aggressive beta-blocker treatment did not predict mortality in the latter study. Elhendy et al. [12] confirmed that CI is a strong independent predictor of all-cause mortality and cardiac mortality in patients subjected to exercise echocardiography. However, worse prognosis was observed in patients who presented with both impaired EF and concomitant CI. In turn, Schmid et al. [13] showed that an exercise-induced increase in HR, by 30 bpm, predicted improvement in physical capacity during cardiac rehabilitation.

The ability to achieve a maximum predicted HR during pharmacologic stress echocardiography was the subject of few previous studies. Elhendy et al. [14] performed DSE (dobutamine 40 μg/kg/min, up to 1 mg atropine whenever needed) in 512 patients with suspected ischaemic heart

Table 4. Echocardiographic parameters in subsets of patients defined on the basis of the quartile values for heart rate indices

Dependent variable	DOB HR 0 w < 62 bpm		DOB HR 0 w 62–70 bpm		DOB HR 0 w 71–77 bpm		DOB HR 0 w ≥ 78 bpm		p
	N	Median	N	Median	N	Median	N	Median	
VTI LVOT 0 w	19	20*	23	16*	16	16	23	15	0.01
Dependent variable	**DOB HR S < 74**		**DOB HR S 74–85**		**DOB HR S 86–99**		**DOB HR S ≥ 100**		**p**
	N	Median	N	Median	N	Median	N	Median	
VTI LVOT 0 w	18	20*	21	16	19	14*	23	17	0.009
LVDd 0 w	23	71	23	71	25	74*	26	68*	0.017
LVEDV 0 w	23	233	23	217	25	258*	26	207*	0.045
Dependent variable	**ΔDOB HR < 7 bpm**		**ΔDOB HR 7–12 bpm**		**ΔDOB HR 13–23 bpm**		**ΔDOB HR ≥ 24 bpm**		**p**
	N	Median	N	Median	N	Median	N	Median	
LA area 0 w	25	26	19	25	28	28*	23	22*	0.01
Dependent variable	**DOB HR 0 w < 62 bpm**		**DOB HR 0 w 62–70 bpm**		**DOB HR 0 w 71–77 bpm**		**DOB HR 0 w ≥ 78 bpm**		**p**
	N	Median	N	Median	N	Median	N	Median	
VTI LVOT 6 w	16	21*	18	17	16	19	20	15*	0.03
Dependent variable	**DOB HR S < 74 bpm**		**DOB HR S 74–85 bpm**		**DOB HR S 86–99 bpm**		**DOB HR S ≥ 100 bpm**		**p**
	N	Median	N	Median	N	Median	N	Median	
LVEDV 6 w	18	193	20	200	19	254*	21	165*	0.011
LVESV 6 w	18	127	20	145	20	167*	21	101*	0.021
Dependent variable	**ΔDOB HR < 7 bpm**		**ΔDOB HR 7–12 bpm**		**ΔDOB HR 13–23 bpm**		**ΔDOB HR ≥ 24 bpm**		**p**
	N	Median	N	Median	N	Median	N	Median	
LA area 6 w	19	26	16	20	19	27*	17	19*	0.01
LVEF 6 w	20	27*	20	34	21	31	18	38*	0.03
LVDs 6 w	19	65*	18	53	21	57	18	52*	0.02
LVEDV 6 w	20	241*	18	183	22	213	18	168*	0.04
LVESV 6 w	20	160*	19	123	22	141	18	103*	0.03
Dependent variable	**ΔDOB HR% < 11%**		**ΔDOB HR% 11–17%**		**ΔDOB HR% 18–35%**		**ΔDOB HR% ≥ 36%**		**p**
	N	Median	N	Median	N	Median	N	Median	
LVEF 6 w	22	28*	21	32	20	31	16	39*	0.021

Asterisks (*) indicate median values that differ significantly between quartiles (according to p value). DOB HR S — heart rate at peak dobutamine load, other abbreviations as in Table 2 and 3.

disease, non-treated with beta-adrenolytics. Target HR was not achieved in up to 38% of the subjects, especially in young men with low baseline HR and LV systolic dysfunction at rest. Chaowalit et al. [15] conducted a multivariate analysis of the data from more than 3000 DSEs with no evidence of ischaemic heart disease; they revealed that the occurrence of CI during the test exerted a significant effect on further incidence of cardiovascular episodes. Unfortunately, few previous studies analysed HR in patients with chronic HF during beta-mimetic stress echocardiography. Colucci et al. [16] demonstrated that patients with chronic systolic HF (EF 20 ± 4%), either exposed to physical exercise or administered intravenous isoproterenol, were characterised by relatively low increase in HR compared to the controls. VO_2peak correlated strongly with peak HR and increase in HR during exercise. The authors of this study reported that a nearly two-fold weaker chronotropic response

Table 5. Coefficients of correlation between heart rate indices determined during dobutamine stress echocardiography and changes in echocardiographic parameters documented over a six-week follow-up

Variables	n	R	p
DOB HR 0 w & ΔLVEF	79	-0.247	0.028
ΔDOB HR & ΔLVEF	79	0.261	0.020
ΔDOB HR & ΔLVEDV	78	–0.226	0.047
ΔDOB HR & ΔLVESV	79	–0.228	0.043
ΔDOB HR% & ΔLVEF	79	0.275	0.014
ΔDOB HR% & ΔLVEDV	78	–0.224	0.049
ΔDOB HR% & ΔLVESV	79	–0.238	0.035

Δ — absolute change over a six-week follow-up period, other abbreviations as in Tables 2 and 3.

of patients with chronic HF resulted from beta-adrenergic desensitisation of their cardiomyocytes. Bristow et al. [17] found histochemical evidence of adrenergic stimulation disorders in this group of patients. Comparative analysis of myocardial specimens from healthy subjects (heart donors) and HF patients revealed multi-level neuro-effector abnormalities, such as a decrease in the amount of neurotransmitter present within the synaptic space, decreased beta-1 receptor density, beta receptor functional decoupling, and enhanced activity of G_i protein. An electrophysiology study conducted by Sanders et al. [18] documented abnormalities in the sinoatrial pacemaker cells of HF patients, which might result in an inadequate chronotropic response of these subjects.

The aim of the hereby presented multicentre ViaCRT trial was to determine myocardial viability during low-dose DSE conducted prior to CRT. The presence of a contractile reserve may facilitate identification of patients who are likely to benefit from CRT [5]. Although the protocol of this examination assumed only a modest increase in HR, the analysis of DSE-induced changes in HR provided valuable prognostic information on post-CRT outcomes. In most patients, an inotropic effect was observed whenever HR increased by ca. 10% of its baseline value. Our findings imply that the abovementioned beta-adrenergic desensitisation, progressing with the severity of HF, may exert a significant effect on chronotropic response of the heart, also after a low dose of beta-mimetic. Even a slight increase in HR (< 20 bpm) during DSE was associated with a statistically significant change of EF six weeks after the CRT system implantation. Our findings suggest that better chronotropic response of the heart to low-dose beta-mimetic (i.e. greater sensitivity to catecholamines) may result in a better response to CRT. This was associated with a decrease in LV size and volume, as well as an increase in EF, particularly evident in patients who showed extreme changes in HR during DSE. On the other hand, resting HR, a marker of sympathetic tone, exerted a less prominent effect on an increase in EF after a six-week follow-up.

Limitations of the study

Our study was conducted retrospectively by reviewing HR responses in patients who underwent low dose dobutamine infusion to evaluate myocardial viability, and it was not done specifically to investigate HR responsiveness.

CONCLUSIONS

In conclusion, patients with stronger chronotropic response to low-dose dobutamine show a significant improvement in LV echocardiographic parameters, especially EF, within six weeks of implantation of the CRT system. The ability to adequately increase HR during pharmacological stress test may be used as a predictor of response to CRT in patients qualified for this type of treatment.

Conflict of interest: *none declared*

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