Fitness in chronic heart failure : effects of exercise training and of biventricular pacing

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CHAPTER 8

BIVENTRICULAR PACING-INDUCED ACUTE RESPONSE IN BAROREFLEX SENSITIVITY HAS PREDICTIVE VALUE FOR MID-TERM RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY

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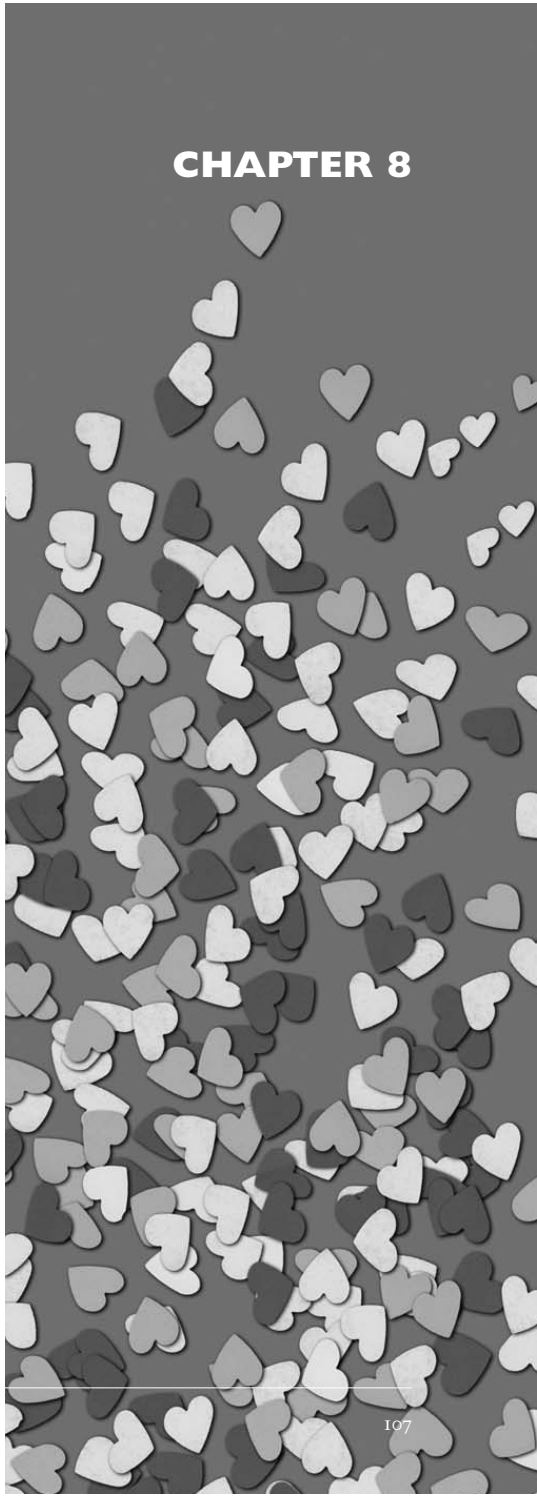

ABSTRACT

Background. In a previous study we demonstrated that institution of biventricular pacing in chronic heart failure (CHF) acutely facilitates the arterial baroreflex. The arterial baroreflex has important prognostic value in CHF. We hypothesized that the acute response in baroreflex sensitivity (BRS) after institution of cardiac resynchronization therapy (CRT) has predictive value for mid-term response.

Methods. One day after implantation of a CRT device in 33 CHF patients (27 male / 6 female, age 66.5 ± 9.5 years, left ventricular ejection fraction 28 ± 7%) we measured noninvasive BRS and heart rate variability (HRV) in two conditions: CRT device switched-on and switched-off (on/off order randomized). Echocardiography was performed prior to implantation (baseline) and 6 months after implantation (follow-up). CRT responders were defined as patients in whom left ventricular end systolic volume (LVESV) at follow-up had decreased by ≥ 15%.

Results. Responders (69.7%) and non-responders (30.3%) had similar baseline characteristics. In responders, CRT increased BRS by 30% (P=0.03); this differed significantly (P=0.02) from the average BRS change (-2%) in the non-responders. Also, CRT increased HRV by 30% in responders (P=0.02), but there was no significant difference found compared to the increase in HRV (8%) in the non-responders. Receiver-operating characteristic (ROC) curve analysis revealed that the percetage BRS increase had predictive value for the discrimination of responders and non-responders (area-under-the-curve 0.69; 95% confidence interval 0.51-0.87; maximal accuracy 0.70).

Conclusions. Our study demonstrates that a CRT-induced acute BRS increase has predictive value for the anatomical response to CRT. This finding suggests that the autonomic nervous system is actively involved in CRT-related reverse remodelling.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a relatively new and effective therapy in drug-refractory chronic heart failure (CHF). Studies have demonstrated that CRT decreases mortality and symptoms, and improves quality of life and New York Heart Association (NYHA) class[1,9]. Unfortunately, not all CHF patients experience positive effects of biventricular pacing: about 30% of the patients with an implanted device do not respond to CRT[3,4,22]. Therefore, several studies have been and are being conducted to identify measures that predict a positive response to CRT.

Permanent neurohumoral activation, *i.e.*, elevated sympathetic tone, depressed parasympathetic tone and activation of the renin-angiotensin-aldosterone system, is a hallmark of CHF. Simultaneously with neurohumoral activation, CHF patients have an increased peripheral chemoreflex and a decreased arterial baroreflex. Most therapies in CHF aim to diminish the detrimental influences of this neurohumoral activation and autonomic derangement by pharmacological interruption of the formation of the involved neurohormones or by blocking their effect at the receptor level.

CRT seems to have an acute beneficial effect on the permanent neurohumoral activation and autonomic derangement in CHF. Hamdan et al. found that biventricular pacing acutely reduced muscle sympathetic nerve activity (MSNA) when compared to right ventricular pacing[13]. Also, Najem et al.[17] showed that MSNA acutely increased in responders of CRT when biventricular pacing was switched off, this was not the case in non-responders of CRT. Furthermore, as we recently demonstrated, the arterial baroreflex sensitivity (BRS) is acutely improved with CRT[11]. It is, however, currently unknown if such acute CRT-induced autonomic responses are associated with clinical outcome.

As BRS is an important independent prognostic parameter in CHF[16], we hypothesized that patients showing an acute CRT-induced BRS increase one day after implantation, will respond positively to CRT.

METHODS

Patients

The protocol was approved by the local Medical Ethics Committee. Consecutive CHF patients eligible for CRT implantation were included in this study. Patients with atrial fibrillation, AV-conduction defects or frequent supraventricular or ventricular ectopy were not included, as sinus rhythm is a prerequisite for reliable noninvasive BRS measurement.

Protocol

One day after implantation, a BRS and heart rate variability (HRV) evaluation was performed. BRS and HRV were measured in each patient in two conditions: CRT device switched on and switched off (on/off order randomized). After the first BRS and HRV evaluation the CRT modality was changed according to the randomization protocol. After changing CRT modality, 10 minutes of rest followed, hereafter, the second BRS and HRV evaluation took place. Echocardiography was performed prior to the implantation procedure on the day of implantation, and was repeated 6 months after implantation.

BRS and HRV evaluation

Instrumentation

During BRS and HRV evaluation the patients were in the supine position. The upper part of the bed was inclined in accordance with the individual sleeping habit, to prevent respiratory discomfort. Around the second phalanx of the left middle finger, the fingercuff of a continuous noninvasive arterial blood pressure measurement device (Finometer, Finapres Medical Systems, Amsterdam, NL) was attached. Around the right upper arm, the armcuff of an automatic sphygmometer (Accutorr 3, Datascope Corp., Montvale, NJ, USA) was attached. A standard 12-lead ECG was continuously recorded during the measurement procedure. To the lateral sides of the lower part of the thorax, two electrodes were applied in order to monitor respiration (impedance method). Blood pressure, ECG and respiration were recorded with an ST-surveyor monitoring system (Mortara Rangoni Europe, Casalechio di Reno, BO, Italy) with a 500 Hz sampling rate.

Measurements

First, blood pressure and heart rate (Accutorr, average of 5 subsequent readings) were measured after a 15-minute resting period. These blood pressure measurements were used as a gold standard and were compared with the noninvasive arterial blood pressure measurement device. In this way, a reliable noninvasive arterial blood pressure measurement could be established. When the patient had been lying for 30 minutes, the noninvasive continuous arterial blood pressure signal, the ECG and the respiration signal were recorded during 10 minutes for later HRV and BRS calculation. During this period, patients performed 0.25 Hz metronome respiration (preventing the direct mechanical component of respiration and the respiratory gating effect to enter the low-frequency band (0.04-0.15 Hz), in which we compute BRS)[10]. This measurement was repeated, after switching the CRT device on or off and an additional 10 minutes of rest.

Analysis

To characterize arterial baroreflex function we computed BRS, the reflex-induced increase/decrease of the interval between heart beats, in milliseconds, per unit rise/fall of systolic blood pressure. All signals were blindly analyzed. First, the arrhythmia free and stationary periods longer than 60 seconds in the metronome respiration episode were selected (stationary sinus rhythm and blood pressure are prerequisites for a reliable BRS value). Compliance to the metronome respiration protocol was visually verified in the respi-

ration signal. Then, BRS was computed in each of the selected episodes. The BRS algorithm computes the magnitude of the transfer function between the systolic blood pressure variability (baroreflex input) and the interbeat interval variability (output), averaged over the 0.04-0.15 Hz band. Additionally, it calculates 95% two-sided BRS confidence intervals (CI)[27]. Finally, the overall BRS was composed from all data segments by the best linear unbiased estimator (BLUE) method[30]. Mean systolic blood pressure (SBP) and mean inter beat interval (IBI) were computed by taking the average of all SBP and IBI values from the selected episodes. HRV was also computed from the selected episodes and expressed as the standard deviation of the intervals between normal beats (SDNN).

Echocardiography

Echocardiographic images were obtained in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric – Vingmed, Milwaukee, WI, USA). A minimum of two consecutive heart beats was recorded from each view and the images were digitally stored for off-line analysis (EchoPac 7.0.0, General Electric Vingmed Ultrasound, Milwaukee, USA). Left ventricular (LV) end-systolic and end-diastolic volumes and LV ejection fraction (LVEF) were calculated from the apical 2- and 4-chamber images, using the modified biplane Simpson's rule[23].

Lv dyssynchrony was assessed by tissue Doppler imaging on the apical 2- and 4-chamber views and calculated as the maximum time delay between the peak systolic velocities of 4 basal walls[2]. The sample volume was placed between the tips of the mitral leaflets to assess Doppler pulsed-wave mitral inflow.

Clinical evaluation

Prior to implantation and after 6 months of CRT, clinical evaluation took place consisting of NYHA class assessment, the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and the 6-minute walk test. MLWHFQ was used to assess quality of life[20]. The 6-minute walk test was used to assess exercise tolerance[14]. Evaluation of heart failure symptoms was coded as NYHA functional class.

Response to CRT

Patients were classified as responder when patients showed a decrease of ≥ 15% in left ventricular end systolic volume (LVESV) after 6 months of CRT5. Patients not fulfilling this criterion were classified as non-responders.

Statistics

Results are presented as mean ± SD. Paired or unpaired Student's t-test were used to compare data, when appropriate. A Wilcoxon signed rank test was used to evaluate changes in NYHA class within groups. To determine if BRS has predictive value for the echocardiographic responses to CRT, receiver-operating characteristic (ROC) curve analysis was applied. The ROC curve is a graphical display of trade-offs of the true-positive (sensitivity) and false-positive (1-sensitivity) rates that correspond to each possible discrimination level of the test or variable under consideration: each cut-off level generates a point on the graph. The closer the curve follows the left-hand border and then the top-border of the ROC space, the more accurate the test. The closer the curve comes to the 45 degree diagonal of the ROC space, the less accurate the test. For all tests, a *P*-value < 0.05 was considered significant.

Table 1. *Baseline patient characteristics.*

Sex	27M/6F
Age (years)	66.5 ± 9.5
NYHA class	2.5 ± 0.7
Etiology of cardiomyopathy	
Ischemic	17 (52%)
Non-ischemic	16 (48%)
QRS duration (ms)	157 ± 30
LVEF (%)	157 ± 30
LVEDV (ml)	218 ± 76
LVESV (ml)	159 ± 62
LV dyssynchrony (ms)	57 ± 44
Medication	
ACE inhibitor/AII blocker	31 (94%)
Diuretic	22 (67%)
Spironolactone	18 (55%)
Beta-blocker	29 (88%)
Amiodarone	6 (18%)

Legend to Table 1. LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association.

RESULTS

Study group

Thirty-five CHF patients were included. Two patients were excluded from follow-up (1 patient because of suspected lung cancer, the other because of poor quality of the acoustic window during echocardiography that prevented reliable LVEF assessment), thus leaving 33 subjects in our study group. Thirty of them attended in our previous study[11]. Baseline characteristics of the study group are listed in *Table 1*.

All CRT devices were successfully implanted (Contak Renewal (n=18), Guidant, MN, USA; InSync Sentry (n= 13), Medtronic Inc., MN, USA; Concerto (n= 1), Medtronic Inc., MN, USA; Lumax (n= 1), Biotronic, MI, USA). The atrioventricular delay (AV-delay) was optimized by 2D echocardiography so that it provided the longest filling time for completion of the end-diastolic filling flow before LV contraction (the mean AV-delay was 120 ± 10 ms). No individual adjustments were made to the interventricular delay; the V-V interval was set at 0 ms in all subjects.

Responders and non-responders

After 6 months of CRT, 23 patients (70%) were classified as responders and 10 patients as non-responders (30%), according to the criterion of a decrease of ≥ 15% in LVESV. No deaths occurred during follow-up. There were no significant differences between responders and non-responders in baseline variables (*Table 2*). In responders, substantial reverse remodelling was present, LVEF increased by 34%, left ventricular end diastolic volume (LVEDV) decreased by 16% and LVESV decreased by 28% (*P*<0.003, *Table 2*). In non-responders reverse remodelling did not occur; changes over time in LVEF, LVEDV and LVESV were limited and not statistically significant (*Table 2*). Responders and non-responders both significantly improved in NYHA class and 6-minute walk test, after 6 months of CRT (*Table 2*). In neither of the groups there was a significant change in MLWHFQ.

Table 2. *Clinical and echocardiographic outcome measures in responders and non-responders.*

	Responders		Non-responders	
	Baseline	Follow-up	Baseline	Follow-up
LVEF (%)	27.6 ± 5.6	37.1 ± 7.8*	28.5 ± 10.0	29.3 ± 9.6
LVEDV (ml)	209.3 ± 70.9	175.4 ± 57.4*	239.1 ± 70.6	233.1 ± 69.8
LVESV (ml)	154.5 ± 60.2	112.4 ± 46.3*	178.3 ± 57.2	169.2 ± 66.6
NYHA class	2.5 ± 0.7	1.9 ± 0.7*	2.4 ± 0.7	1.8 ± 0.6 *
MLWHFQ	29.2 ± 18.2	21.9 ± 18.7	25.8 ± 18.0	20.4 ± 14.9
6-min walk test	339.7 ± 113.4	392.8 ±111.8*	306.4 ± 62.6	391.3 ± 62.0*

Legend to Table 2. MLWHFQ: Minnesota Living With Heart Failure Questionnaire; NYHA: New York Heart Association; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; 6-min walk test: 6-minute walk test; *: *P*< 0.01 within group.

Baroreflex sensitivity and heart rate variability

No significant differences in BRS (*P*= 0.59) and HRV (*P*= 0.89) between responders and non-responders existed at baseline (*Table 3*). In responders, CRT increased BRS considerably (30%) as compared to the non-responders (*P*=0.02, *Table 3*). CRT also improved HRV in responders (30%, *P*=0.02), but there was no significant difference with the change in the non-responders (*P*=0.24, *Table 3*). In non-responders, CRT did not acutely change BRS or HRV (*Table 3*). ROC analysis revealed that the percentual BRS increase had predictive value for the discrimination of responders and non-responders (area-under-the-curve 0.69; 95% CI 0.51-0.87, maximal accuracy 0.70, see *Figure 1*).

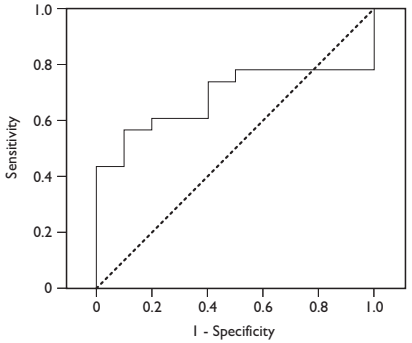

Figure 1. ROC *curve analysis of the predictive value of* CRT*-induced acute* BRS *change for the echocardiographic response to* CRT. *The area-under-the-curve equals 0.69, 95% with a confidence interval of 0.51-0.87.* BRS*: baroreflex sensitivity;* CRT*: cardiac resynchronization therapy.*

DISCUSSION

Response to CRT was defined as echocardiographic reverse remodeling. According to this criterion 70% of our patients were classified as responders and 30% as non-responders. We observed that CRT acutely increased BRS in responders but not in non-responders. ROC curve analysis showed that the CRT-induced acute BRS change at baseline had predictive value for the echocardiographic response to CRT.

A positive effect of CRT on autonomic derangement is not a novel finding per se. In 2006 Sarzi et al.[21] described in a case report that BRS normalized after three months of CRT. Recently, we described an acute positive effect of CRT on BRS[11], while Piepoli et al.[19] demonstrated that BRS and HRV improved with respect to baseline after 12 months of CRT. Also, Burri et al.[8] observed a decrease in sympathetic nerve activity in CRT responders as evidenced by a lowered ^{123}I-MIBG washout. In addition, Najem et al.[17] showed, in clinical responders, that temporarily switching of CRT increased MSNA. These findings suggest that one of the effects of CRT is the reduction of the autonomic derangement associated with CHF. Our current study adds a new element to this, namely the predictive value of a positive autonomic response to CRT for an echocardiographic response, since we demonstrated a positive association between an acute BRS increase after CRT institution and reverse remodelling at mid-term follow-up.

Table 3. *Baseline baroreflex sensitivity and heart rate variability with and without biventricular pacing.*

	Responders		Non-responders	
	CRT off	**CRT on**	**CRT off**	**CRT on**
BRS (mmHg/ms)	2.74 ± 3.7	3.55 ± 4.5*#	3.39 ± 1.6	3.34 ± 1.6
HRV (ms)	18.2 ± 11.0	23.6 ± 15.9*	17.7 ± 3.6	19.2 ± 6.7

Legend toTable 3. BRS: baroreflex sensitivity; CRT: cardiac resynchronization therapy; HRV: heart rate variability (standard deviation of inter-beat intervals); *: *P*< 0.05 within group; #: *P*< 0.05 the percentage of change between groups.

The positive association between acute CRT-induced baroreflex improvement and reverse remodelling suggests that the autonomic nervous system is actively involved in reverse remodelling. Possibly, CRT decreases the permanent neurohumoral activation (a hallmark of CHF) by decreasing the involvement of the cardiac sympathetic afferent reflex (CSAR)[8,11]. CSAR is activated by mechanical stretch and by various metabolites which are elevated during myocardial ischemia and with cardiac stretch[18,29]. Improvement of the mechanical activation pattern by CRT may have lowered mechanical stretch[26,31] in part of our patients, and may thus have deactivated CSAR. The arterial baroreflex is known to be suppressed by CSAR[12,32], and the observed baroreflex improvement in part of our study population might well be caused by CRT-induced deactivation of CSAR.

Although sympathoexcitation, possibly induced by cardiac sympathetic afferents, is generally observed in heart failure, cardiac vagal afferents might also play a role in the effects observed in our study. No experiments have been conducted to establish the effect of cardiac vagal afferent stimulation on BRS in the setting of heart failure. In healthy animals, stimulation of cardiac vagal receptors resulted in BRS attenuation[35]. Hence, cardiac vagal afferent firing, like cardiac sympathetic afferent firing, may well inhibit the effect of baroreceptor firing at the level of the nucleus tractus solitarii (NTS). As a consequence, possible CRT-induced decrease of cardiac vagal afferent firing would, like possible CRT-induced decrease of cardiac sympathetic afferent firing, lead to facilitation of the baroreflex. This reasoning would become more complicated when both sympathetic and vagal afferents are involved, because it was reported that major part of these fibers have an occlusive interaction at the NTS[28].

In addition to baroreflex improvement, one would also expect improvement (decrease) in the neurohormone levels. Unfortunately, little research has been conducted about the effects of CRT on neurohormone levels, and the results reported in the literature are inconsistent[6,7,15,24]. We have not systematically measured neurohormone plasma levels in our study population, hence, a positive association between a positive BRS response to CRT and normalization of the neurohormone levels remains hypothetical.

An echocardiographic outcome for evaluation of the response to CRT was chosen, since it is a robust measure and less subject to both the patient's and clinician's interpretation then clinical outcome variables[1,5]. A limitation of this outcome variable is that there are clinical responders that exhibit a decrease of >15% in LVESV, these patients were not indicated as responder in our study. However, Yu et al.[34] showed that clinical outcome variables did not predict mortality, more over, LVESV was the only independent predictor of all cause mortality. Also Ypenburg et al.[33] found that long-term prognosis after CRT is related to the extend of left ventricular reverse remodeling at 6 months of follow-up.

Obviously, the predictive value of the CRT-induced acute BRS change can not be used to reduce the number of CRT implantations in those who appear to become non-responders. The clinical use of our findings would rather lie in additional attempts to adjust the pacemaker settings in expected non-responders to CRT (subjects not showing an acute BRS increase).

Currently A-V optimization is recommended over V-V optimization[25]. If an acute positive BRS change is predictive for a positive response to CRT, it could be considered to attempt V-V optimization in cases where an acute BRS increase does not occur. To maximize the beneficial effect of CRT by means of V-V optimization, aiming for the largest BRS might prove as valuable as the assessment of

pulsed-wave Doppler measurements over the LV outflow tract. Of course, the usefulness of such a procedure has to be demonstrated in a prospective study.

Obviously, the limited size of our study group opposes a limitation to the statistical armament suitable for analysis of the data. For a larger group, a multivariate logistic regression would have been appropriate, thus controlling for major confounders like age, sex, heart failure severity (NYHA class), ejection fraction, etc. For our relatively small group we have chosen for a simple ROC analysis, that unlike regression analysis, does not model the data but straightforwardly uses the original data for the computation of the confidence interval. To further corroborate the results of our study, a larger study group is needed, thus allowing to control for major confounders.

CONCLUSIONS

The current results demonstrated that the CRT-induced acute BRS increase has predictive value for the anatomical response (reverse remodelling) to CRT. The present findings underscore the relevance of the autonomic nervous system as an effect pathway/mechanism of CRT in CHF.

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