The Effects of Cardiac Resynchronization Therapy on Left Ventricular Function, Myocardial Energetics, and Metabolic Reserve in Patients With Dilated Cardiomyopathy and Heart Failure

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OBJECTIVES

The effects of long-term cardiac resynchronization therapy (CRT) on left ventricular (LV) energetics and metabolic reserve were evaluated.

BACKGROUND

Cardiac resynchronization therapy is a new therapy for patients with drug-refractory severe heart failure (HF).

METHODS

Ten patients with idiopathic dilated cardiomyopathy who had undergone implantation of biventricular pacemaker 8 ± 5 months earlier were studied during two conditions: CRT switched on, and after CRT was switched off for 24 h. Left ventricular function was measured using echocardiography and oxidative metabolism using [11C]acetate positron emission tomography. Both measurements were performed at rest and during dobutamine-induced stress (5 μg/kg/min). Basal- and adenosine-stimulated (140 μg/kg/min) myocardial blood flow were quantitated using [15O]water.

RESULTS

During CRT off, LV stroke volume was significantly reduced at rest (72 ± 18 ml vs. 63 ± 15 ml, p < 0.05), but LV oxidative metabolism (Kmono) remained unchanged (0.046 ± 0.008 vs. 0.054 ± 0.016 min⁻¹) leading to a significant deterioration of myocardial efficiency of forward work (from 48.2 ± 16.7 to 36.6 ± 11.7 mm Hg/l/g, p < 0.05). During dobutamine-induced stress, stroke volume and Kmono values were not different whether CRT was on or off. However, myocardial efficiency (56.1 ± 16.1 vs. 49.8 ± 18.0 mm Hg/mlg⁻¹min⁻¹, p = 0.099) and metabolic reserve, the response of Kmono to dobutamine (0.023 ± 0.014 vs. 0.013 ± 0.014 min⁻¹, p = 0.09), tended to reduce when CRT was switched off. Cardiac resynchronization therapy had no effects on myocardial perfusion. Natriuretic peptides increased significantly during CRT-off period.

CONCLUSIONS

Long-term CRT has beneficial effects on LV function and myocardial efficiency at rest in patients with HF. These effects are not associated with changes in myocardial perfusion or oxygen consumption. During dobutamine-induced stress, CRT does not affect functional parameters, but myocardial efficiency and metabolic reserve may be increased.

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The incidence of patients with heart failure (HF) has increased exponentially over the last decade and has become an enormous public health problem (1). Besides coronary artery disease, idiopathic dilated cardiomyopathy is frequently the underlying cause of chronic HF. Despite advances in medical therapy (β-blockers, angiotensin-converting enzyme inhibitors, spironolactone), many patients remain severely symptomatic. Cardiac resynchronization therapy (CRT) is a recently introduced technique to improve the treatment of patients with HF and intraventricular conduction delay. Cardiac resynchronization therapy has beneficial effects on left ventricular (LV) function, symptoms, and exercise capacity, and it may even improve prognosis (2–8). However, limited data are available about the long-term effects of CRT on myocardial energetics, metabolic reserve, and perfusion.

Positron emission tomography (PET) enables the measuring of myocardial oxidative metabolism and blood flow noninvasively, qualitatively, and accurately in humans (2,9,10). The present PET study was designed to evaluate the long-term effects of CRT on LV function, oxidative metabolism, forward work efficiency, myocardial perfusion, and natriuretic peptide concentrations. In addition to the resting studies, all measurements were repeated during dobutamine-induced pharmacologic stress. The performance of the measurements during dobutamine infusion provides insight into the responses of all aforementioned parameters during stress. In particular, no data are currently available on the performance of CRT in combination with stress; all previous studies evaluating the response to CRT were performed under resting conditions.
METHODS

Subjects. The characteristics of the patients are summarized in Table 1. Ten subjects with symptomatic HF and idiopathic dilated cardiomyopathy (LV ejection fraction <45%, left bundle branch block) were included. Before CRT, New York Heart Association (NYHA) class was ≥III, QRS duration >140 ms (175 ± 25 ms), and LV ejection fraction <35% (25 ± 6%) in the study subjects. The patients underwent implantation of a biventricular pacemaker 8 ± 5 months before the study. Six patients had received a DDD-based biventricular pacemaker, and four had a DDD-based biventricular pacemaker/defibrillator device. No patients had atrial fibrillation or atrioventricular conduction disorders. All patients were clinically stable, treated with CRT and optimal medical therapy, and did not have evidence of decompensated HF at the time of the study. The study was conducted according to the guidelines of the Declaration of Helsinki, and the Ethics Committee of the Turku University Central Hospital accepted the study protocol. Each subject gave written informed consent.

Study design. The study was performed at the Turku PET Centre (Turku University Central Hospital, Turku, Finland) in a randomized, blinded fashion. The dose of β-blockade was gradually reduced during six days before the PET studies (to avoid rebound effect), withdrawn completely two days before the PET studies, and restarted again after the PET studies. This was done to avoid antagonistic actions of β-blockade on the effects of dobutamine. Other cardiac medication was continued during the PET studies. All PET studies were performed after an overnight fast. Additionally, the patients were instructed to avoid all caffeine-containing drinks and foods for 12 h before the PET studies.

The study design is illustrated in a schematic manner in Figure 1. All study procedures were completed under the same conditions, and the patients were studied at the same time of day. Each patient was studied on two separate occasions: during CRT and after CRT was switched off for 24 h. Serum natriuretic peptides were measured immediately preceding the positron emission tomography (PET) studies. Myocardial flow was quantitated using PET and [15O]H2O at baseline and during adenosine infusion (140 μg/kg/min for 7.5 min). Left ventricular oxidative metabolism was measured using PET and [11C]acetate at baseline and during low-dose dobutamine infusion (5 μg/kg/min for 60 min). Left ventricular function was measured using two-dimensional echocardiography first at rest and then during dobutamine infusion. Open bars = perfusion measurement; solid bars = oxidative metabolism measurement.

Table 1. Characteristics of the Patients (Mean [SD])

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean [SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M:F)</td>
<td>8:2</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59 (11)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.5 (4.8)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>32.2 (7.9)</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>315.1 (97.7)</td>
</tr>
<tr>
<td>Mitral regurgitation grade</td>
<td>1.9 (0.9)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>114/72 (13/8)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.3 (0.5)</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>135 (16)</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of the Patients (Mean [SD])

<table>
<thead>
<tr>
<th>Medications</th>
<th>10/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>6/10</td>
</tr>
<tr>
<td>Angiotensin II blocker</td>
<td>4/10</td>
</tr>
<tr>
<td>β-blockers</td>
<td>10/10</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1/10</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; LV = left ventricle; NYHA = New York Heart Association.
Echocardiographic examination. All echocardiographic recordings and analyses were performed by the same experienced investigator (E.E.) using a commercially available ultrasound scanner (Acuson Sequoia C 256, Siemens, Mountain View, California). Standard echocardiographic views of the LV were obtained, and end-diastolic and end-systolic LV dimensions, volumes, and LV mass were determined. Left ventricular dimensions were measured according to the American Society of Echocardiography recommendations, and LV mass was calculated by the cube equation: 
\[ \text{LV mass} = \frac{4}{3} \pi r^3 \times \text{wall thickness} \]
where \( r \) is systolic internal radius of the LV, and \( Wth \) is systolic wall thickness. The echocardiograms were recorded at baseline before the PET studies and during dobutamine infusion immediately after the last PET scan. External, or forward, LV work power was calculated as: systolic blood pressure \( \times \) stroke volume \( \times \) heart rate.

Measurement of myocardial perfusion and oxidative metabolism. The positron emitting tracers \([^{15}\text{O}]\text{water}\) and \([^{11}\text{C}]\text{acetate}\) were produced as previously described (10). The subjects were positioned supine in a 15-slice ECAT 931/08-12 tomograph (Siemens/CTI Inc., Knoxville, Tennessee). After the transmission scan, myocardial perfusion was measured with an intravenous injection of \([^{15}\text{O}]\text{water}\) (~1.5 GBq) at rest and 60 s after intravenous administration of adenosine (140 \(\mu\)g/kg/min for 7.5 min intravenously). Each dynamic scan lasted for 6 min (6 \(\times\) 5, 6 \(\times\) 15, 8 \(\times\) 30 s). Thereafter, an intravenous bolus of \([^{11}\text{C}]\text{acetate}\) (724 ± 19 MBq) was administered simultaneously with the start of a 29-min (10 \(\times\) 10, 1 \(\times\) 60, 5 \(\times\) 100, 5 \(\times\) 120, 2 \(\times\) 240 s) dynamic emission scan. After tracer decay, \([^{11}\text{C}]\text{acetate}\) PET was repeated during dobutamine infusion (for 1 h, at an infusion rate of 5 \(\mu\)g/kg/min). All data were corrected for dead time, radioactive decay, and photon attenuation. Images were processed using an iterative median root prior reconstruction algorithm (12).

Analysis and calculation of myocardial blood flow and coronary flow reserve. On the myocardial \([^{15}\text{O}]\text{water}\) images, a region of interest (ROI) was drawn in the whole wall (including the lateral, anterior, and septal parts) of the LV in four representative transaxial slices in each study as previously described (13). The ROI outlined in the baseline images was copied to the images obtained after adenosine administration. Values of myocardial blood flow (expressed in ml/g of tissue per min) were calculated according to the previously published method using the single compartment model (14). The arterial input function was obtained from the LV time-activity curve using a previously validated method (15) in which corrections were made for the limited recovery of the LV ROI and the spillover from the myocardial signals. The average blood flow of the whole wall of the LV was used in further analysis. Coronary flow reserve
was defined as the ratio of the myocardial blood flow during adenosine infusion to flow at baseline.

Analysis and calculation of oxidative metabolism and myocardial efficiency. Myocardial $[^{13}]C$-acetate studies were analyzed with the MunichHeart software (16,17). Briefly, monoexponential fitting was applied, and $[^{13}]C$-acetate clearance rate ($K_{\text{mono}}$) was calculated. In each patient, reconstructed PET tomograms were evaluated, and global LV $K_{\text{mono}}$ was determined. Myocardial efficiency (the relation between the forward work and oxygen consumption) was estimated as: forward LV work power per gram/LV $K_{\text{mono}}$.

Assessment of natriuretic peptide. Serum N-terminal atrial natriuretic peptide was measured using an in-house immunofluorometric assay method (reagents: Medix Biochemica, Espoo, Finland; instrument: Delfia Research Fluorometer; Wallac, Turku, Finland). Serum N-terminal pro-brain natriuretic peptide was measured using an electrochemiluminesimetric method (reagent kit: Roche, Mannheim, Germany; instrument: Elecsys, Roche, Mannheim, Germany; analyzed at Limbach Laboratory, Germany).

Statistical analysis. The results are expressed as mean ± SD. Student paired $t$ test was used within the group comparisons, and Student unpaired $t$ test when two different groups were compared. A $p$ value <0.05 was interpreted as statistically significant. All statistical tests were performed with SAS statistical analysis system (SAS Institute Inc., Cary, North Carolina).

RESULTS

Hemodynamic measurements during PET. Heart rates, blood pressures, and rate-pressure products during the various parts of the PET study protocol are presented in Table 2. Adenosine and dobutamine infusions induced a significant increase in heart rate and rate-pressure products. Echocardiographic parameters. Stroke volumes are shown in Figure 2, and other echocardiographic parameters in Table 3. When CRT was switched off, LV stroke volume significantly reduced at rest (72 ± 18 ml vs. 63 ± 15 ml, $p$ = 0.04). Dobutamine infusion increased cardiac output and decreased LV end-systolic diameter ($p < 0.05$; Table 3).

Cardiac resynchronization therapy had no significant effect on LV stroke volume during dobutamine stress (79 ± 23 ml vs. 74 ± 24 ml, CRT on and off; $p$ = NS; Fig. 2).

Myocardial blood flow and coronary flow reserve. Myocardial blood flow values are shown in Figure 3. No significant differences were detected in basal (0.7 ± 0.2 and 0.8 ± 0.3 ml g$^{-1}$ min$^{-1}$, CRT on and off; $p$ = NS) or adenosine-stimulated (1.8 ± 1.1 and 1.6 ± 0.9 ml g$^{-1}$ min$^{-1}$, respectively; $p$ = NS) myocardial blood flow. Similarly, CRT had no significant effect on coronary flow reserve (2.2 ± 1.4 and 2.0 ± 1.0, respectively; $p$ = NS).

Myocardial oxidative metabolism and efficiency. Left ventricular $K_{\text{mono}}$ values are presented in Figure 4 and myocardial efficiency in Figure 5. At rest, LV $K_{\text{mono}}$ was not significantly changed by CRT (0.046 ± 0.008 vs. 0.054 ± 0.016 min$^{-1}$, CRT on and off, $p$ = 0.1; Fig. 4). Resting myocardial efficiency was significantly deteriorated when CRT was switched off (from 48.2 ± 16.7 to 36.6 ± 11.7 mm Hg$^{-1}$ g$^{-1}$, $p$ = 0.02; Fig. 5).

During dobutamine infusion, $K_{\text{mono}}$ values were similar, independent of whether CRT was on or off (0.070 ± 0.016

![Figure 3](image363x94to490x207)  
**Figure 3.** Cardiac resynchronization therapy (CRT) had no significant effect on basal- or adenosine-stimulated myocardial blood flow.

![Figure 4](image92x76to245x193)  
**Figure 4.** Left ventricular (LV) oxidative metabolism ($K_{\text{mono}}$) was unchanged by cardiac resynchronization therapy (CRT), but dobutamine-induced stress significantly increased $K_{\text{mono}}$ values. Open bars = CRT on; solid bars = CRT off.
Effects of Cardiac Resynchronization Therapy

Sundell et al.

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The present study demonstrates that, in symptomatic patients with dilated cardiomyopathy and intraventricular conduction delay, long-term CRT has maintained its beneficial effects on LV function and myocardial forward work efficiency at rest. These effects were not associated with changes in myocardial perfusion or oxygen consumption. During dobutamine-induced pharmacologic stress, CRT does not induce a significant effect on functional parameters, but LV work efficiency and metabolic reserve may be increased.

The number of patients with drug-refractory HF is increasing rapidly and has become a major clinical problem, in terms of costs and management. Cardiac resynchronization therapy is a new therapy for these patients, and an improvement in HF symptoms, quality of life, and exercise capacity has been demonstrated following CRT (5–8). Moreover, in a meta-analysis of randomized controlled trials, CRT has been found to significantly reduce HF hospitalization and death from progressive HF (4). The benefit of CRT may be related to improvement of systolic function, resynchronization, reduction of mitral regurgitation, and/or reverse remodeling (5). Still, the precise mechanism underlying the benefit of CRT is not entirely clear. Limited previous data are available regarding the effects of CRT on LV oxidative metabolism and myocardial efficiency. Nelson et al. (3) found in an invasive catheterization study of 10 dilated cardiomyopathy patients that short-term ventricular resynchronization enhances systolic function while modestly lowering energy cost. In a recent PET study investigating patients with congestive HF mainly due to coronary artery disease (n = 8), Ukkonen et al. (2) found that long-term CRT improves LV function without increasing global LV oxidative metabolism, resulting in improved myocardial efficiency. In the present study, the patients had been receiving CRT for a mean of eight months. During that period, the adaptive mechanisms have been suggested to have taken place. However, when CRT was turned off for 24 h, LV function had deteriorated, myocardial efficiency of forward work was reduced, and concentrations of natriuretic peptides were increased. These findings indicate that CRT appears to have a clinically significant long-term effect beyond its short-term responses.

Interestingly, during the CRT-off period, LV stroke volume was decreased, but myocardial oxygen consumption remained at the same absolute level. This inversely indicates that the positive effect of CRT on LV function is achieved without raising energy demand. This finding is concordant with the results of previous short-term studies of CRT (2,3) and indicates the unique characteristics of this treatment. Most inotropic HF therapies increase myocardial oxygen consumption and LV performance concomitantly (for example, short-term dobutamine stimulation, as seen in the present study, increases LV stroke volume but also significantly increases myocardial oxygen consumption, which, in the long-term, may be considered a detrimental effect).

In the present study, we also investigated myocardial perfusion and coronary flow reserve. Coronary flow reserve ranges about 3 to 5 × the baseline values in healthy subjects (18). In concordance with the previous studies, coronary flow reserve was blunted in patients with dilated cardiomyopathy (19). However, CRT had no effect on myocardial perfusion either at rest or during hyperemia. This further indicates that the mechanisms behind the improvement of LV function are not related to improved oxygen supply.

In order to investigate the effect of CRT on functional and metabolic reserve, all measurements were repeated during dobutamine infusion. The performance of the measurements during dobutamine infusion provides insight into the responses during stress, which can be considered to
better mimic patients’ normal active life than measurements only during resting conditions. No data are currently available on the performance of CRT in combination with stress, because all previous studies evaluating the response to CRT were performed under resting conditions. The overall response to dobutamine was blunted, indicating reduced functional and metabolic reserve (20), which is in agreement with previous studies in patients with HF. Interestingly, stroke volume and oxygen consumption were not different whether CRT was on or off during dobutamine stress. However, myocardial metabolic reserve, the response of $K_{mono}$ to dobutamine, tended to be higher when CRT was on. In addition, myocardial efficiency tended to be higher when CRT was on. However, this effect appeared to be smaller during stress than at rest, suggesting that resynchronization has less influence on myocardial efficiency during stress.

Somewhat surprising, serum natriuretic peptide concentrations showed a significant increase 24 h after turning CRT off. The plasma concentrations have been correlated with NYHA class and systolic dysfunction and also have prognostic value (21). This immediate increase of natriuretic peptide concentrations rapidly after turning off CRT further emphasizes the beneficial effects of CRT. Cardiac resynchronization therapy improves intraventricular conduction delay in patients with conduction disturbances (left bundle branch block) by resynchronizing conduction (22). The findings in the present study that CRT was able to improve LV stroke volume without increasing oxygen demand suggest that cardiac dyssynchrony leads to inefficient contraction and oxygen use as related to forward work. Although the majority of the patients selected for CRT respond well, about 20% of the patients’ symptoms do not improve (23). Currently, there are no objective parameters to predict the effect of the therapy. In the present study, we analyzed several potential parameters, but none of them were useful to predict the stroke volume response to CRT.

**Study limitations.** In the present study, we had no possibility to investigate the patients before the implantation of the biventricular pacemaker, and the CRT-off period was only 24 h because of safety reasons. In addition, only a limited number of patients were investigated. However, the study protocol was complicated and laborious. Despite the limited study population and short off period, we were able to demonstrate significant changes in myocardial energetics, further emphasizing the significant nature of the responses. Low-level dobutamine stress was used in the present study, and it may not be possible to extrapolate our results to higher levels of stress. However, in this kind of patient population with severe HF, higher dobutamine levels or stress are not tolerated and frequently lead to severe arrhythmias. In addition, the attenuated response to dobutamine could have been due to the fact that patients were receiving $\beta$-blockade therapy before the study. However, $\beta$-blocker therapy was gradually withdrawn two days before the measurements, and $\beta$-blocker therapy should have, at least partially, reversed the myocardial $\beta$-receptor uncoupling and downregulation (24). On the other hand, the effects of CRT were not studied under optimal medical therapy for HF. However, by continuing $\beta$-blockers, the dobutamine responses would have been strikingly blunted. Further studies are needed to investigate these issues and the regional effects of CRT on both the left and right ventricles.

**Summary.** In summary, the results of the present study demonstrate that long-term CRT has maintained beneficial effects on LV function, and it enhances myocardial forward work efficiency at rest in patients with dilated cardiomyopathy and HF. These effects are not associated with changes in perfusion or perfusion reserve and do not result in an increase in myocardial oxygen consumption. During dobutamine-induced stress, CRT does not exhibit a significant effect on functional parameters, but LV work efficiency and metabolic reserve may be increased.

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**REFERENCES**