Clinical research

Effect of cardiac resynchronization therapy on global and regional oxygen consumption and myocardial blood flow in patients with non-ischaemic and ischaemic cardiomyopathy

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Received 10 March 2004; revised 20 September 2004; accepted 14 October 2004; online publish-ahead-of-print 30 November 2004

Aims We studied the effects of cardiac resynchronization therapy (CRT) on global and regional myocardial oxygen consumption (MVO2) and myocardial blood flow (MBF) in non-ischaemic (NICM) and ischaemic dilated cardiomyopathy (ICM).

Methods and results Thirty-one NICM and 11 ICM patients, all of them acute responders, were investigated. MVO2 and MBF were obtained by 11C-acetate PET before and after 4 months of CRT. In NICM global MVO2 and MBF did not change during CRT, while the rate pressure product (RPP) normalized MVO2 increased (P = 0.03). Before CRT regional MVO2 and MBF were highest in the lateral wall and lowest in the septum. Under therapy, MVO2 and MBF decreased in the lateral wall (P = 0.045) and increased in the septum (P = 0.045) resulting in a more uniform distribution. In ICM, global MVO2, MBF, and RPP did not change under CRT. Regional MVO2 and MBF showed no significant changes, but a similar tendency in the lateral and septal wall to that in NICM.

Conclusion CRT induces changes of MVO2 and MBF on a regional level with a more uniform distribution between the myocardial walls and improved ventricular efficiency in NICM. Based on the investigated parameters, CRT appears to be more effective in NICM than in ICM.

KEYWORDS
Cardiomyopathy; Bundle branch block; Pacing; Oxygen; Perfusion; Positron emission tomography

Introduction
Congestive heart failure is a major health care problem with increasing prevalence and considerable economic consequences.1 New medical treatment options have gone along with a significant prognostic improvement. Cardiac resynchronization therapy (CRT) has been introduced in patients with poor left ventricular function and conduction delays, predominantly left bundle branch block (LBBB), for improving symptoms and prolonging survival.2,3 The rationale of CRT is to correct the unfavourable LBBB associated ventricular activation
and contraction sequence and to improve cardiac output and efficiency by these means.

Meanwhile, multiple trials have demonstrated improvements in New York Heart Association (NYHA) functional class, exercise capacity, and quality of life, under this therapy. However, these studies did not separately examine patients with non-ischaemic dilated cardiomyopathy (NICM) and ischaemic dilated cardiomyopathy (ICM). An echocardiographic analysis of patients enrolled in the MIRACLE trial demonstrated that CRT caused significant reverse left ventricular remodelling with improvement in left ventricular size and function to a greater extent in NICM than in ICM.6

With regard to these mechanical and morphological effects of CRT, we hypothesized that chronic CRT could also lead to changes of: (i) myocardial blood flow (MBF) at rest; (ii) myocardial oxygen consumption (MVO2); and (iii) ventricular efficiency. Therefore, this study investigated effects of CRT on a global and on a regional level (iii) ventricular efficiency. Therefore, this study investigated effects of CRT on a global and on a regional level of perfusion and metabolism in NICM and ICM patients.

Methods

Patient characteristics

Within the 18 months inclusion period, 42 consecutive patients were studied (Table 1); 31 patients with NICM and 11 patients with ICM. One patient had atrial fibrillation, the others were in sinus rhythm. All patients were in NYHA functional class III. In the NICM patients, a significant coronary artery disease narrowing >50% had been excluded angiographically. The ICM patients had known coronary artery disease, 10 of them history of myocardial infarction, and six coronary revascularization surgery. Before the study, all patients were on their individually optimized heart failure medication which accounted for the different aetiologies of cardiomyopathy. In detail, 99% of the NICM patients took angiotensin converting enzymes, or angiotensin receptor blockers, 16% amiodarone, 87% beta-blockers, 87% digoxin, 97% diuretics, 19% nitrates; in the ICM collective, 97% received angiotensin converting enzymes, or angiotensin receptor blockers, 18% amiodarone, 90% beta-blockers, 64% digoxin, 91% diuretics, and 63% nitrates. During the study, heart failure medication was not changed qualitatively. An up-titration of beta-blocker dose to its optimal dosage occurred in seven NICM and in four ICM patients in whom this level could not be reached before CRT.

Prior to definite pacemaker implantation, all patients had undergone a haemodynamic test in the electrophysiological laboratory in order to differentiate responders from non-responders. Only responders with a pulse pressure increase of ≥10% above baseline were included (Table 1). The device implantation was performed as described in detail earlier.

Except for the aetiology of cardiomyopathy, the two groups did not differ significantly in their baseline clinical characteristics (Tables 1 and 2). The different group sizes resulted from the inclusion criteria and the duration of the observation period.

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
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<tbody>
<tr>
<td>NICM</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>PR, ms</td>
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<tr>
<td>QRS, ms</td>
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<tr>
<td>Haemodynamic testing</td>
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<tr>
<td>Increase in pulse pressure, mm Hg</td>
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<td>Increase in pulse pressure, %</td>
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Values are as mean ± SD.

<table>
<thead>
<tr>
<th>Table 2 Haemodynamic and clinical data</th>
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<tr>
<td>NICM</td>
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<tr>
<td>Baseline</td>
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<tr>
<td>HR, L/min</td>
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<tr>
<td>SBP, mmHg</td>
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<tr>
<td>DBP, mmHg</td>
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<td>RPP, mmHg/min</td>
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<tr>
<td>LV ED, mm</td>
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<tr>
<td>EF, %</td>
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<tr>
<td>VO2 max, mL/kg/min</td>
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<tr>
<td>6 min walk, m</td>
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<tr>
<td>NYHA class</td>
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</tbody>
</table>

Values are mean ± SD. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LV ED, left ventricular end-diastolic diameter; EF, left ventricular ejection fraction; VO2 max, peak oxygen uptake.
PET imaging and data analysis

A 11C-acetate positron emission tomography (PET) study had been performed prior to pacemaker implantation (11 ± 12 days) and ≈4 months (115 ± 24 days) under CRT with an ECAT-951 R scanner (CTI/Siemens Medical systems, Knoxville, TN, USA). Blood pressure and heart rate were assessed oscillometrically immediately before tracer injection. 11C-acetate PET processing was performed using a reversible one-tissue compartment model.13,14 The modelling procedure resulted in 20-segment parametric polar maps of acetate uptake (K1, perfusion) and acetate clearance (K2, index of MVO2).15 To obtain global MVO2 and MBF, the individual values of all segments of each measurement were added and than averaged. For regional analysis the segments were assigned either to the anterior, lateral, inferior, or septal wall. Then the segmental values of the myocardial walls were averaged. By these means, four regional values of each parameter were obtained for every patient. The apical segments were excluded from analysis. Although there is great variability in the coronary artery blood supply to myocardial segments, the segments which were summarized according to our polar maps, the anterior wall can be assigned to the left anterior descendens (LAD), those of the lateral wall to the left circumflex artery (LCX), those of the inferior wall to the right coronary artery (RCA), and those of the septum to the RCA and the LAD.

Segments with an MBF <50% of the two segments with the maximal MBF were regarded irreversibly dysfunctional and excluded from analysis.16 Segments outside the field-of-view of the PET scanner, or with a fractional blood volume >0.50 indicating an incorrect wall detection, were also excluded. In the NICM group, 1137 out of 1240 segments were analysed. Forty-five segments (3.6%) were disregarded due to a fractional blood volume >0.50 and 52 segments (4.2%) lay outside the field-of-view. Six segments (0.5%) were regarded irreversibly dysfunctional (five apical segments and one septal segment). In the ICM group, 343 out of 440 segments were included, 24 segments (5.5%) were rejected due to a fractional blood volume >0.50, 22 segments (5%) lay outside the field-of-view, and 51 segments (11.6%) were regarded irreversibly dysfunctional (22 apical, 14 anterior, 12 septal, and three lateral segments).

To account for changes in MVO2 by different cardiac work at baseline and follow-up investigations, the MVO2 was normalized with the rate pressure product (RPP). This parameter has been shown to correlate closely with acetate clearance and the MVO2, respectively.16–19 The normalization of MVO2 was done by multiplication with the ratio between the median of all RPPs (7119 mmHg/min) of the baseline PET scans and the individual RPP measured immediately before the tracer application.

MBF is given in mL/min/g and MVO2 indirectly by the acetate clearance rate in 1/min.

### Table 3 Global MBF and MVO2

<table>
<thead>
<tr>
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<th>NICM</th>
<th>ICM</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>MBF</td>
<td>0.51 ± 0.10*</td>
<td>0.52 ± 0.12</td>
</tr>
<tr>
<td>MVO2</td>
<td>0.080 ± 0.015</td>
<td>0.082 ± 0.020</td>
</tr>
<tr>
<td>nMVO2</td>
<td>0.081 ± 0.017*</td>
<td>0.072 ± 0.018</td>
</tr>
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Values are mean ± SD. MBF in mL/min/g, MVO2 and nMVO2 in 1/min. nMVO2, the RPP normalized MVO2.

*P < 0.05 vs. NICM; †P = 0.03 vs. baseline.

### Statistical analysis

Data are given as mean value ± 1 standard deviation (SD). The non-parametric Mann–Whitney U-test for unpaired groups was used to compare global MVO2 and MBF between the groups. Comparisons of paired parameters at baseline and under CRT were performed with the Wilcoxon signed rank test. Probability values were calculated using two-sided tests and if <0.05 considered statistically significant.

Comparisons of regional MBF (in the anterior, lateral, inferior, and septal walls) and of regional MVO2 were analysed with ANOVA for repeated measures followed by a post hoc Bonferroni analysis. Statistical analyses were performed with StatView 5.0 software (SAS Institute Inc.).

### Results

#### Haemodynamic and clinical findings

Table 2 shows the results for the NICM and the ICM patients. In the NICM group systolic blood pressure and the RPP increased significantly during CRT. Heart rate and diastolic blood pressure remained unchanged. No change of haemodynamic parameters was found in ICM. All investigated clinical data of the NICM group improved significantly. The ICM group revealed a significant improvement in the NYHA functional class and the 6 min walk.

#### Global MVO2 and MBF

The data for the global parameters are given in Table 3. At baseline, global MVO2 tended to be lower in ICM than in NICM. The MVO2 of both groups did not significantly alter during CRT. Under therapy, the RPP-normalized MVO2 declined (P = 0.03) in NICM but increased insignificantly in ICM. At baseline, global MBF was lower in ICM than in NICM (P = 0.04) and did not alter during therapy.
**Regional MVO₂ and MBF in non-ischaemic dilated cardiomyopathy**

The results are presented in Table 4 and Figure 1. The ANOVA revealed differences for MVO₂ between the myocardial walls at baseline \((P < 0.0001)\) and under therapy \((P = 0.0004)\). In detail, baseline MVO₂ in the lateral wall was higher than in the other myocardial walls \((P < 0.0001)\) and MVO₂ in the septum lower than in the anterior \((P = 0.0008)\) and the lateral walls \((P < 0.0001)\).

Under therapy, MVO₂ in the inferior wall was lower than in the anterior wall \((P < 0.0001)\) and the lateral wall \((P = 0.0007)\). The other myocardial walls showed no differences. MVO₂ increased in the septal wall \((P = 0.045)\) and decreased in the lateral wall \((P = 0.045)\) from baseline to therapy. Figure 2 illustrates these findings.

Baseline MBF revealed regional differences between the myocardial walls \((P < 0.0001)\) in NICM. The lateral wall showed a higher perfusion than all other myocardial walls (anterior vs. lateral, \(P < 0.0001\); inferior vs. lateral, \(P = 0.0035\); lateral vs. septal, \(P < 0.0001\)). During therapy there were no longer significant regional differences \((P = 0.55)\). MBF increased by CRT in the anterior \((P = 0.03)\) and septal \((P = 0.001)\) walls and decreased in the lateral wall \((P = 0.02)\).

The MVO₂/MBF ratio was nearly identical for all the myocardial walls before and during therapy.

**Regional MVO₂ and MBF in ischaemic dilated cardiomyopathy**

The results are given in Table 4 and Figure 1. The ANOVA of MVO₂ revealed no significant differences either among the myocardial walls at baseline or during therapy. Only insignificant changes occurred from baseline to follow-up. However, there was the tendency of a higher baseline MVO₂ in the lateral wall than in the septal wall and also of a balance of MVO₂ between these walls under CRT.

MBF demonstrated the same characteristics as MVO₂. The MVO₂/MBF ratio was nearly identical to that of the NICM group and remained constant from baseline to follow-up.

**Discussion**

We investigated 31 NICM and 11 ICM patients, all of them acute responders with similar clinical baseline characteristics, before and during 4 months of continuous CRT. The study results document that mid-term CRT did not substantially affect global MVO₂ and MBF in either group.

Transforming the measured ¹¹C-acetate clearance rates into an absolute MVO₂, it amounts to 5.9 ± 0.8 in NICM and to 5.1 ± 1.0 mL/min/100 g in ICM, respectively. These data indicate a reduced MVO₂ in both groups (normal range >7.6 mL/min/100 g²) which reflects the overall depressed contractility due to the cardiomyopathy. Correspondingly, MBF was found to be...
below the normal limit, and consistent with perfusion values (0.49 \pm 0.17 \text{ mL/min/g} \text{ in NICM}; 0.38 \pm 0.15 \text{ mL/min/g} \text{ in ICM}) measured with the microsphere technique.

Previous studies, which considered short-term effects of CRT, also demonstrated an unchanged global MVO2 and MBF. Obviously, the same accounts for mid-term CRT and indicates that the global state of the myocytes was not affected during the observation period.

Nevertheless, the left ventricular end-diastolic diameter documents that CRT initiated a reverse ventricular remodeling process in NICM and therefore also in ICM. In line with these morphological changes, clinical and haemodynamic parameters improved mostly in the NICM group, which also showed a better ventricular efficiency. In contrast, ICM patients demonstrated no change in efficiency.

The finding of improved efficiency by CRT is consistent with other studies which examined patients after 2 min of pacing/stimulation and NICM patients after temporary cessation of CRT. Ukkonen et al. found a 13% improvement of efficiency in eight patients (six of them with ICM) with 11C-acetate PET. This result is similar to that of our NICM group but differs from the ICM group. The discrepancy may be caused by a greater extent of irreversibly dysfunctional and/or ischaemic segments in our ICM patients.
Mechanisms of CRT have been found to be a reduced mitral regurgitation, a better atrioventricular co-ordination, and an improved ventricular co-ordination, which enable the ventricles to act more efficiently.\textsuperscript{30,31} In particular, the ability of reco-ordination depends on preserved mechanical function.\textsuperscript{32} We suppose that the response to CRT in ICM turns out to be poorer than in NICM for two reasons: (i) ICM patients had more irreversibly dysfunctional segments, which may affect mechanical function; and (ii) ICM patients showed a significantly lower MBF, which suggests that regional or even global ischaemia was likely to be present.

These considerations are further supported by the echocardiographic analysis of NICM and ICM patients enrolled in the MIRACLE trial, which demonstrated greater changes in NICM than in ICM.\textsuperscript{6} The clinical and haemodynamic results of the ICM group, however, may be regarded as a therapeutic benefit, because they consistently indicate a trend towards an improvement.

Regional MVO\textsubscript{2} and MBF

As pointed out above, ventricular reco-ordination represents one of the main pillars of CRT. To assess this effect on MVO\textsubscript{2} and MBF the parameters were analysed on a regional level.

Before CRT, regional MVO\textsubscript{2} and MBF of the NICM patients were characterized by a significant imbalance between the myocardial walls with the highest values in the lateral wall and the lowest in the septum. This pattern can be explained as follows: the dys-synchronous contraction in LBBB is associated with a delayed activation of the lateral wall.\textsuperscript{33,34} During the cardiac cycle, the contraction of the early activated segments distends the still inactivated lateral wall and increases intraventricular pressure. Consequently, the delayed activated lateral wall segments have to perform a higher work,\textsuperscript{35} and therefore exhibit a higher MVO\textsubscript{2} than the other walls, as confirmed by our study. On the other hand, the low MVO\textsubscript{2} in the septum results from its early contraction and a reduced regional ejection fraction.\textsuperscript{36}

Due to the close match of MBF to MVO\textsubscript{2},\textsuperscript{37} which was reflected in the constant MVO\textsubscript{2}/MBF ratios, MBF demonstrated nearly the same characteristics as MVO\textsubscript{2}.

Previous studies have shown that CRT is able to reduce the intraventricular delay caused by LBBB.\textsuperscript{31} By these means, an improved co-ordination and a more effective ventricular contraction is induced with a more uniform distribution of cardiac work among the myocardial walls.\textsuperscript{40} Accordingly, the effect of resynchronization was reflected in our NICM patients by a more uniform distribution of MVO\textsubscript{2} and MBF between the myocardial walls. This occurred by a decrease of both in the lateral wall and an increase in the septum. The changes in the lateral wall indicate a lower regional workload due to the suspended delay. Those of the septum suggest a higher regional workload that documents a more effective integration of this wall into the cardiac cycle than under LBBB conditions. In addition, glucose metabolism has also shown a more homogeneous distribution in the myocardium by CRT.\textsuperscript{26}

The ICM group failed to show significant changes by CRT but at least the trend of changes was similar to those of the NICM group.

In summary and in conclusion, our study provides evidence that mid-term CRT affects MBF and MVO\textsubscript{2} on a regional level and that it appears to be more effective in NICM than in ICM. However, it has to be considered that the ICM results are biased for reasons of patient recruitment on a small sample size. Therefore they have to be interpreted cautiously, especially in comparison with the NICM results. Nevertheless, as pointed out above, they are in line with echographic data.\textsuperscript{6} Against this background, our study implies: (i) that NICM and ICM represent two different CRT groups which require a separated analysis with larger sample sizes concerning clinical benefits and outcome; and (ii) that studies have to clarify whether long-term CRT is able to improve perfusion and metabolism on a global level suggesting a real regression of cardiomyopathy.

Acknowledgements

The authors thank Dr Ansgar Steland, Faculty of Mathematics, Ruhr-University Bochum, Germany for his advice concerning the statistical analysis, and Martina Spickender, Heike Wittemeyer, Heidi Soesanto, and Ines Haubrock for their excellent technical assistance, and Erich Bierre for revising the manuscript.

References