Effects of Cardiac Resynchronization Therapy on Myocardial Perfusion Reserve

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Background—Cardiac resynchronization therapy (CRT) is a relatively new treatment strategy for patients with heart failure and mechanical asynchrony. Reported effects of CRT on regional myocardial blood flow (MBF) are conflicting, and effects on hyperemic MBF are scarce. The aim of the present study was to assess serial changes of MBF and MBF reserve in patients receiving a biventricular pacemaker.

Methods and Results—Fourteen patients with heart failure (NYHA class III or IV; left ventricular ejection fraction <35%), QRS width >120 ms, and sinus rhythm were studied (mean age, 58±10 years; 8 men). MBF and hyperemic MBF were measured at baseline, 3 months after biventricular pacing (CRT on), and after cessation of pacing (CRT off) with PET and H15O. CRT had no significant effect on resting MBF (baseline versus CRT on versus CRT off: 0.82±0.25 versus 0.69±0.24 versus 0.74±0.24 mL · min⁻¹ · mL⁻¹; P=NS). Hyperemic MBF increased during CRT (1.91±1.03 versus 2.66±1.66 versus 1.92±1.06 mL · min⁻¹ · mL⁻¹; P=0.01 by MANOVA), as did MBF reserve (2.25±1.00 versus 3.76±2.38 versus 2.49±0.94 mL · min⁻¹ · mL⁻¹; P=0.023). CRT (reversibly) resulted in a more homogeneous distribution of regional resting MBF as demonstrated by the septal-to-lateral ratio. The decrease in the ratio of left ventricular end-diastolic volume to left ventricular mass, as a reflection of wall stress, was related to the increase in hyperemic MBF (r=0.53, P<0.05). Left ventricular ejection fraction increased from 25±7% to 37±9% (P<0.01).

Conclusions—Resting MBF is unaltered by CRT despite an increase in left ventricular function. However, the distribution pattern of resting MBF becomes more homogeneous. Hyperemic MBF and consequently MBF reserve are enhanced by CRT.

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Key Words: blood flow ♦ heart failure ♦ pacing ♦ tomography, emission-computed

In recent years, cardiac resynchronization therapy (CRT) has emerged as a new treatment strategy for a subgroup of patients with heart failure and an asynchronous contraction pattern.1,2 It has been demonstrated that CRT improves hemodynamic function,1,4 heart failure symptoms, exercise capacity, and quality of life (QOL) and that it reduces morbidity and mortality.5 A number of studies have shown that function improves without an increase in oxygen consumption, indicating increased efficiency.6–9 Furthermore, oxygen consumption seems to be distributed more homogeneously during CRT.7 These findings support the hypothesis that CRT rebalances the loading condition of the heart.1,2 Changes in oxygen consumption are expected to be accompanied by similar changes in myocardial blood flow (MBF). Nevertheless, conflicting results have been reported with regard to the effects of CRT on regional MBF.6,8,10–13 These studies, however, are difficult to compare because MBF was evaluated with different imaging modalities and at varying follow-up periods. In addition, in none of these studies were serial measurements performed before, during, and after cessation of pacing therapy. Furthermore, data on the effects of CRT on MBF reserve are scarce,9 despite its important role in the pathophysiology of the failing heart. Therefore, the present study was performed to serially assess the effects of CRT on regional MBF and MBF reserve with PET and H15O.

Methods

Patients

Sixteen consecutive patients with heart failure (NYHA class III or IV despite optimized medical therapy), left ventricular ejection fraction (LVEF) <35%, intraventricular conduction delay (QRS width >120 ms), LV end-diastolic diameter >55 mm, and sinus rhythm were enrolled in the study. The cause of heart failure was idiopathic dilated cardiomyopathy in 9 patients and ischemic heart failure in 7. Angiography revealed severe coronary artery disease not eligible for further revascularization procedures in 4 of these patients. The remaining 3 patients had suffered from large myocardial infarctions leading to heart failure. No significant coronary artery stenoses were present after percutaneous interventions in the latter patients. At the
time of enrollment, all patients were in a clinically stable condition on standard heart failure medication, including ACE inhibitors (n=4), angiotensin receptor antagonist (n=2), β-blockers (n=13), diuretics (n=14), and digoxin (n=3). The doses of this background medication were stable for ≥3 months. Medication was kept constant during the study. Serial resting MBF and hyperemic MBF measurements were performed <1 month before and 3 months after biventricular pacemaker implantation. The postimplantation measurements were performed both during biventricular pacing (CRT on) and shortly after reprogramming the pulse generator to AAIR mode with a lower rate of 40 bpm (CRT off). Effectively, the latter pacing mode results in a normal sinus rhythm comparable to baseline. The order of the postimplantation studies was randomized. In 8 patients, this sequence was “on-off”; in the remaining 6, it was “off-on.” Two patients died during the follow-up period because of sudden death and progressive pump failure, resulting in 14 completed protocols. QOL was assessed with the Minnesota Living With Heart Failure questionnaire44 before and after 3 months of CRT. Scores range from 0 to 105; higher scores reflect a worse QOL. All subjects gave written informed consent, and the Medical Ethics Committee of the VU University Medical Center approved the protocol.

Biventricular Pacemaker Implantation
Three transvenous pacing leads were inserted, 1 in the atrial appendage and 1 in the right ventricular apex. In addition, a coronary sinus lead was positioned in the posterolateral (n=12) or anterolateral (n=4) position. The pacing leads were connected to a biventricular pacemaker (either Insync II, Medtronic, or TriPlos L.V., Biotronik). The pacemaker was programmed in DDD mode. A predisharge AV optimization was performed in all patients.15

Positron Emission Tomography
All scans were performed in 2D mode with an ECAT EXACT HR+ (Siemens CTI). Subjects were constantly monitored with single-lead ECG, and blood pressure was measured every 3 minutes. After a transmission scan, 1100 MBq of H215 O dissolved in 5 mL saline was injected intravenously via a pump in 2 seconds, followed by a 40-mL saline flush at a rate of 4 mL/s (bolus injection). A dynamic scan was acquired, consisting of 40 frames with variable frame length for a total time of 10 minutes (12×5, 12×10, 6×20, and 10×30 seconds). After the rest study, a hyperemic study was performed by infusing adenosine at a rate of 140 μg · kg−1 · min−1. Subsequently, blood pool imaging was performed. During a 2-minute period, the patient inhaled ≥2000 MBq of C15 O, and a single frame was acquired for a duration of 6 minutes, starting 1 minute after the end of inhalation to allow for equilibration in the blood pool.

The postimplantation study was identical to the baseline study except that resting MBF and hyperemic MBF measurements were performed both during CRT on and CRT off. Emission data were corrected for physical decay of 15 O and for dead time, scatter, randoms, and photon attenuation. Reconstruction of the H215 O and C15 O emission sinograms was performed with filtered back projection with a Hanning filter at 0.5 of the Nyquist frequency, resulting in a transaxial spatial resolution of ~7 mm full width at half-maximum.

Anatomic tissue images were generated by subtracting the blood pool image from the transmission image16 and resliced into short-axis images according to the anatomic axis of the heart. The same reslicing parameters were automatically applied to the dynamic H215 O images. Thirteen regions of interest (ROIs) (6 basal, 6 distal, 1 apical) were defined as described previously.17 Additional ROIs were defined on the anatomic tissue images in left and right ventricular chambers for image-derived input functions. The set of ROIs was projected onto the dynamic H215 O images to generate time-activity curves. With the standard single-compartment model, MBF (mL · min−1 · mL−1 of perfusible tissue) was determined from these time-activity curves. Corrections were made for left and right ventricular spillover effects by use of the method described by Hermansen et al.18 Global MBF was calculated by grouping all ROIs. In addition, septal and lateral MBFs were determined by grouping of the corresponding septal and lateral ROIs. MBF reserve was calculated as the ratio of hyperemic MBF to resting MBF. Because resting MBF is related to the rate-pressure product (RPP; RPP=systolic blood pressure × heart rate), corrected resting MBF (MBF/RPP×10.000) was also determined. Myocardial vascular resistance was calculated by dividing mean arterial pressure by MBF.

Echocardiography
All patients underwent complete 2D and Doppler echocardiography at baseline and after 3 months of follow-up to determine LV and valve function. Standard parasternal and apical views were recorded on VHS videotape for subsequent offline analysis. LV end-diastolic volume (LVEDV), LV end-systolic volume, LV EF, LV mass, LV ejection time, and LV filling time were determined according to the recommendations of the American Society of Echocardiography.19 The ratio of LVEDV to LV mass (LVM) was calculated as a reflection of global end-diastolic LV wall tension, as described by Gia sch.20

Diastolic Perfusion Time Calculation
The R-R interval was measured at rest and during hyperemia on the ECGs obtained during the PET scans. Diastolic perfusion time (DPT; DPT (s/min)=[(R-R interval−LV ejection time)/heart rate])21,22 was calculated during baseline and CRT on for both rest and hyperemia.

Statistical Analysis
Data were expressed as mean±SD. For comparison of 2 data sets, a paired Student’s t test was performed. Intragroup comparisons of hemodynamic and PET data were tested for significance with a general linear model for repeated measures (MANOVA). Linear regression was used to test the relationship between variables. A value of P<0.05 was considered significant. All analyses were performed with SPSS 9 (SPSS Inc).

Results
Biventricular pacemaker implantation was uncomplicated in all 14 patients. Patient characteristics are summarized in Table 1.

Hemodynamic Data
Table 2 lists the hemodynamic results. CRT did not have an effect on heart rate or blood pressure. Infusion of adenosine consistently caused an increase in heart rate and a decrease in systolic blood pressure, resulting in a higher RPP.

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Sex, M/F</td>
</tr>
<tr>
<td>Cause, ischemic/nonischemic</td>
</tr>
<tr>
<td>NYHA class, III/V</td>
</tr>
<tr>
<td>QOL score</td>
</tr>
<tr>
<td>Conduction, LBBB/RBBB</td>
</tr>
<tr>
<td>QRS duration, ms</td>
</tr>
<tr>
<td>LVEF, %</td>
</tr>
<tr>
<td>LVEDV, mL</td>
</tr>
<tr>
<td>LVESV, mL</td>
</tr>
</tbody>
</table>

LBBB indicates left bundle-branch block; RBBB, right bundle-branch block; and LVESV, left ventricular end-systolic volume. n=14.
Myocardial Blood Flow
There were no significant differences in resting global MBF between the 3 measurements (Table 3 and Figure 1), although there was a trend toward a reduction in MBF during CRT on compared with baseline (0.69±0.24 versus 0.82±0.25 mL · min⁻¹ · mL⁻¹; P=0.092). Corrections for RPP did not alter the results (baseline versus CRT on versus CRT off, 1.12±0.39 versus 0.95±0.32 versus 0.98±0.30 mL · min⁻¹ · mL⁻¹; P=NS). Microvascular resistance did not change significantly during the different pacing modes.

Hyperemic MBF
Hyperemic global MBF before implantation was blunted in the study population (mean, 1.91±1.03 mL · min⁻¹ · mL⁻¹). During CRT, hyperemic MBF increased to 2.66±1.66 mL · min⁻¹ · mL⁻¹ (P=0.013 versus baseline). After cessation of CRT, hyperemic MBF returned to baseline values (1.92±1.06 mL · min⁻¹ · mL⁻¹; P=0.018 versus CRT). As a result of the increased hyperemic MBF, MBF reserve was also increased during CRT. Changes in hyperemic MBF were independent of the protocol (on-off or off-on; see Methods).

Nonischemic dilated cardiomyopathy patients had a more pronounced response to CRT (baseline versus CRT on versus CRT off, 2.35±0.98 versus 3.49±1.43 versus 2.46±0.99 mL · min⁻¹ · mL⁻¹; P=0.021) compared with ischemic dilated cardiomyopathy patients (1.32±0.96 versus 1.55±1.31 versus 1.19±0.66 mL · min⁻¹ · mL⁻¹; P=NS), although both showed an increase in hyperemic MBF during CRT. Mean QOL score and NYHA class decreased by 19% and 0.86, respectively (both P<0.01). However, nonischemic patients tended to benefit more from CRT (QOL score and NYHA class decrease, 23% and 1.0, respectively) than ischemic patients (decrease, 15% and 0.67, respectively).

MBF Distribution Pattern
At baseline, resting MBF distribution was inhomogeneous with a septal-to-lateral ratio (SLR) of 0.77±0.27. CRT resulted in a more homogeneous resting MBF pattern, with an SLR of 0.97±0.34 (P=0.049 versus baseline). SLR returned to baseline after cessation of CRT (0.77±0.26, P=0.023 versus CRT; Figure 3). There were no significant changes in SLR for hyperemic MBF during CRT (Table 3).

Echocardiography
At baseline, mean LVEDV, LV end-systolic volume, and LVEF were 273±84 mL, 207±72 mL, and 25±7%, respectively. After 3 months of CRT, LV end-systolic volume decreased to 164±69 mL (P<0.01). Although not significant, LVEDV decreased to 256±88 mL (P=0.08). LVEF increased to 37±9% (P<0.01). Filling time increased from

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**TABLE 2. Hemodynamic Data (n=14)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>CRT On</th>
<th>CRT Off</th>
<th>P (MANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>65±12</td>
<td>79±11*</td>
<td>65±9</td>
<td>0.015</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>117±20</td>
<td>112±20</td>
<td>112±17</td>
<td>0.17</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>70±13</td>
<td>70±10</td>
<td>67±8</td>
<td>0.17</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>85±14</td>
<td>84±11</td>
<td>83±10</td>
<td>0.17</td>
</tr>
<tr>
<td>RPP, bpm/mm Hg</td>
<td>7632±1911</td>
<td>8931±2246*</td>
<td>7442±1381</td>
<td>0.015</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; MAP, mean arterial pressure. *P<0.05 vs rest.

**TABLE 3. PET Data**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>CRT On</th>
<th>CRT Off</th>
<th>P (MANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average MBF</td>
<td>0.82±0.25</td>
<td>0.69±0.24</td>
<td>0.74±0.24</td>
<td>NS</td>
</tr>
<tr>
<td>MBF stress</td>
<td>1.91±1.03</td>
<td>2.66±1.66*</td>
<td>1.92±1.06</td>
<td>0.01</td>
</tr>
<tr>
<td>Flow reserve</td>
<td>2.25±1.00</td>
<td>3.76±2.38*</td>
<td>2.49±0.94</td>
<td>0.02</td>
</tr>
<tr>
<td>Septal MBF</td>
<td>0.70±0.27</td>
<td>0.71±0.22</td>
<td>0.64±0.21</td>
<td>NS</td>
</tr>
<tr>
<td>MBF stress</td>
<td>1.82±0.90</td>
<td>2.82±1.56*</td>
<td>1.83±1.00</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Flow reserve</td>
<td>3.04±2.42</td>
<td>4.33±2.95</td>
<td>2.95±1.10</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral MBF</td>
<td>0.93±0.29</td>
<td>0.77±0.24</td>
<td>0.90±0.34</td>
<td>NS</td>
</tr>
<tr>
<td>MBF stress</td>
<td>2.03±1.14</td>
<td>2.50±1.60</td>
<td>2.00±1.15</td>
<td>NS</td>
</tr>
<tr>
<td>Flow reserve</td>
<td>2.05±0.74</td>
<td>3.16±1.58*</td>
<td>2.25±0.80</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Septal/lateral MBF</td>
<td>0.77±0.27</td>
<td>0.97±0.34*</td>
<td>0.77±0.26</td>
<td>0.04</td>
</tr>
<tr>
<td>Rest</td>
<td>0.98±0.34</td>
<td>1.24±0.30</td>
<td>1.03±0.49</td>
<td>NS</td>
</tr>
<tr>
<td>Average MVR</td>
<td>111±39</td>
<td>130±40</td>
<td>126±37</td>
<td>NS</td>
</tr>
<tr>
<td>MVR stress</td>
<td>57±30</td>
<td>48±35</td>
<td>56±31</td>
<td>NS</td>
</tr>
</tbody>
</table>

MBF indicates myocardial blood flow (mL · min⁻¹ · mL⁻¹); MVR, microvascular resistance (mm Hg·mL⁻¹ · min⁻¹ · mL⁻¹). *P<0.05 vs baseline and CRT off.
367±101 to 401±107 ms (P<0.01). At baseline, DPT decreased from 39.3±9.6 s/min during rest to 34.0±13.4 s/min (P<0.01) during adenosine infusion because of a higher heart rate. CRT did not alter DPT (rest versus stress, 40.3±9.0 versus 34.9±12.9 s/min) compared with baseline.

**Interrelation Among Measured Parameters**

There was a significant relation between the decrease in wall stress, expressed as the LVEDV/LVM ratio, and increase in hyperemic MBF during CRT compared with baseline (Figure 4), whereas there was no correlation between changes in hyperemic DPT time and hyperemic MBF (Figure 5).

**Discussion**

Resynchronization therapy is a relatively new treatment for patients with heart failure and mechanical LV dyssynchrony, usually identified by the presence of intraventricular conduction delay such as left bundle-branch block.1,2 Left bundle-branch block reduces myocardial perfusion in the septum because of impaired systolic thickening and augmented intramyocardial pressure in the septum.24 The present findings also demonstrate an inhomogeneous perfusion pattern, with a reduced SLR of resting MBF. In line with data from Nowak et al10 using SPECT, CRT was found to have a homogenizing effect on perfusion. Similar effects on perfusion were observed by the same group using PET.13 Although not signif-

Figure 2. Serial changes in MBF before implantation of biventricular pacemaker, 3 months after CRT, and immediately after cessation of CRT. *During CRT, hyperemic MBF is significantly higher compared with baseline MBF (P=0.013) and MBF after cessation of CRT (P=0.018).

Figure 3. Serial changes in SLR of resting MBF before implantation of biventricular pacemaker, 3 months after CRT, and immediately after cessation of CRT. *During CRT, SLR is significantly higher compared with baseline SLR (P=0.049) and SLR after cessation of CRT (P=0.023).

Figure 4. Relationship between changes induced by CRT in hyperemic MBF and LVEDV/LVM ratio (r=0.53, P<0.05).

Figure 5. Relationship between changes induced by CRT in hyperemic MBF and DPT time during hyperemia (r=−0.17, P=NS).
sating for these changes by vasodilatation. During pharmacologically induced maximum vasodilatation, however, this autoregulatory mechanism is exhausted, and augmentation of filling pressures and wall stress might lead to a reduction in hyperemic myocardial perfusion. CRT results in a reduction in LV filling pressures and wall stress. The reduction in LVEDV/LVM ratio, as a reflection of end-diastolic wall stress, was directly related to the increase in hyperemic MBF during CRT in the present study, supporting the hypothesis of a relation between the 2 parameters.

Second, myocardial perfusion is a predominantly diastolic process. Dyssynchrony of the heart reduces diastole by prolonging the overall tension development time during the cardiac cycle and shortening of LV filling time. The latter phenomenon is even more pronounced in patients with dilated cardiomyopathy. In the presence of autoregulation of vascular tone, myocardial perfusion is unaffected by changes in DPT. A reduction in DPT, however, could cause a reduction in hyperemic MBF when autoregulation is abolished. Resynchronization of the heart by means of biventricular pacing increases diastolic filling time, which may prolong DPT. CRT could therefore in theory be responsible for the enhanced hyperemic perfusion observed in the present study. DPT, however, was unaltered in the present study because ejection time is hardly affected by CRT, even though filling time was increased. Furthermore, there was no correlation between the change in hyperemic DPT and hyperemic MBF in our study population. Our data suggest that, in contrast to wall stress, DPT does not play an important role in the changes observed in hyperemic perfusion during CRT.

Independent of the mechanism for the increase in hyperemic MBF and MBF reserve, the observation is important from a pathophysiological point of view. Impairment of MBF reserve in congestive heart failure, independent of its cause, is believed to cause repetitive stunning (intermittent periods of ischemia), leading to chronic reversible LV dysfunction, which in turn is associated with an adverse prognosis. Restoration of flow reserve by revascularization therapy can induce recovery of function and improve prognosis. Although the benefit of biventricular pacing is related to mechanical resynchronization of the interventricular septum and lateral free wall, the present study suggests that enhancement of MBF reserve might also play a role in the recovery of function associated with CRT.

Follow-up PET studies were performed after 3 months of CRT. In general, reverse remodeling occurs over this period of time. The reversed remodeling process could have contributed to the effects of CRT on myocardial perfusion. The immediate return to baseline values after cessation of pacing, however, suggests that the effect of remodeling is limited. Furthermore, once reverse remodeling has occurred, some of the benefits of CRT are lost gradually over time after suspension of pacing. This is in contrast to the acute changes in regional MBF and hyperemic MBF observed in the present study.

Because the present study population was relatively small, the value of subgroup analyses is very limited. There was, however, a tendency toward greater augmentation of hyperemic MBF by CRT in nonischemic than in ischemic patients. Flow-limiting stenoses and the presence of scar tissue may be responsible for these differences.

Recently, Sundell et al did not observe a significant change in hyperemic MBF after cessation of CRT in 10 nonischemic heart failure patients after an average period of 8 months of pacing, although a slight decrease occurred. A possible explanation for the discrepancy between that study and the present one could be a difference in patient population. Hyperemic perfusion after cessation of CRT was substantially lower compared with nonischemic patients in our study (1.6 ± 0.9 versus 2.5 ± 1.0 mL · min⁻¹ · mL⁻¹), indicating a more advanced stage of dilated cardiomyopathy. Interestingly, in the present study, enhancement of hyperemic perfusion was observed predominantly in patients with relatively preserved baseline hyperemic perfusion (Figure 2), which may be responsible for the discrepancy compared with the results from Sundell et al. This issue, in addition to underlying mechanisms responsible for the perfusion changes during CRT, needs to be addressed in future studies.

Conclusions

CRT does not alter resting MBF despite an increase in LV function, suggesting increased efficiency. The heterogeneous regional distribution of resting MBF, however, is normalized by CRT. Furthermore, hyperemic MBF and consequently MBF reserve are enhanced by CRT.

References


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