Effect of Cardiac Resynchronization on Myocardial Efficiency and Regional Oxidative Metabolism

Heikki Ukkonen, MD; Rob S.B. Beanlands, MD; Ian G. Burwash, MD; Robert A. de Kemp, PhD; Claude Nahmias, PhD; Ernest Fallen, MD; Michael R.S. Hill, PhD; Anthony S.L. Tang, MD

Background—Recent studies have demonstrated increased left ventricular contractility with cardiac resynchronization therapy (CRT) using atrioventricular stimulation. This study evaluated the effect of CRT on myocardial oxidative metabolism and efficiency.

Methods and Results—Eight patients with New York Heart Association functional class III-IV congestive heart failure were studied during atrial pacing (control) and atrioventricular stimulation at the same rate. The monoexponential clearance rate of $[^{11}C]$acetate ($k_{mono}$) was measured with positron emission tomography to assess myocardial oxidative metabolism in the left and right ventricles (LV and RV, respectively). Myocardial efficiency was measured using the work metabolic index (WMI). Stroke volume index improved by 10% ($P=0.011$) with CRT, although both global LV and RV $k_{mono}$ were unchanged compared with control. Septal $k_{mono}$ increased by 15% ($P=0.04$), and the septal/lateral wall $k_{mono}$ ratio increased by 22% ($P=0.01$), WMI increased by 13% ($P=0.024$) with CRT.

Conclusions—CRT improves LV function without increasing global LV oxidative metabolism, resulting in improved myocardial efficiency. Oxidative metabolism of the interventricular septum increases relative to the lateral wall, which suggests successful resynchronization. (Circulation. 2003;107:28-31.)

Key Words: heart failure ■ pacemakers ■ oxygen ■ metabolism ■ tomography

Despite major advances in pharmacological treatment, mortality and morbidity of patients with advanced heart failure (HF) (New York Heart Association functional class III-IV) remain high. Furthermore, quality of life is poor and the annual hospitalization rate is over 15%. A subgroup of HF patients exhibit a prolonged QRS complex (ie, delayed ventricular activation) and asynchronous ventricular contraction, which further impairs cardiac pump function. Cardiac resynchronization therapy (CRT) is an attractive therapy that simultaneously stimulates both ventricles and improves HF symptoms and ventricular function. Therapies that improve left ventricular (LV) function, however, may do so at the expense of increasing global myocardial oxygen consumption, which can be deleterious in long-term treatment. This study was designed to evaluate the effect of CRT on both global and regional oxidative metabolism and on myocardial efficiency in patients with advanced HF.

Methods

Eight patients with a dilated cardiomyopathy (DCM) (all male, age 63±8 years, 6 with ischemic etiology) and New York Heart Association functional class III-IV congestive HF were implanted with an atrioventricular pacemaker (Medtronic InSync) for CRT.

Detailed patient characteristics are in Table 1.

We used $[^{11}C]$acetate positron emission tomography (PET) imaging to measure oxidative metabolism and an echocardiographic examination to measure LV volumes and stroke work. These measurements were obtained when the cardiac resynchronization device was programmed to atrial pacing (control) at 10 bpm above sinus rate with natural atrioventricular conduction (control) and during atrioventricular stimulation at the same rate. The device was programmed to the setting at least 2 hours before the PET and echocardiographic studies. The PET and echocardiographic examinations were performed 58±26 weeks after CRT implantation. The protocol was approved by the institutional ethic review boards of McMaster University Medical Center and University of Ottawa Heart Institute and was carried out in accordance with institutional guidelines.

Patients were positioned in a whole body PET scanner (Siemens ART), and $[^{11}C]$acetate PET imaging was performed as previously described.

The reconstructed dynamic PET images were analyzed by applying 5 regions of interest (ROI) covering the septum, anterior wall, lateral wall, whole LV myocardium (“horseshoe” ROI), and free wall of the right ventricle (RV), respectively, in 3 to 5 midventricular transaxial planes. A monoexponential function was fitted to the myocardial time-activity data, and monoexponential clearance rates ($k_{mono}$) were determined for each ROI and averaged across planes.
Two-dimensional and Doppler echocardiographic examinations were performed using a cardiac ultrasound system (Hewlett Packard 2500 or 5500). Stroke volume (SV) was assessed using Doppler and stroke work index (SWI) was calculated as \( \frac{7.10 \times SVI}{SBP} \), where SVI is the SV indexed for body surface area and SBP is the systolic blood pressure. LV volumes were calculated using the method of discs. Mitral regurgitation (MR) was quantified by measuring the largest regurgitant jet area on Doppler color flow imaging.

Myocardial efficiency was assessed using the concept of work metabolic index \( WMI = \frac{SWI \times HR}{k_{mono}} \), where HR is heart rate.

All PET and echocardiographic data were analyzed blinded to the patient’s treatment arm and clinical data.

**Statistical Analysis**

Data are expressed as mean±SD. Comparisons were performed using a paired t test and univariate repeated measurements ANOVA where applicable.

**Results**

Table 2 indicates the hemodynamic results. The HR and SBP were similar between groups. Diastolic BP was higher with CRT. CRT was associated with a decreased LV end-diastolic volume index (LVEDVI), a 10% higher SVI and a 15% higher LV ejection fraction (LVEF). There was a trend for increased SWI and decreased MR with reduction of MR jet area with CRT.

The mean rate of myocardial oxidative metabolism was similar with and without CRT. This phenomenon was observed for both the LV (\( k_{mono} = 0.042 ± 0.006 \) versus \( 0.041 ± 0.006 \) per minute, \( P = 0.86 \)) and RV (\( k_{mono} = 0.040 ± 0.009 \) versus \( 0.039 ± 0.011 \) per minute, \( P = 0.62 \)) (Figure 1A).

CRT increased septal \( k_{mono} \) by 15% (\( 0.045 ± 0.007 \) versus \( 0.040 ± 0.005 \), \( P = 0.04 \)) (Figure 1B). However, there were no statistically significant changes in anterior or lateral walls (\( 0.040 ± 0.008 \) versus \( 0.038 ± 0.008 \), \( P = 0.38 \) and \( 0.042 ± 0.006 \) versus \( 0.046 ± 0.011 \), \( P = 0.23 \), respectively). Furthermore, the septal/lateral wall \( k_{mono} \) ratio increased by 22% (\( 0.913 ± 0.237 \) to \( 1.113 ± 0.249 \) per minute, \( P = 0.01 \)).

The WMI was 13% higher during CRT compared with control (\( 6.68 ± 3.45 \) versus \( 5.91 ± 3.10 \) mm Hg · L · m⁻², \( P = 0.024 \); Figure 2).

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Etiology</th>
<th>NYHA</th>
<th>VO₂max, mL · kg⁻¹ · min⁻¹</th>
<th>LVEF, %</th>
<th>QRS Duration, ms</th>
<th>Conduction Abnormality</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ischemic</td>
<td>30</td>
<td>13.1</td>
<td>30</td>
<td>160</td>
<td>LBBB</td>
<td>ARB, DIG, DIU</td>
</tr>
<tr>
<td>2</td>
<td>Ischemic</td>
<td>28</td>
<td>17.8</td>
<td>3</td>
<td>190</td>
<td>LBBB</td>
<td>ACEI, BB, DIG, DIU</td>
</tr>
<tr>
<td>3</td>
<td>Ischemic</td>
<td>17</td>
<td>13.8</td>
<td>3</td>
<td>160</td>
<td>LBBB</td>
<td>ACEI, AMIO, DIG, DIU</td>
</tr>
<tr>
<td>4</td>
<td>Ischemic</td>
<td>20</td>
<td>10.8</td>
<td>4</td>
<td>164</td>
<td>LBBB</td>
<td>ARB, BB, DIU</td>
</tr>
<tr>
<td>5</td>
<td>Ischemic</td>
<td>14</td>
<td>13.9</td>
<td>3</td>
<td>200</td>
<td>LBBB</td>
<td>ACEI, BB, DIG, DIU</td>
</tr>
<tr>
<td>6</td>
<td>Nonischemic</td>
<td>22</td>
<td>13.4</td>
<td>3</td>
<td>172</td>
<td>LBBB</td>
<td>ARB, BB, DIG, DIU</td>
</tr>
<tr>
<td>7</td>
<td>Ischemic</td>
<td>26</td>
<td>14.4</td>
<td>3</td>
<td>130</td>
<td>LBBB</td>
<td>ARB, BB, DIU</td>
</tr>
<tr>
<td>8</td>
<td>Nonischemic</td>
<td>22</td>
<td>15.5</td>
<td>3</td>
<td>200</td>
<td>LBBB</td>
<td>ACEI, BB, DIG, DIU</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin converting enzyme inhibitors; AMIO, amiodarone; ARB, angiotensin receptor blocker; BB, \( \beta \)-blockers; DIG, digoxin; DIU, diuretic; LBBB, left bundle branch block; and NYHA, New York Heart Association.

**Table 2. Hemodynamic Results**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>CRT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>63±10</td>
<td>65±9</td>
<td>0.47</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>109±18</td>
<td>113±21</td>
<td>0.42</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>66±12</td>
<td>75±8</td>
<td>0.050</td>
</tr>
<tr>
<td>LVEDVI, mm/m²</td>
<td>118±36</td>
<td>112±36</td>
<td>0.004</td>
</tr>
<tr>
<td>SVI, mL/m²</td>
<td>33±7</td>
<td>36±9</td>
<td>0.011</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26±9</td>
<td>30±9</td>
<td>0.010</td>
</tr>
<tr>
<td>LVSWI, L · mm Hg</td>
<td>3.77±1.26</td>
<td>4.27±1.76</td>
<td>0.070</td>
</tr>
<tr>
<td>MR jet area, cm²</td>
<td>10.2±6.2</td>
<td>8.4±5.0</td>
<td>0.058</td>
</tr>
</tbody>
</table>

LVEDVI indicates left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; and LVSWI, left ventricular stroke work index. Values are mean±SD.
Cardiac resynchronization therapy did not have any effect on global LV or RV oxidative metabolism, which suggests that metabolic demand does not increase with CRT. CRT caused an increase in LV stroke volume, ejection fraction, and stroke work, however, resulting in a 13% enhancement of LV myocardial efficiency.

Previous studies have demonstrated favorable acute hemodynamic effects of multisite pacing in HF patients with conduction disturbances, including decrease in LVEDVI, pulmonary capillary wedge pressure, MR severity, and increase in SV. A mild decrease in LVEDVI and MR severity and increase in SV were also observed in this study. RV apex pacing causes an activation pattern similar to left bundle-branch block (LBBB), and it reduces mechanical work in the septum by 50% but increases LV free wall work by 50%. In our patients, regional oxidative metabolism was not significantly different during intrinsic ventricular conduction. CRT increased septal oxidative metabolism, however, whereas oxidative metabolism remained unchanged in both the LV anterior and lateral walls. The increase in oxidative metabolism of the septum after a more synchronized LV contraction reflects increased septal workload as it contracts against a greater LV load and actively contributes to LV ejection. The role of the septum in global LV function has been recognized earlier in patients with HF. There are no data on regional efficiency in isolated LBBB. Impaired septal glucose uptake but not oxidative metabolism has been reported in patients with isolated LBBB.

The oxidative metabolism in the RV is also high relative to the LV in this study, which indicates increased RV work. RV oxidative metabolism did not change with CRT. The effect of CRT on RV myocardial efficiency cannot be determined from this data because RV work was not measured.

In acute setting, LV pacing has been reported to increase pulse pressure and dP/dTmax and decrease global myocardial oxygen consumption in patients with nonischemic dilated cardiomyopathy, LBBB, and very mild MR. These findings suggest increased myocardial efficiency, although efficiency was not specifically reported. Most of our patients had ischemic cardiomyopathy and moderate to severe MR. Part of the observed increase in SV is likely due to the reduction of MR. However, the increase in forward SV did not result in increase in oxidative metabolism, although this would have been expected with the higher afterload in the aorta (versus left atrium). Therefore, a 13% improvement in efficiency with CRT is not due to the decrease in MR severity but is due to more efficient LV contraction.

In the current study, the observed improvements in left ventricular SVI and LVEF with CRT were somewhat less than in previous reports. Because the resynchronization device was implanted before the study (median 380 days), CRT may have already had a benefit, and the acute effects may have been underestimated in the current study.

Conclusions
Cardiac resynchronization therapy improves LV function without increasing global LV oxidative metabolism, hence improving LV efficiency. Oxidative metabolism of the interventricular septum increased relative to the lateral wall, likely reflecting enhanced work of the septum as a result of successful resynchronization. These results support the use of cardiac resynchronization to improve LV function in advanced HF patients with ventricular dyssynchrony.

Acknowledgments
The project was supported by grants from Heart & Stroke Foundation of Canada and Medtronic Inc. Dr Ukkonen was supported by the International Fellowship Program at the University of Ottawa, the Academy of Finland, and the Finnish Medical Foundation. Dr Beanlands is a Research Scientist supported by Canadian Institutes of Health Research (CIHR) (Ottawa, Canada). Drs Tang and Beanlands were co-primary investigators. The authors thank Erin Niven, MSc, Patricia Theoret-Patrick, RN, Clare Carey, RN, and Karen Hay for technical assistance and Sherri Nipius for her help in preparing the manuscript.

References
Effect of Cardiac Resynchronization on Myocardial Efficiency and Regional Oxidative Metabolism
Heikki Ukkonen, Rob S.B. Beanlands, Ian G. Burwash, Robert A. de Kemp, Claude Nahmias, Ernest Fallen, Michael R.S. Hill and Anthony S.L. Tang

_Circulation_. 2003;107:28-31; originally published online December 9, 2002;
doi: 10.1161/01.CIR.0000047068.02226.95

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/1/28