Effects of Mitral Valve Surgery on Myocardial Energetics in Patients With Severe Mitral Regurgitation

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Background—Hemodynamically significant mitral regurgitation (MR) may alter left ventricular (LV) myocardial energy requirements. The effects of MR and subsequent corrective mitral valve (MV) surgery on myocardial energetics are not well understood. A better understanding of myocardial energetics and the LV responses to changes in preload and afterload may assist with the understanding of mitral regurgitation and its effect on the LV. We sought to determine the effects of MV surgery on forward stroke work, myocardial oxidative metabolism, and myocardial efficiency.

Methods and Results—Prospectively enrolled patients with chronic, severe, nonischemic mitral regurgitation underwent echocardiography, radionuclide angiography, and C-11 acetate positron emission tomography to measure LV volumes, ejection fraction, and oxidative metabolism before and 1 year after MV surgery. Forward and total stroke work corrected for oxidative metabolism was used to estimate efficiency using the work metabolic index. Fourteen patients (age, 59 ± 8 years) with myxomatous MV were enrolled. One year after MV surgery, there was a reduction in LV end-diastolic and end-systolic volumes (231 ± 86 to 131 ± 21 mL; P < 0.01 and 98 ± 53 to 55 ± 17 mL; P < 0.01). Forward stroke volume increased (58.1 ± 15.0 to 75.5 ± 23 mL; P < 0.01), LV ejection fraction was preserved without a significant change in oxidative metabolism. Forward work metabolic index improved (4.99 ± 1.32 × 10^6 to 6.59 ± 2.45 × 10^6 mm Hg×mL/m^2; P = 0.02). This was not at the expense of total work metabolic index, which was preserved.

Conclusions—MV surgery has a beneficial effect on forward stroke volume and forward work metabolic index without adverse effects on oxidative metabolism or total work metabolic index. (Circ Cardiovasc Imaging. 2010;3:308-313.)

Key Words: mitral valve □ regurgitation □ remodeling □ metabolism □ imaging

Hemodynamically significant mitral regurgitation (MR) alters left ventricular (LV) anatomy and physiology.1 MR affects both preload and afterload, may elevate left atrial (LA) volume and pressure, reduce forward stroke volume (SV), and increase LV end-diastolic pressure. To meet systemic needs, the total LV SV must increase to compensate for the low-impedance regurgitant stroke work while maintaining forward stroke work.2–4

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With the reduced afterload and increased preload state of MR, the LV ejection fraction (LVEF) can remain normal until late in the disease.5,6 Such preservation of LVEF raises concern that it may be a suboptimal predictor of myocardial contractility and thus may not accurately predict the need for mitral valve (MV) surgery and outcomes for postoperative MV surgery. Starling2 has demonstrated that such patients with preserved LVEF have impaired LV contractility that can improve 1 year after MV surgery. Starling has also suggested that MV surgery improves myocardial efficiency, further supporting the notion that MR-induced LV injury may be reversible. However, such data are limited, and, due to the invasive nature of pressure-volume loop measurements, may not be routinely available.

The myocardial kinetics of radiolabeled C-11-acetate measured noninvasively with positron emission tomography (PET) have been used to assess oxidative metabolism.7–9 Combining measures of oxidative metabolism with assessments of LV performance, one can calculate the work metabolic index (WMI), which is an estimate of myocardial energetics.10–16 Whether or not changes in LV contractile function after MV surgery occur at the expense of oxidative metabolism has not been well investigated. This study examines the effects of MV surgery on myocardial metabolism and the WMI as an estimate of myocardial efficiency in patients with chronic, severe, nonischemic MR. Further understanding of myocardial metabolism and myocardial efficiency before and after surgery.
surgeon correction may enable the development of better predictors of MV surgical outcome in this patient population.

Methods
This prospective study enrolled patients with chronic (at least 3 months in duration) nonischemic MR who were scheduled for MV surgery. Patients were excluded if they had acute MR or progression to severe MR within 3 months of enrollment, mixed valvular heart disease, previous myocardial infarction, or were unable to provide informed consent. During the study period (15 months), a total of 118 patients underwent mitral valve surgery. Of these, 61 were excluded for coronary artery disease or mixed valve disease. Of the remaining 80 patients, 6 were excluded for acute MR. A total of 14 patients underwent transthoracic echocardiography, radionuclide angiography (RNA), and C-11 acetate PET before and 12 months after MV surgery. This study was approved by the local institutional human research ethics board.

Positron Emission Tomography
On positioning the patient in the Siemens/CTI ART PET scanner (Knoxville, Tenn), a 5-minute transmission scan was performed for attenuation correction. Then, 6 to 10 mCi (222 to 370 MBq) of C-11 acetate was administered intravenously and a dynamic PET acquisition was initiated (10×10 seconds; 1×60 seconds; 5×100 seconds; 3×180 seconds). The reconstructed dynamic PET images were analyzed by applying a region of interest over the whole LV myocardium in 3 to 5 midventricular transtaxial planes. A monoexponential function was fit to the myocardial time-activity data, and the myocardial clearance rate constant (k-mono) was determined as described previously. The monoexponential fit began at the point when the blood pool was stable (usually 2 to 4 minutes after injection) (Figure 1).

Echocardiography
A complete 2D color and Doppler echocardiogram (ECHO) was performed immediately before C-11 acetate PET study. As described previously, ventricular function was assessed using a Sonos 7500 ultrasound system (Phillips, Andover, Mass) equipped with a 3.2-MHz phased-array transducer. All measurements were performed off-line and averaged from 3 cardiac cycles.

Forward SV was derived from the velocity-time integral of the pulsed Doppler LV outflow tract velocity signal and the LV outflow tract diameter. Forward SV index (SVI) was derived by dividing forward SV by the body surface area (BSA). Mitral regurgitant volumes were determined using the PISA method. Peak LA pressure was estimated from the brachial systolic blood pressure (SBP) minus the systolic pressure gradient across the MV derived from the velocity of the mitral regurgitant jet (LA pressure = SBP−4×peak MR jet velocity).

WMI Determination
Scintigraphic C-11 clearance data (k-mono) and the forward stroke work data were used to calculate forward LV WMI (forward WMI = forward SWI×HR/k-mono, where SWI = [SV/BSA]; HR indicates heart rate), as we have described previously. To account for the additional work related to the regurgitant volume against the LA pressure, the regurgitant work was estimated using a regurgitant work index (RWI), where RWI = (regurgitant volume/peak LA pressure/BSA). A regurgitant WMI (rWMI) was then calculated as RWI/k-mono. A total WMI was then used to estimate the overall efficiency of the LV considering both forward and regurgitant work whereby total WMI = forward WMI + rWMI.

Radionuclide Angiography
Equilibrium planar RNA was used to calculate the LV end-systolic and end-diastolic volumes and LVEF. RNA imaging with Tc-99m-labeled red blood cells was performed with a small field-of-view Siemens ZLC gamma camera and a low-energy all-purpose collimator, according to a standard protocol. Gated acquisition was performed for 24 frames per cardiac cycle with a beat rejection window of 10%. Scans were acquired in the left anterior oblique, anterior, and lateral views. Six million counts were acquired for each orientation with an acquisition time of 7 to 9 minutes per scan. Calculations of LV volumes were performed using software that has been validated locally.

Statistical Analysis
Continuous values are reported as means±standard deviation. Paired samples of continuous variables were evaluated with a paired t test using SPSS Version 12.0.1 (Chicago, Ill).

Results
A total of 14 patients (age, 59±8 years old; 10 men) with myxomatous MV were enrolled into the study (Table). The
Both LV end-diastolic volumes (LVEDV) and end-systolic volumes (LVESV) decreased 43% and 44%, respectively (Figure 2a). After surgery, forward SV increased from 15 mL to 75.5 mL (P<0.01) and there was a significant improvement in forward myocardial efficiency as estimated by forward WMI.

**Myocardial Oxidative Metabolism**

Compared with preoperative baseline, there was no significant change in oxidative metabolism as measured by C-11 acetate kinetics (k-mono) 1 year after MV surgery (0.056±0.014/min versus 0.052±0.011/min; P=0.32) (Figure 2a).

**LV Function and Volumes**

Similarly, there was no change in LVEF (59±11% versus 57±10%; P=0.52). After surgery, forward SV increased from 58.1±15.0 mL to 75.5±23 mL (P<0.01) and there was a significant reduction in LV volumes by RNA after MV surgery. Both LV end-diastolic volumes (LVEDV) and end-systolic volumes (LVESV) decreased 43% and 44%, respectively (Figure 2b and 2c).

**Myocardial Energetics**

Forward WMI increased 35% after surgery and occurred in the absence of significant changes in k-mono, SBP, or HR (Figure 2d). Total WMI did not change significantly after surgery (5.69±1.76×10^6 to 6.61±2.42×10^6; P=0.22) (Figure 2e).

**Discussion**

This study demonstrates that MV surgery for chronic severe nonischemic MR improves LV volumes and increases forward SV while preserving LVEF. These changes occur without adverse effects on oxidative metabolism. Such changes demonstrate a significant improvement in forward myocardial efficiency as estimated by forward WMI.

The concept of myocardial efficiency was developed by Starling and Vissher in the early 20th century, conceptualized as the measure of minute SW corrected for oxygen consumption and first applied in humans by Bing et al. The relationship of oxygen consumption and C-11 acetate kinetics has been well validated. As such, the WMI represents an estimate of myocardial efficiency. This has been widely applied by many investigators to evaluate different forms of heart failure and response to therapy. Though this approach has not been previously applied to patients with significant MR, it is a widely accepted approach to estimate efficiency noninvasively and thus was used for this study.

The previous applications of the WMI have generally used stroke work in which MR was not severe or used forward stroke work and therefore determine forward WMI. However, estimation of forward WMI does not consider the added work that the ventricle of a patient with MR must face. To our knowledge, the current study represents one of the first studies applying WMI to mean LVEF before MV surgery was 59±11%; 8 patients had an LVEF ≥60%, 5 patients had an LVEF between 45% and 59%, and 1 patient had LVEF of 31%. All 14 patients underwent successful MV surgery; after surgery, the regurgitant volume decreased from 34±19 mL to 2.8±10 mL (P<0.01).

### Table. Preoperative and Postoperative Characteristics

<table>
<thead>
<tr>
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<th>Preoperative</th>
<th>Postoperative</th>
<th>Difference</th>
<th>P</th>
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</thead>
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<tr>
<td>Age, y</td>
<td>59±8</td>
<td>57±10</td>
<td>2±11</td>
<td>0.52</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>10 (71%)</td>
<td>11 (79%)</td>
<td>11%</td>
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<tr>
<td>BSA, m²</td>
<td>1.9±0.2</td>
<td>1.76±0.2</td>
<td>0.02</td>
<td>0.32</td>
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<td>New York Heart Association</td>
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<tr>
<td>Class I</td>
<td>3 (21%)</td>
<td>5 (36%)</td>
<td>25%</td>
<td>0.01</td>
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<tr>
<td>Class II</td>
<td>11 (79%)</td>
<td>12 (86%)</td>
<td>31%</td>
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<tr>
<td>Serum creatinine, μmol/L</td>
<td>85±15</td>
<td>86±17</td>
<td>1±9</td>
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<tr>
<td>MV surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MV repair</td>
<td>12 (86%)</td>
<td>10 (71%)</td>
<td>15%</td>
<td>0.22</td>
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<tr>
<td>MV replacement</td>
<td>2 (14%)</td>
<td>2 (14%)</td>
<td>0</td>
<td>0.45</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>98±53</td>
<td>55±17</td>
<td>43%</td>
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<tr>
<td>LVEDV, mL</td>
<td>159±52</td>
<td>87±20</td>
<td>44%</td>
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<tr>
<td>Peak LA pressure, mm Hg</td>
<td>27±15</td>
<td>40±19</td>
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<td>E:A</td>
<td>1.02±0.35*</td>
<td>1.42±0.39*</td>
<td>35%</td>
<td>0.01</td>
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<td>Metabolic parameters</td>
<td></td>
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<tr>
<td>k-mono C-11, clearance/min</td>
<td>0.056±0.013</td>
<td>0.051±0.011</td>
<td>0.004±0.014</td>
<td>0.32</td>
</tr>
<tr>
<td>Forward WMI, mm Hg×mL/m²</td>
<td>4.99±1.32×10^6</td>
<td>6.59±2.45×10^6</td>
<td>1.60±2.30×10^6</td>
<td>0.01</td>
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<tr>
<td>rWMI, mm Hg×mL/m^2^</td>
<td>7.05±1.76×10^5</td>
<td>0.218±7.86×10^5</td>
<td>6.85±7.52×10^5</td>
<td>0.01</td>
</tr>
<tr>
<td>Total WMI, mm Hg×mL/m^2^</td>
<td>5.69±1.76×10^6</td>
<td>6.61±2.42×10^6</td>
<td>0.92±2.66×10^5</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Values are mean±SD (n=14).

*Patients in atrial fibrillation (4 patients before surgery and 1 patient after surgery) excluded.
account for the added work of the regurgitant volume against the LA pressure. In keeping with original concepts for WMI as a noninvasive estimate of efficiency, we applied the RWI, using the product of the peak LA pressure and MR volume determined from echocardiographic parameters to derive rWMI. A total WMI could then be determined as an estimate of efficiency that considers the sum of both forward and regurgitant work of the LV. This may better reflect the burden of MR and the total work of the LV.

MR-induced volume overload of the LV and LA results in LV eccentric hypertrophy and elongation of sarcomeres. As preload increases, the LV remodels and dilates to maintain a normal forward SV and forward stroke work. Increases in afterload associated with LA dilatation are offset by the low-impedance circuit (the LA). Therefore, afterload associated with MR may be variable, with initial reduction only to elevate in the later stages of the disease as LV size increases further.

The hemodynamic consequence of correcting MR is the resultant decrease in preload and increase in afterload, as the low-impedance LA is no longer available. One may expect that increases in afterload might increase metabolic demand and thus reduce ventricular pump function and efficiency. This would certainly be expected if the ventricular injury is irreversible.

However, as proposed by Starling, the pathobiology of severe MR, stimulated by the volume load state, is gradual and appears to be reversible early in the disease. Compensatory mechanisms including preload reserve, altered gene expression, stimulation of cytokines, and sympathetic nervous system activation may be protective. In cases of reversible myocardial injury, the reduced volume that occurs after surgery enables the ventricle to overcome the increased afterload in an efficient manner, without increasing metabolic rate or myocardial oxygen consumption while preserving LV function.

As previously observed, our study confirmed a reduction in both LVED and LVES volumes after MV surgery. Using invasive measurements, Starling demonstrated that these volume changes led to an increase in forward pump efficiency after surgery, measured by pressure-volume area. In the current study, we observed that forward SV increased after MV surgery. This occurred without a detrimental effect on myocardial oxidative metabolism. As a result, a significant improvement in forward WMI was observed and the total WMI was preserved. The rise in forward WMI observed in our patient population indicates that the LV directs more of the preserved total WMI to the delivery of forward cardiac output after MV surgery similar to the observations of Starling. Since forward WMI increased after

Figure 2. Preoperative and postoperative measurements (mean and standard deviations) for a, k-mono; b, LVEDV by RNA; c, LVESV by RNA; d, forward WMI; and e, total WMI.
surgery in the absence of changes in k-mono, HR, and SBP, this is consistent with the notion that LV pump efficiency, as judged by WMI, is preserved initially, despite MR and LV dilatation. Improvements in forward WMI probably are explained by the redirection of the regurgitant work portion, resulting in the preservation of the total WMI. This is also manifested as improved LVEDV, LVESV, and forward SV 1 year after surgery. With preserved contractility and efficiency, the myocardium, after surgery, is able to improve forward stroke work with the utilization of the same amount of oxidative fuel.

The LVEF values of most of the patients in the current study suggest minimal or no contractile dysfunction. The preservation of ventricular efficiency after surgery may imply that reversible changes occur and probably precede irreversible structural and contractile dysfunction.

In the single patient with moderate to severe LV dysfunction (EF, 31%), the preoperative forward WMI (1.81×10^{-6} \text{ mm Hg x mL/m}^2) was 2 SD below the mean of the study group and below the previously reported normal range of 6.20±2.25×10^{-6} \text{ mm Hg x mL/m}^2.\textsuperscript{15} This patient demonstrated an improvement in forward WMI (3.83×10^{-6} \text{ mm Hg x mL/m}^2) and no change in LVEF after surgery (31%). This patient’s preoperative total WMI (2.05×10^{-6} \text{ mm Hg x mL/m}^2) was also below average but increased (4.11×10^{-6} \text{ mm Hg x mL/m}^2) after surgery, which may reflect suboptimal correction of the MR with moderate residual postoperative MR (regurgitant volume, 39 mL). This case suggests that postoperative improvements in energetics can occur in those with LV dysfunction but that the initial energetics as well as the improvements are blunted in the setting of LV dysfunction. The energetics in those with EF 45% to 59% compared with those ≤60% were not significantly different. Whether or not a very low WMI (forward or total) may predict a lack of significant improvements or minimal improvements in forward WMI, is preserved initially, despite MR and LV dilatation. Therefore its effects on energetics are uncertain.

Conclusions

In patients with severe chronic nonischemic MR, MV surgery can improve SV without increasing oxidative metabolism (k-mono), thus resulting in improved forward myocardial efficiency. The end-diastolic and end-systolic volumes decreased after surgery, suggesting that the increase in forward WMI was related to reverse remodeling of the LV after surgery. These changes did not occur at the expense of oxidative metabolism and suggest that reversible changes in ventricular energetics occur before irreversible structural changes. Measurement of such changes in energetics may prove useful in the management of MR and other disease states that alter hemodynamics.

Limitations and Technical Considerations

This study was not powered to distinguish between responders and nonresponders to surgery; therefore, further investigation is required in a cohort with varying preoperative characteristics and varying postoperative success.

Simultaneous assessment of ventricular function with ECHO and oxidative metabolism with C-11 PET acetate clearance cannot be performed. Thus, small variations in loading conditions and contractile state may occur in the short time interval between PET and ECHO and thus may affect the estimation of the WMI. These variations were minimized by ensuring that the ECHO was performed immediately before the PET study.\textsuperscript{10–13,24} Peak instantaneous LA pressure rather than mean LA pressure was used to estimate rWMI. The use of peak pressure is consistent with the traditional method of calculating WMI using SBP.

Newer PET scanners with list mode are now capable of simultaneous gating for LV function, volume estimates, and dynamic acquisition for tracer kinetics.\textsuperscript{33} This may enable the simultaneous assessment of oxidative metabolism, LV volume and function needed for WMI determination, with a single data acquisition. As the interests in single-photon emission computed tomography, PET, and MRI metabolic imaging increase, combined measures of metabolism and contractile performance may also become possible with other single or hybrid modalities.\textsuperscript{34–36}

Although the measurement of efficiency and energetics has prognostic value, whether their noninvasive measurement in patients with severe MR can be used to distinguish those patients with irreversible from those with reversible injury requires further long-term investigation. Because all patients had a similar etiology of MR, it is unclear if our results may be translated to the other etiologies of MR. As well, the chronicity of MR in each patient was unknown, and therefore its effects on energetics are uncertain.

Acknowledgments

We thank May Aung, Micheala Garkisch, Kim Gardner, Debbie Gauthier, Patricia Grant, Sandina Jamieson, and Matt Raegerle for their expertise and dedication to cardiac PET research.

Sources of Funding

This study was funded by the Ontario Research Development Challenge Fund. During the course of the study, Dr Chow was a research fellow supported by a Toronto Dominion Research Fellowship and supervised by Dr Ruddy. Dr Chow is now supported by a Canadian Institutes of Heart Research New Investigator Award No. MSH-83718. Dr Beanlands is a Career Investigator supported by the Heart and Stroke Foundation. Dr Abunassar was a medical student supervised by Dr Chow and Dr Beanlands.

Disclosures

None.

References

Clinical Perspective

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Circ Cardiovasc Imaging. 2010;3:308-313; originally published online March 1, 2010; doi: 10.1161/CIRCIMAGING.109.859843

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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http://circimaging.ahajournals.org/content/3/3/308