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

Running Title: Chow et al; MV Surgery and Myocardial Energetics

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Journal Subject Codes: [19] Valvular Disease), [32] Nuclear cardiology/PET; [115] Remodeling
Abstract:

Background: Hemodynamically significant mitral regurgitation (MR) may alter left ventricular 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 left ventricular responses to changes in preload and afterload may assist with the understanding of mitral regurgitation and its effect on the left ventricle. 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, non-ischemic mitral regurgitation underwent echocardiography, radionuclide angiography and C-11 acetate PET 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 (WMI). Fourteen patients (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 (SV) 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 WMI improved (4.99 ± 1.32 x10^6 to 6.59 ± 2.45 x10^6 mmHg x mL/m^2; p=0.02). This was not at the expense of total WMI which was preserved.

Conclusions: MV surgery has a beneficial effect on forward SV and forward work-metabolic index without adverse effects on oxidative metabolism or total work-metabolic index.

Key Words: Mitral Valve, Regurgitation, Remodeling, Metabolism, Imaging
Background

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

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 post-operative MV surgery. Starling has demonstrated that such patients with preserved LVEF, have impaired LV contractility that can improve 1 year after MV surgery (2). 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 is 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 non-invasively with positron emission tomography (PET) have been used to assess oxidative metabolism (7-9). Combining measures of oxidative metabolism with assessments of left ventricular 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 following mitral valve surgery occur at the expense of oxidative metabolism has not been well investigated. This study examines the
effects of mitral valve surgery on myocardial metabolism and the work-metabolic index as an estimate of myocardial efficiency in patients with chronic, severe, non-ischemic mitral regurgitation. Further understanding of myocardial metabolism and myocardial efficiency before and after surgical correction may enable the development of better predictors of mitral valve surgical outcome in this patient population.

Methods

This prospective study enrolled patients with chronic (at least 3 months in duration), non-ischemic 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, coronary artery disease (documented with coronary angiography), 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 mitral valve surgery. This study was approved by the local institutional human research ethics board.

Positron Emission Tomography

Upon positioning the patient in the Siemens/CTI ART PET scanner (Knoxville, TN), a 5-minute transmission scan was performed for attenuation correction. Then, 6-10 mCi (222-370 MBq) of C-11 acetate was administered intravenously and a dynamic PET acquisition was initiated (10x10 sec; 1x60sec; 5x100sec; 3x180sec). The reconstructed dynamic PET images were analyzed by applying a region of interest over the whole LV myocardium in 3 to 5 midventricular transaxial
planes (\(^{11}\)). A mono-exponential function was fit to the myocardial time activity data, and the myocardial clearance rate constant (k\(_{\text{mono}}\)) was determined as described previously (\(^{13}\)). The mono-exponential fit began at the point when the blood pool was stable (usually 2 to 4 min after injection) (Figure 1).

**Echocardiography**

A complete two-dimensional colour and Doppler echocardiogram (ECHO) was performed immediately prior to C-11 acetate PET study. As described previously (\(^{13}\)) ventricular function was assessed using a Sonos 7500 ultrasound system (Phillips, Andover, Massachusetts) equipped with a 3.2-MHz phased-array transducer. All measurements were performed off-line and averaged from 3 cardiac cycles (\(^{17-18}\)).

Forward stroke volume (SV) was derived from the velocity-time integral of the pulsed Doppler LV outflow tract velocity signal and the LV outflow tract diameter. Forward stroke volume index (SVI) was derived by dividing forward SV by the body surface area (\(^{10-13}\)). Mitral regurgitant volumes were determined using the PISA method. Peak left atrial (LA) pressure was estimated from the brachial systolic blood pressure (SBP) minus the systolic pressure gradient across the mitral valve derived from the velocity of the mitral regurgitant jet (LA pressure = SBP – 4 x (peak MR jet velocity)\(^2\)).

**Work Metabolic Index Determination**

Scintigraphic C-11 clearance data (k\(_{\text{mono}}\)) and the forward stroke work data were used to calculate forward LV work-metabolic index (forward WMI = forward SWI x HR / k\(_{\text{mono}}\)) where SWI = [SV X SBP] / BSA and HR = heart rate, SBP = systolic blood pressure and BSA = body surface area) as we have described previously (\(^{10-13}\)). 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 x peak left atrial pressure)/BSA. A regurgitant WMI (rWMI) was then calculated as rWMI = RWI x HR/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 (19;20). 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 (19). 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 (21). Calculations of LV volumes were performed using software that has been validated locally (19;20).

**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, Illinois).

**Results**

A total of 14 patients (59 ± 8 years old; 10 men) with myxomatous MV were enrolled into the study (Table 1). The mean LVEF prior to MV surgery was 59 ± 11%, 8 patients had an LVEF ≥ 60%, 5 patients had an LVEF between 45-59% and one patient had LVEF of 31%. All 14 patients
underwent successful mitral valve surgery, post-operatively the regurgitant volume decreased from 34 ± 19 ml to 2.8 ± 10; (p< 0.01).

**Myocardial Oxidative Metabolism**

Compared to pre-operative 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 ± 0.013/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). Post-operatively, forward stroke volume increased from 58.1 ± 15.0 to 75.5 ± 23 mL (p < 0.01) and there was a significant reduction in LV volumes by RNA after MV surgery. Both left ventricular end-diastolic volumes (LVEDV) and end-systolic volumes (LVESV) decreased 43% and 44%, respectively. (Figures 2b, 2c)

**Myocardial Energetics**

Forward work-metabolic index increased 35% after surgery and occurred in the absence of significant changes in k-mono, systolic blood pressure or heart rate (Figure 2d). Total WMI did not change significantly post-operatively (5.69 ± 1.76 x 10⁶ to 6.61 ± 2.42 x 10⁶; p = 0.22) (Figure 2e).

**Discussion**

This study demonstrates that mitral valve surgery for chronic severe non-ischemic mitral regurgitation improves LV volumes, 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 EH Starling and Vissher in the early 20th century, conceptualized as the measure of minute stroke work corrected for oxygen consumption (22) and first applied in humans by Bing et al (23). The relationship of oxygen consumption and C-11 acetate kinetics has been well validated (7-9; 12). 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(10-13; 15; 16; 24-31). Though this approach has not been previously applied to patients with significant MR, it is a widely accepted approach to estimate efficiency non-invasively and thus was used for this study.

The previous applications of the WMI have generally used stroke work where mitral regurgitation 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 account for the added work of the regurgitant volume against the LA pressure. In keeping with original concepts for WMI as non-invasive estimate of efficiency, we applied the regurgitant work index, using the product of the peak left atrial pressure and MR volume determined from echocardiographic parameters, to derive a regurgitant WMI. A total WMI could then be determined as an estimate of efficiency which 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 left atrium results in LV eccentric hypertrophy and elongation of sarcomeres. As preload increases and the left ventricle remodels and dilates to maintain a normal forward stroke volume and forward stroke work (1). Increases in afterload associated with left ventricular dilatation, are offset by the low impedance circuit (the left atrium).
Therefore, afterload associated with MR may be variable, with initial reduction only to elevate in the later stages of the disease as left ventricular size increases further (4).

The hemodynamic consequences of correcting MR is the resultant decrease in preload and increase in afterload, as the low impedance left atrium 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 (3;4;32). 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 (2;3).

As previously observed, our study confirmed a reduction in both LVED and LVES volumes after mitral valve surgery (2;3). Using invasive measurements, Starling demonstrated that these volume changes led to an increase in forward pump efficiency post-operatively measured by Pressure-Volume Area (2;3). 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 left ventricle 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 post-operatively in the absence of changes in k-mono, heart rate, and systolic blood pressure, this is consistent with the
notion that LV pump efficiency, as judged by WMI, is preserved initially, in spite of MR and LV dilatation. Improvements in forward WMI are likely 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 stroke volume 1 year post-operatively. With preserved contractility and efficiency, the myocardium, post-operatively, 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 no or minimal contractile dysfunction. The preservation of ventricular efficiency after surgery may imply that reversible changes occur and likely precede irreversible structural and contractile dysfunction.

In the single patient with moderate to severe LV dysfunction (EF = 31%), the pre-operative forward WMI (1.81 x 10^6 mmHg X mL/m^2) was 2 standard deviations below the mean of the study group and below the previously reported normal range 6.20 ±/ 2.25 x 10^6 mmHg X mL/m^2 (15). This patient demonstrated an improvement in forward WMI (3.83 x 10^6 mmHg x mL/m^2) and no change in LVEF post-operatively (31%). This patient’s pre-operative total WMI (2.05 x 10^6 mmHg X mL/m^2) was also below average, increased (4.11 x 10^6 mmHg X mL/m^2) post-operatively which may reflect suboptimal correction of the MR with moderate residual post-operative MR (regurgitant volume of 39cc). This case suggests that post-operative 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 = 45-59% compared to 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 LVEF, LV volumes or WMI post-operatively requires further study.
**Limitations and Technical Considerations**

This study was not powered to distinguish between responders and non-responders to surgery therefore further investigation is required in a cohort with varying pre-operative characteristics and varying post-operative 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 (10-13;24). Peak instantaneous LA pressure rather than mean LA pressure was used to estimate regurgitant WMI. The use of peak pressure is consistent with the traditional method of calculating WMI using systolic blood pressure.

Newer PET scanners with list mode are now capable of simultaneous gating for LV function, volume estimates and dynamic acquisition for tracer kinetics (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 SPECT, PET and MRI metabolic imaging increase, combined measures of metabolism and contractile performance may also become possible with other single or hybrid modalities (34-36). While the measurement of efficiency and energetics has prognostic value, whether their non-invasive 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.

Since all patients had a similar etiology of mitral regurgitation, 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.
Conclusions

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

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Conflict of Interest Disclosures: None
Reference:


Table 1. Pre and Post-operative Characteristics (n = 14), means ± SD are presented.

<table>
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<tr>
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<th>Pre-operative</th>
<th>Post-operative</th>
<th>Difference</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>59 ± 8</td>
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<tr>
<td>Male Gender</td>
<td>10 (71%)</td>
<td></td>
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<tr>
<td>BSA (m²)</td>
<td>1.9 ± 0.2</td>
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<td>New York Heart Association</td>
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<tr>
<td>Class I</td>
<td>3 (21%)</td>
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<tr>
<td>Class II</td>
<td>11 (79%)</td>
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<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>
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<td>MV repair</td>
<td>12 (86%)</td>
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<tr>
<td>MV replacement</td>
<td>2 (14%)</td>
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<td>RNA Measurements:</td>
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<tr>
<td>LV ejection fraction (%)</td>
<td>59 ± 11</td>
<td>57 ± 10</td>
<td>2 ± 11</td>
<td>0.52</td>
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<tr>
<td>LV end-diastolic volume (mL)</td>
<td>231 ± 86</td>
<td>131 ± 21</td>
<td>88 ± 86</td>
<td>&lt;0.01</td>
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<td>LV end-systolic volume (mL)</td>
<td>98 ± 53</td>
<td>55 ± 17</td>
<td>37 ± 48</td>
<td>&lt;0.01</td>
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<td>ECHO Measurements:</td>
<td></td>
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<tr>
<td>Forward Stroke volume (cc/beat)</td>
<td>58 ± 15</td>
<td>75 ± 23</td>
<td>17 ± 20</td>
<td>&lt;0.01</td>
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<td>Metabolic Parameters</td>
<td>0.056 ± 0.013</td>
<td>0.051 ± 0.011</td>
<td>0.004 ± 0.014</td>
<td>0.32</td>
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<td>--------------------------------------------</td>
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<tr>
<td>Forward WMI (mmHg X mL/m²)</td>
<td>4.99 ± 1.32 x 10^6</td>
<td>6.59 ± 2.45 x 10^6</td>
<td>1.60 ± 2.30 x 10^6</td>
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<td>rWMI (mmHg X mL/m²)</td>
<td>7.05 ± 1.76 x 10^5</td>
<td>0.218 ± 7.86 x 10^5</td>
<td>6.85 ± 7.52 x 10^5</td>
<td>&lt;0.01</td>
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<td>Total WMI (mmHg X mL/m²)</td>
<td>5.69 ± 1.76 x 10^6</td>
<td>6.61 ± 2.42 x 10^6</td>
<td>0.92 ± 2.66 x 10^5</td>
<td>0.22</td>
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BSA = body surface area; ECHO = echocardiography; MV = mitral valve; LV = left ventricular; WMI = work metabolic index; RNA = radionuclide angiography; rWMI = regurgitant work metabolic index

* Patients in atrial fibrillation (4 patients pre-operatively and 1 patient post-operatively) excluded.
Figure Legend:

**Figure 1.** Representative myocardial C-11 acetate mono-exponential clearance kinetics as determined by PET. The mono-exponential curve (red line) is fit to the measured myocardial time-activity data (green crosses) from 4 to 35 minutes. Data outside the fitted interval are shown in blue.

**Figure 2.** Pre-operative and post-operative measurements (mean and standard deviations) for: (a) $k_{\text{mono}}$, (b) left ventricular end-diastolic volume by RNA, (c) end-systolic volume by RNA, (d) forward work metabolic index, and (e) total work metabolic index.
half-life = 14.2 [min]

clearance = 0.071 [/min]

kmono = 0.049 [/min]

95% C.I. = 0.042 to 0.056 [/min]
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