Chapter 6

Right Ventricular Energetics in Patients with Hypertrophic Cardiomyopathy and The Effect of Alcohol Septal Ablation


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Abstract

Background: Diastolic dysfunction in hypertrophic cardiomyopathy (HCM) is accompanied by augmented left ventricular (LV) end-diastolic pressure, above all in the presence of LV outflow tract (LVOT) obstruction. Increased backpressure may augment right ventricular (RV) afterload, and induce an oxidative metabolic imbalance between the 2 ventricles. The aim was to study right-to-left ventricular oxidative metabolism in HCM and the effects of alcohol septal ablation (ASA).

Methods: Twenty-one HCM patients were enrolled. Eleven healthy subjects served as a control group. Subjects underwent 2D-echocardiography to assess LVOT gradient, left atrial size and diastolic function. [$^{11}$C]acetate PET was performed to determine RV$k_2$ and LV$k_2$, as a non-invasive index of oxidative metabolism. Seven HCM patients with LVOT obstruction, scheduled to undergo ASA, were also studied 6 months after the procedure.

Results: RV$k_2$ was higher in HCM patients than controls (0.081±0.021 min$^{-1}$ vs. 0.061±0.017 min$^{-1}$, $p = 0.05$), whereas LV$k_2$ was comparable between groups. Consequently, RV$k_2$/LV$k_2$ was increased in the patients (0.85±0.19 vs. 0.59±0.13, $p = 0.004$). In patients with obstructive HCM, ASA reduced RV$k_2$ (0.085±0.021 min$^{-1}$ to 0.072±0.022 min$^{-1}$, $p = 0.001$). Inasmuch as LV$k_2$ remained unaffected by the procedure, RV$k_2$/LV$k_2$ was decreased after ASA (0.66±0.18, $p = 0.03$). The absolute change in LVOT gradient was related to the absolute change in RV$k_2$ ($r = 0.77, p = 0.044$).

Conclusion: In HCM patients, RV oxygen consumption is increased in relation to the LV. ASA reduces RV oxygen consumption in HCM patients with LVOT obstruction, suggesting that increased LV loading conditions and diastolic dysfunction play a predominant role in augmenting RV workload in these patients.
Introduction

The majority of patients with hypertrophic cardiomyopathy (HCM) exhibit a certain degree of left ventricular (LV) diastolic dysfunction, presumably mediated by a combination of increased passive LV stiffness and abnormal active relaxation. (1) Concordantly, LV end-diastolic and pulmonary artery/wedge pressure are frequently raised in these patients, as compared to healthy individuals. (2, 3) It has been postulated that increased back-pressure may augment right ventricular (RV) afterload and oxygen consumption, and induce an oxidative metabolic imbalance between the two ventricles. In analogy to patients with dilated cardiomyopathy, this may hold prognostic relevance with regard to symptomatology and exercise capacity. (4) Although evidence of RV involvement in the HCM disease process is emerging, the main focus has always been on assessment of the LV, and data on RV energy metabolism are currently lacking.

In a subset of HCM patients, LV pre- and afterload conditions are also increased by the presence of left ventricular outflow tract (LVOT) obstruction. (5) Reduction of LVOT obstruction by alcohol septal ablation (ASA) alleviates symptomatology in obstructive HCM and has been shown to improve haemodynamic loading conditions, e.g. reduced LV end-diastolic pressures, as well pulmonary artery pressures. (3, 6) Therefore, ASA may have beneficial effects on RV oxidative metabolism as well, and could improve the interplay between right to left ventricular oxygen consumption. The present study was conducted to study the effect of ASA on RV oxidative metabolism in obstructive HCM, using $^{[11]}$Cacetate positron emission tomopgraphy (PET).

Methods

Study population

Twenty-one patients with HCM were enrolled in the study. HCM was diagnosed by the presence of a nondilated and hypertrophied LV, in the absence of any other systemic or cardiac causes of LV hypertrophy, on 2-dimensional (2D) echocardiography (maximal wall thickness > 15 mm in adult patients). All patients exhibited an asymmetrical pattern of septal hypertrophy. A total of 11 subjects with normal physical examination, electrocardiogram, and 2D echocardiography were enrolled, to serve as a control group. All study subjects underwent 2D echocardiography and $^{[11]}$Cacetate PET at baseline. To prevent unnecessary radiation burden, the size of the control group was kept relatively small. A subset of seven HCM patients with LVOT obstruction, who were scheduled to undergo ASA, were also studied 6 months postoperatively.
according to the same protocol. The indication for ASA was based on a significant peak LVOT gradient (i.e. ≥ 50 mmHg at rest or during Valsalva manoeuvre measured with Doppler echocardiography) and symptoms (New York Heart Association (NYHA) Class II or III, despite medical therapy). The ASA procedure was performed as described previously.(7) Medication was kept constant during the study.

**Imaging protocol**

**PET**

All scans were performed in 2D mode, using an ECAT EXACT HR+ (Siemens/CTI, Knoxville, Tennessee, USA). The protocol was performed as previously described.(8,9) In short, after overnight fasting, myocardial oxidative metabolism was measured under resting conditions, using 550 MBq [¹¹C]acetate, and subsequently performing a dynamic 29 frame acquisition lasting 48 minutes. Data were normalised and corrected for dead time, random coincidences, scatter, and decay using the corrections included in the ECAT 7 software (Siemens/CTI, Knoxville, Tennessee, USA). Images were reconstructed using filtered back projection, applying a Hanning filter with cut-off at 0.5 of the Nyquist frequency, into 63 image planes of 128x128 voxels with dimensions 2.1x2.1x2.1 mm.

**Data analysis**

Data were transferred to a SUN workstation and analyzed using ECAT 7 software and MATLAB. Regions of interest (ROIs) were defined manually on the maximum intensity [¹¹C]acetate short axis images according to a standard 12-segment model. In short, each basal and midventricular slice was divided into 6 equidistant sectors angulated 60° apart, starting from the posterior insertion of the RV free wall into the LV myocardium. The arterial input function was determined by drawing a circular ROI in the center of the left atrium, with a diameter of 15 mm. Additional ROIs were defined in the RV chamber, and the RV free wall. ROIs that did not display acetate uptake after ASA (i.e. indicative of scar tissue) were excluded from analysis. This set of ROIs was projected onto the dynamic [¹¹C]acetate images in order to generate image derived input functions and myocardial time activity curves. Using the standard single tissue compartment model, $k_2$ as an index of myocardial oxidative metabolism, was determined for all tissue time activity curves.(10) This model combines the myocardial release of $^{11}\text{CO}_2$ and other $^{11}\text{C}$-labelled metabolites in the rate constant $k_2$, thereby directly reflecting the oxidative flux through the TCA cycle; and includes model based corrections for spillover from blood – to myocardium.
and partial volume effects. The ratio between RV and LV oxidative metabolism (RV\(k_2/LVk_2\)) was also calculated to determine the oxidative metabolic imbalance between the two ventricles.(4)

**Echocardiography**

Transthoracic echocardiography was performed using a Vivid 7 (General Electrics-Vingmed, Milwaukee, Wisconsin, USA), according to the ACC/AHA/ASE guidelines.\(^\text{11}\) Pulsed-wave Doppler was used to derive the peak LVOT gradient across the subvalvular obstruction. Diastolic filling was assessed by the Doppler ratio of early to late transmitral flow velocity (E/A). Maximal left atrial volumes were measured using the biplane method during end-diastole.

**Statistics**

Results are displayed as mean ± SD. Differences between study groups were tested for statistical significance according to the appropriate Student’s t-test. Correlations between variables were evaluated with linear regression analysis. All tests were performed two-sided and a p value < 0.05 was considered statistically significant.

**Results**

Baseline characteristics, haemodynamics and [\(^{11}\)C]acetate clearance rates (\(k_2\)) for all study groups are listed in table 1. Heart rate and systolic blood pressure during the PET studies were comparable between controls and HCM patients. RV\(k_2\) was higher in HCM patients, whereas LV\(k_2\) was not significantly different between the groups. As a result, RV\(k_2/LVk_2\) was significantly higher HCM patients (0.81 ± 0.21) as compared to controls (0.59 ± 0.13, \(p = 0.004\), Fig. 1).

In the HOCM subset, heart rate and systolic blood pressure did not significantly differ between the baseline and follow up PET studies. LVOT gradient was significantly decreased after ASA, as well as LA size and E/A ratio. RV\(k_2\) was significantly decreased postoperatively, whereas LV\(k_2\) remained unaffected. As a result, RV\(k_2/LVk_2\) was decreased after ASA (from 0.85 ± 0.19 to 0.66 ± 0.18, \(p = 0.03\), Fig. 1), not being significantly different from controls (\(p = 0.38\)).

Univariate analysis revealed a moderate linear relationship between the absolute change in LVOT gradient and the absolute change in RV\(k_2\) after ASA (\(r = 0.77, p = 0.044\), Fig. 2).
<table>
<thead>
<tr>
<th></th>
<th>Controls ($n = 11$)</th>
<th>HCM ($n = 21$)</th>
<th>$p$</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age</td>
<td>54 ± 15</td>
<td>48 ± 10</td>
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<tr>
<td>Sex</td>
<td>7 men (64%)</td>
<td>13 men (62%)</td>
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<td>BSA (m$^2$)</td>
<td>2.0</td>
<td>2.0</td>
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<td><strong>Haemodynamics</strong></td>
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<tr>
<td>HR (bpm)</td>
<td>68 ± 11</td>
<td>63 ± 10</td>
<td>0.31</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>123 ± 11</td>
<td>128 ± 21</td>
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<td>Diastolic BP (mmHg)</td>
<td>72 ± 8</td>
<td>69 ± 6</td>
<td>0.25</td>
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<td><strong>$[^{11}]C$acetate PET</strong></td>
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<tr>
<td>RV $k_2$ (min$^{-1}$)</td>
<td>0.061 ± 0.017</td>
<td>0.081 ± 0.021</td>
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<td>LV $k_2$ (min$^{-1}$)</td>
<td>0.105 ± 0.025</td>
<td>0.099 ± 0.023</td>
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<td>RV $k_2$/LV $k_2$</td>
<td>0.59 ± 0.13</td>
<td>0.81 ± 0.21</td>
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<td>HOCM ($n = 7$)</td>
<td>HOCM FU ($n = 7$)</td>
<td>$p$</td>
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<tr>
<td><strong>Haemodynamics</strong></td>
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<tr>
<td>HR (bpm)</td>
<td>62 ± 11</td>
<td>68 ± 14</td>
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<tr>
<td>Systolic BP (mmHg)</td>
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<td>Diastolic BP (mmHg)</td>
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<td><strong>Echocardiography</strong></td>
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<td>LVOTG (mmHg)</td>
<td>51 ± 38</td>
<td>18 ± 14</td>
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<td>LA size (mL)</td>
<td>162 ± 42</td>
<td>135 ± 32</td>
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<td>E/A ratio</td>
<td>1.3 ± 0.5</td>
<td>0.9 ± 0.3</td>
<td>0.03</td>
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<tr>
<td><strong>$[^{11}]C$acetate PET</strong></td>
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<tr>
<td>RV $k_2$ (min$^{-1}$)</td>
<td>0.085 ± 0.021</td>
<td>0.072 ± 0.022</td>
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<td>LV $k_2$ (min$^{-1}$)</td>
<td>0.101 ± 0.023</td>
<td>0.108 ± 0.015</td>
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<tr>
<td>RV $k_2$/LV $k_2$</td>
<td>0.85 ± 0.19</td>
<td>0.66 ± 0.18</td>
<td>0.03</td>
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</tbody>
</table>

Table 1. Overview of haemodynamic and $[^{11}]C$acetate PET data for (A) controls and HCM patients, and (B) HOCM patients at baseline (HOCM B) and during follow up (HOCM FU). *HR*, heart rate; *BP*, blood pressure; *LVOTG*, left ventricular outflow tract gradient; *LA* size, left atrial size.
Figure 1. Aligned scatter plot depicting RV\(k_2/LV\kappa_2\) per study group for controls, the entire HCM group (HCM), HCM patients with LVOT obstruction at baseline (HOCM B) and during follow up after alcohol septal ablation (HOCM FU).

Figure 2. Scatter plots depicting the relationship between the absolute change (\(\Delta\)) in RV\(k_2\) and the absolute change in LVOT gradient after alcohol septal ablation.
Discussion

In the studied HCM population, RV oxidative metabolism was higher as compared to controls, despite the fact that heart rates were comparable between study groups. In the subset of HCM patients with significant LVOT obstruction, ASA reduced RV oxygen consumption, indicating that the detrimental effects of outflow obstruction extend beyond the LV, and at least in part augment RV workload. The linear relationship between the absolute change in LVOT gradient and the absolute change in RV oxidative metabolism underscores the fact that increased RV workload in HCM is presumably mediated by increased RV afterload due to augmented LV loading conditions.

RV oxidative metabolism in obstructive HCM

The development of PET and myocardial substrate-based tracers such as $[^{11}C]$acetate provide the opportunity to investigate myocardial oxidative metabolism noninvasively on a global and regional level,(12,13) hence facilitating separate, yet simultaneous assessment of RV and LV oxygen consumption.(14) To date, data on myocardial oxidative metabolism in HCM is scarce and limited to the LV.(9,15-18) Where the current findings imply that oxygen consumption of the RV in HCM is augmented, previous studies have shown that LV oxygen consumption is comparable to healthy subjects. In contrast, however, work generation per gram of hypertrophied myocardium was disproportionally depressed in relation to oxygen usage, suggesting pseudonormalization of LV oxygen consumption at the expense of myocardial metabolic efficiency (i.e. increased cost-to-force ratio).(9)

$[^{11}C]$acetate PET studies in patients with symptomatic dilated cardiomyopathy have previously shown that RV oxygen consumption is increased in relation to LV oxygen consumption also,(4,19) a higher ratio of which ($\geq 0.8$) has been associated with a significant decrease in exercise capacity, as measured by peak VO$_2$.(4) RV workload and performance, as reflected by the metabolic and energetic state of the RV, are related to symptomatology and hold prognostic relevance.(20) Although the pathophysiological mechanisms underlying augmented RV oxygen consumption in hypertrophic and dilated cardiomyopathy are not fully understood, both diseases are characterized by elevated end-diastolic pressure, suggesting that a reduced diastolic reserve serves as a common mechanism for increased LV back-pressure and RV afterload.(1,21) The cause for diastolic dysfunction in HCM is multifactorial, presumably being a combination of increased passive LV stiffness and abnormal active
relaxation.\textsuperscript{(1,23)} The presence of LVOT obstruction may amplify these pathophysiological processes.\textsuperscript{(3)} Indeed, pulmonary artery pressures are higher in patients with obstructive HCM versus non-obstructive HCM, suggesting that LVOT obstruction contributes to augmented RV afterload in these patients.\textsuperscript{(3)}

The favourable effect of outflow obstruction relief on RV oxygen consumption in obstructive HCM suggests that increased RV loading and work due to LV diastolic dysfunction play a substantial role in augmenting RV oxygen consumption, although inefficient RV sarcomere ATP-utilization,\textsuperscript{(22)} or altered RV substrate metabolism \textsuperscript{(18)} should not be disregarded. Therefore, in analogy to patients with dilated cardiomyopathy, a high RV oxygen consumption in relation to LV oxidative metabolism (i.e. high $RVk_2/LVk_2$ ratio) in HCM patients, is suggestive of compromised functional capacity and unfavourable interventricular energetics.

**The effects of ASA on RV oxidative metabolism**

Although data are limited, it has been shown that ASA decreases RV workload, as reflected by decreased pulmonary artery pressures,\textsuperscript{(3)} and increased RV ejection fraction. Yet, to date it remained unclear whether this was accompanied by a concomitant decrease in RV oxidative metabolism. The beneficial effects of ASA on RV oxygen consumption are therefore presumably related to a reduction in RV afterload due to improved LV diastolic function, and provide insight into the mechanisms underlying this phenomenon in HCM. ASA has been shown to improve LV diastolic function by a combination of several factors, including enhancement of passive ventricular filling,\textsuperscript{(24)} shortening of isovolumetric relaxation,\textsuperscript{(3,25)} and reduction of subendocardial ischemia due to microvascular dysfunction.\textsuperscript{(26,27)} Accordingly, the E/A ratio and left atrial size significantly decreased postoperatively in the obstructive HCM group, likely reflecting favourable effects of ASA on diastolic function.\textsuperscript{(28)}

Interestingly, oxygen consumption of the LV remained unaltered after ASA. Recently, the effects of ASA on LV energetics in HCM have been studied, and showed that the postprocedural reduction in LV mass was associated with an increase in myocardial metabolic efficiency, due to increased work generation per gram of myocardial tissue in the absence of a concomitant increase in oxygen usage.\textsuperscript{(29)}

Obviously, lack of invasive data on pulmonary artery pressures and RV mass hampers the absolute calculation of RV external work efficiency. However, inasmuch as RV oxidative metabolism was reduced after ASA in comparison to
LV, the oxidative metabolic balance between the two ventricles shifted towards the situation in the control group, suggesting more favourable RV workload and interventricular energetics.

It should be noted that ASA might alter substrate metabolism in HCM by inducing a switch to a more energy-efficiency fuel (e.g. glucose). However, data on LV substrate metabolism in HCM is scarce and RV substrate metabolism remains to be studied. LV free fatty acid uptake in HCM patients is readily increased, and, inasmuch as free fatty acids are a less energy efficient fuel, this could explain the increased RV oxygen consumption at baseline.(18) However, future studies are needed to elucidate the effects of surgical intervention on substrate metabolism in obstructive HCM.

**Limitations**

The cohort of obstructive HCM patients is small, limiting the inferences that can be drawn from this study. Nevertheless, the [11C]acetate PET data convincingly indicate augmented RV oxygen consumption in HCM and a significant reduction after ASA.

The presence of RV valvular disease, such as tricuspid regurgitation in HCM, could lead to increased demands on RV performance. Accordingly, RV oxidative metabolism less accurately reflects RV forward work, because part of the RV volume is ejected into the right atrium during systole. However, this issue is expected to be minimal as none of the control subjects displayed haemodynamically significant valvular disease, and only two HCM patient exhibited mild tricuspid regurgitation.

When present, however, TR may be used to calculate RV systolic pressures from velocity measurements of the tricuspid regurgitation jet with continuous-wave Doppler echocardiography during systole. Although this could provide additional evidence for the mechanisms by which ASA exerts beneficial effects on RV energetics, RV systolic pressures could only be estimated reliably in a minority of subjects.
Reference list


PART III

Technical Aspects of Myocardial Perfusion
and Metabolic Imaging