Exercise Radionuclide Ventriculography for Predicting Post-Operative Left Ventricular Function in Chronic Aortic Regurgitation

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OBJECTIVES Ejection fraction (EF) reaction upon exercise by radionuclide ventriculography and standard echocardiographic parameters was evaluated as predictors for post-operative left ventricular (LV) function in chronic aortic regurgitation (AR).

BACKGROUND The optimal timing of surgery for chronic AR is when the left ventricle is still compensating for the volume and pressure overload without irreversible dysfunction. For asymptomatic patients when EF is normal and LV diameters are borderline, exercise testing is recommended by present guidelines. However, only a limited number of studies have been performed, and data are scarce on this subject.

METHODS Radionuclide ventriculography with multiple gated acquisition at rest and during exercise was performed in 29 consecutive patients with severe chronic aortic regurgitation pre-operatively and 6 months post-operatively. Patient subgroups were formed based on pre-operative EF exercise response (ΔEF) and were categorized as decreasing (ΔEF < -5%), unaltered (-5% ≤ ΔEF ≤ 5%), and increasing (ΔEF > 5%). A 5% or higher increase was considered normal. The LV diameters and mass were measured by echocardiography.

RESULTS Pre-operative LV diameters were markedly elevated before surgery and diminished significantly after surgery. Left ventricular diameters, LV mass, EF at rest (EFrest), and EF change from rest to exercise (ΔEF) were independent of New York Heart Association functional class. Pre-operative end-diastolic diameter proved to be a predictor for pre- and post-operative ΔEF (p = 0.003; p = 0.04) but not for the nature of the exercise response post-operatively. Patients with decreasing and unaltered EF pre-operatively presented a significantly higher but still abnormal ΔEF post-operatively. Those with increasing EF pre-operatively had a similar response and a normal ΔEF post-operatively. Pre-operative ΔEF was not only a predictor for post-operative ΔEF (p = 0.02) but also classified patients into post-operative subgroups (EF decreasing, p = 0.03; unaltered, p = 0.02; increasing, p = 0.0008).

CONCLUSIONS An abnormal EF response to exercise may also occur in patients who do not fulfill criteria for surgery based on LV dimensions or EF. A follow-up of exercise LV function and adjusting the timing of surgery according to the nature of exercise response could, therefore, be beneficial. (J Am Coll Cardiol Img 2009;2:48–55) © 2009 by the American College of Cardiology Foundation
Chronic aortic regurgitation (AR) leads to heart failure in the long term, but the heart compensates quite a long time before symptoms appear. According to American College of Cardiology/American Heart Association (ACC/AHA) recommendations, a symptomatic patient needs surgical therapy to preserve normal left ventricular function (LVF) or, if this is not possible any more, to prevent further deterioration of LVF (1,2). From the clinical point of view, the first appearance of symptoms means that the deterioration has already begun, and the damage may be irreversible at this point. The optimal time for surgery is considered to be the point when the patient is asymptomatic and the left ventricle is still compensating for the volume and pressure overload but there is no sign of irreversible dysfunction. In determining the optimal time for intervention, the ACC/AHA recommendations suggest the regular follow-up of LVF by one or a combination of the following techniques: echocardiography, cardiac magnetic resonance imaging, radionuclide ventriculography using multiple gated acquisition, and exercise testing. Radionuclide ventriculography was the “gold standard” for evaluation of left ventricular ejection fraction (LVEF) in the late 1980s and the beginning of the 1990s (3,4), and it is still one of the methods of choice when diagnostic difficulties occur with echocardiography or cardiac magnetic resonance imaging (1,2,5).

In this study, LVF of patients with chronic AR was examined by echocardiography and by radionuclide ventriculography, at rest and during exercise, before and 6 months after surgery. Our aim was to examine the changes in the ejection fraction (EF), from rest to exercise, as a measure of LVF both pre- and post-operatively. Moreover, we wished to study whether any of the pre-operative parameters could reliably predict LVF after surgery.

METHODS

Patients. Twenty-nine consecutive patients referred for surgery with severe chronic AR were included in this study. Patients with concomitant coronary artery disease and with heart valve disease other than chronic AR (aortic stenosis defined as aortic orifice area ≤1.6 cm²; any history of congenital heart disease or active endocarditis) were excluded. Twenty-six patients completed the study. One patient moved abroad, 1 had mild claustrophobic symptoms and abstained from the post-operative study, and 1 patient had a stroke peri-operatively with incapacitating neurological symptoms. The pre-operative results of these patients were analyzed.

Radionuclide ventriculography. Radionuclide ventriculography with radionuclide ventriculography was performed 2 days before planned surgery and 6 months post-operatively. Erythrocytes were labeled with 10 MBq/kg Tc-99m pertechnetate using the modified in vitro technique. Electrocardiogram gated imaging was performed using a General Electric Electric XR/T gamma camera equipped with a general purpose, low-energy collimator and a Genie ACQ-collecting station (General Electric Medical Systems, Milwaukee, Wisconsin). For optimal separation of the left and the right ventricles, left anterior oblique (45°) positioning was used. Supine multigated blood pool imaging was performed first at rest. After this, the patients performed supine bicycle exercise at a pedal rate of 60/min. Besides continuous electrocardiography and heart rate registration, the blood pressure was also measured every 2 min. The initial workload was 50 W and was increased by 50 W at the next level.

The Xeleris Functional Imaging Workstation, EF Analysis (General Electric Medical Systems) was used for image and data analysis. A total of 5 Mcounts were collected at rest and 2.5 Mcounts during steady-state exercise, with 32 frames per heart cycle in a matrix size 64 × 64. Cycle length windowing with dynamic arrhythmia filtration (6) with forward gating was used. A heart rate (HR) histogram was generated and observed for 1 to 3 min. When steady state HR was achieved, a window was centered at a peak HR ±10% for patients with sinus rhythm. Beats outside this interval were rejected. In patients with atrial fibrillation, the window of acceptable beats was widened up to 15% to 20% to reduce imaging time. Left ventricular end-diastolic and systolic outlines were marked manually by each of 2 operators separately, who made 3 measurements each. The mean of these measurements was used. The automatic algorithms of the computer program were used for background (BG) correction. Left ventricular ejection fraction (LVEF) was calculated from LV and BG counts as:

\[
\text{LVEF} = \frac{(LV_{\text{diastole}} - \text{BG}) - (LV_{\text{systole}} - \text{BG})}{(LV_{\text{diastole}} - \text{BG})} \times 100\%
\]
Definition of subgroups. Subgroups were formed based on pre-operative EF exercise response (ΔEF) during radionuclide ventriculography and were categorized as decreasing (ΔEF < -5%), unaltered (-5% ≤ ΔEF ≤ 5%), and increasing (ΔEF > 5%). A 5% or higher increase of EF was considered normal. The above subgroups were defined considering the above limits and a 5% bias of the method (7–9).

Echocardiography. All the patients underwent a transthoracic ultrasonography scan at rest (GE Vingmed, Vivid 5, or Vivid 7 echocardiograph) 1 day before the planned surgery and 6 months post-operatively. Images were recorded, stored digitally, and analyzed off line. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and LV end-diastolic wall thickness were measured by M-mode, and LV mass was calculated according to Devereaux’s formula. The velocity of E and A waves, E/A ratio, and pulmonary venous systolic and diastolic velocity were analyzed and used for an integrated description of diastolic function (10). Left ventricular end-diastolic and –systolic volumes and EF were calculated according to Simpson’s rule. Volume measurements, an average of 3 tracings in each registration, were performed by an experienced investigator who was unaware of the results of radionuclide ventriculography.

Statistical analyses. General discriminant analysis (forward stepwise) model, general linear models, Student’s unpaired t test, Pearson’s correlation coefficient, and Bland-Altman analysis were used to verify connections among variables as applicable for data sets. Comparison of pre- and post-operative data was performed by Wilcoxon’s matched pairs test. Data are presented as mean ± SD. Significance was set at p < 0.05. Analyses were performed by STATISTICA 8.0 (Statsoft, Tulsa, Oklahoma).

RESULTS

Patients. All patients were men. Mean age was 51 ± 14 years, body mass index was 27.4 ± 3.1 kg/m², and body surface area was 2.0 ± 0.2 m². Pre-operatively, 13 patients were in New York Heart Association (NYHA) functional class I, 10 were in NYHA class II, 5 were in NYHA class III, and 1 was in NYHA class IV. Pre-operatively, the majority (25) of the patients were in sinus rhythm and 4 had atrial fibrillation. At the 6-month follow-up, 25 patients were in sinus rhythm and 1 had atrial fibrillation. Eight patients were free from medication pre-operatively whereas 12 were receiving beta-blockers; 14, angiotensin-converting enzyme inhibitors; 1, digitalis; 5, calcium antagonists; and 6, diuretics. Post-operatively, 10 patients received beta-blockers; 6, angiotensin-converting enzyme inhibitors; 3, angiotensin II antagonists; 2, calcium antagonists; and 6, diuretics. Table 1 shows the baseline characteristics of the patients in the different subgroups.

Twenty-six patients received prosthetic aortic valves (20 mechanical, 6 biological), and in 3 patients, the aortic root was reconstructed with the native aortic valve spared. Those with mechanical prostheses were begun on life-long warfarin treatment, whereas patients with biological prostheses had a 3-month regimen with an international normalized ratio of 2.0 to 3.0.

LV diameters, mass, and volumes. Pre-operatively, the patients had a pronounced LV dilatation with wall thickness within the upper normal range, which resulted in a high LV mass. Left ventricular diameters diminished markedly and generally fell within normal limits post-operatively, and the overall comparison of pre- and post-operative LV masses and LV end-diastolic volume showed significant reduction after surgery (Table 2). Pre- and post-operative blood pressure and heart rate are shown in Table 3.

Pre-operative NYHA functional class had no relation to pre- or post-operative LVEDD, LVESD, or LV mass. However, NYHA functional class and the pre-operative LV volume at rest were

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of the Subgroups, Based on ΔEF</th>
<th>ΔEF &lt; -5% (n = 5)</th>
<th>-5% ≤ ΔEF ≤ 5% (n = 13)</th>
<th>ΔEF &gt; 5% (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>54 ± 7</td>
<td>49 ± 16</td>
<td>49 ± 13</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.5 ± 1.2</td>
<td>28.1 ± 3.7</td>
<td>26.8 ± 2.6</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9 ± 0.1</td>
<td>2.1 ± 0.2</td>
<td>2.1 ± 0.1</td>
</tr>
<tr>
<td>NYHA functional class, median (range)*</td>
<td>I (I–II)</td>
<td>II (I–IV)</td>
<td>II (I–III)</td>
</tr>
<tr>
<td>Atrial fibrillation†</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Free from medication</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*BMI = body mass index; BSA = body surface area; ΔEF = change in EF upon exercise; NYHA = New York Heart Association.

†One of the patients who was not able to perform exercise had atrial fibrillation.
significantly connected (p = 0.02), but no other assumptions could be made according to values.

**LV function at rest and during exercise.** Resting EF calculation by echocardiography according to Simpson’s rule gave significantly lower EF compared with radionuclide ventriculography (p = 0.0001). Measurements by the 2 different methods showed a modest correlation at rest (r = 0.53), and upon Bland–Altman analysis, the standard deviation for EF by the 2 methods was 7%.

Figure 1 shows the distribution of pre-operative and post-operative EF at rest (EFrest) by radionuclide ventriculography for the study population, and Figure 2 illustrates EF from rest to exercise for the whole group pre- and post-operatively. Pre-operative EFrest was not a predictor for post-operative EFrest. On the other hand, we found that both pre- and post-operative EF at maximal workload (EFmax) could be predicted from pre-operative EFrest (p = 0.000002 and p = 0.007, respectively). Analyses of subgroups, formed according to ∆EF, showed that patients with decreasing and unaltered EF pre-operatively presented a significantly improved but still abnormal ∆EF during exercise post-operatively. The group of patients with increasing EF pre-operatively responded similarly to exercise post-operatively (Fig. 3, Table 2). Pre-operative ∆EF proved to be a predictor for post-operative ∆EF (p = 0.02) in this study. Moreover, pre-operative ∆EF was the single and only predictor as to which subgroup (EF decreasing, p = 0.03; unaltered, p = 0.02; increasing, p = 0.0008) patients were to be classified post-operatively.

Pre-operative NYHA functional class was independent of both pre- and post-operative EFrest and ∆EF.

**Echocardiographic LV parameters at rest versus EF response to exercise.** Pre-operative LVEDD proved to be a predictor for both pre-operative and post-operative ∆EF (p = 0.003 and 0.04, respectively) in general but did not have any predictive value in placing the patients in the different subgroups based

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**Table 2. Ejection Fraction by Radionuclide Ventriculography and Echocardiographic Characteristics of the Different Subgroups, Based on Pre-Operative EF Reaction Upon Exercise**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>∆EF &lt; −5%</th>
<th>−5% ≤ ∆EF ≤5%</th>
<th>∆EF &gt;5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radionuclide ventriculography EFrest (%)</td>
<td>62 ± 6.9</td>
<td>60 ± 9.2</td>
<td>NS</td>
<td>60 ± 7.6</td>
</tr>
<tr>
<td>Radionuclide ventriculography EFmax (%)</td>
<td>64 ± 11.7</td>
<td>65 ± 11.8</td>
<td>NS</td>
<td>50 ± 8.6</td>
</tr>
<tr>
<td>Radionuclide ventriculography ∆EF (%)</td>
<td>1.8 ± 8.1</td>
<td>5.5 ± 7.1</td>
<td>0.01</td>
<td>−10.3 ± 3.6</td>
</tr>
<tr>
<td>Simpson EFrest (%)</td>
<td>54 ± 7</td>
<td>54 ± 10.5</td>
<td>NS</td>
<td>52 ± 6.4</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>67.6 ± 6.2</td>
<td>55.5 ± 7.7</td>
<td>0.00003</td>
<td>73.2 ± 8.2</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>48.8 ± 7.3</td>
<td>41.4 ± 8.7</td>
<td>0.001</td>
<td>53.6 ± 7.4</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>446 ± 115</td>
<td>331 ± 117</td>
<td>0.0002</td>
<td>517 ± 164</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>201 ± 60</td>
<td>124 ± 42</td>
<td>0.00003</td>
<td>253 ± 69</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>92 ± 32</td>
<td>60 ± 31</td>
<td>0.0002</td>
<td>122 ± 38</td>
</tr>
</tbody>
</table>

The p value denotes statistical significance comparing pre-operative (Pre-op) and post-operative (Post-op) findings.

EFrest = EF at rest; EFmax = EF at maximal workload; ∆EF = EF reaction upon exercise; LV = left ventricular; LVEDD = left ventricular end-diastolic volume; LVEF = left ventricular end-systolic diameter; LVESD = left ventricular end-systolic diameter; LVEV = left ventricular end-systolic volume; NS = not significant.

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**Table 3. Blood Pressure and Heart Rate at Rest and During Exercise**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>∆EF &lt; −5%</th>
<th>−5% ≤ ∆EF ≤5%</th>
<th>∆EF &gt;5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP srest (mm Hg)</td>
<td>144 ± 24</td>
<td>137 ± 19</td>
<td>NS</td>
<td>158 ± 35</td>
</tr>
<tr>
<td>BP drest (mm Hg)</td>
<td>69 ± 12</td>
<td>79 ± 12</td>
<td>0.03</td>
<td>79 ± 3</td>
</tr>
<tr>
<td>BP smax (mm Hg)</td>
<td>194 ± 27</td>
<td>185 ± 19</td>
<td>NS</td>
<td>215 ± 31</td>
</tr>
<tr>
<td>HRrest (beats/min)</td>
<td>66 ± 12</td>
<td>60 ± 10</td>
<td>0.03</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>HRmax (beats/min)</td>
<td>121 ± 20</td>
<td>116 ± 20</td>
<td>NS</td>
<td>124 ± 8</td>
</tr>
</tbody>
</table>

BP = blood pressure (mm Hg); d = diastole; HR = heart rate (beats/min); NA = non-applicable due to sample size; NS = not significant; s = systole; other abbreviations as in Tables 1 and 2.
on EF response post-operatively. However, LVESD was independent of any exercise response. Pre-operative LV volumes could not be connected to EFrest or EF during exercise.

Parameters of diastolic function (velocity of E and A waves, E/A ratio, classification according to diastolic pattern) were not found to be connected to EFrest, EFmax, or ΔEF, either pre- or post-operatively in this study (Table 4).

DISCUSSION

There is general consensus (1,2) that patients with significant AR should be operated upon when signs of LV dysfunction appear, irrespective of symptoms. Ejection fraction at rest is considered to be an insensitive marker, and LV function during exercise has proved to be related to prognosis in symptomatic AR patients (11). Consequently, even if the time point for surgery on a patient with chronic AR has been theoretically well defined and described (1,2), this theory often proves to be difficult to apply in clinical practice to asymptomatic patients with normal EFrest. Our choice of when to evaluate post-operative LV function was a compromise between the risk of losing patients for follow-up, or other factors affecting LV function to interfere, and on the other hand a desire to detect the long-term effects adequately. Remodulation of heart muscle starts as early as a few hours after heart valve surgery (12). Left ventricular function shows improvement at discharge and at 6-month follow-up, but according to data from Gelsomino et al. (13), there was no significant difference in LVF at rest between 6-month and 1-year follow-up. Earlier studies on the absolute maximal EF during exercise after surgery showed an improvement up to 3 years in patients with severe chronic AR (14). As EF at rest and during exercise is influenced by the presence or absence of valve regurgitation, we have studied ΔEF as a more independent parameter, and found a relation between the pre- and post-operative reaction, which would be of interest to evaluate also after a longer observation period.

It was a clinical decision not to withdraw the medication before the examinations. This may possibly have influenced the results, although this effect would be reduced by evaluating ΔEF rather than absolute data. The incidence and the prevalence of chronic aortic insufficiency explain the lack of women among patients in this study (15–17), and there was no selection bias involved. The decision about surgery was based on either progressive LV dilation, indication of a declining LV function despite a normal EF, or the appearance of symptoms, together with an awareness not to delay surgery too long. Our patient population had an overall normal EFrest. We did not find any connection or correlation between NYHA functional class and LVEF, which is concordant with results from earlier studies (18). Radionuclide ventriculography is dependent upon accumulation of data over several cardiac cycles. When irregular beats constitute >10% of the electrocardiographic cycles, errors are introduced into the shape of the time-activity curve (19). Most of these errors are introduced in the diastolic part of the cardiac cycle with minor effect on the systolic part and calculation of ejection fraction (20). Cycle length windowing was introduced to reduce the problems caused by irregular beats (20,21). Wallis et al. (22) reported that windowing in cardiac blood pool studies in atrial fibrillation did not give significant differences in EF determination and that the exact location of the window was not critical. Thus, it is possible to analyze EF by radionuclide ventriculography also in patients with atrial fibrillation, and therefore we did not exclude those patients from this study.

Previous studies of radionuclide ventriculography showed that EF during exercise and exercise EF response have predictive value for the predicted length of the period until symptoms develop and there is an absolute indication for surgery (23,24). These studies were performed in an era when...
asymptomatic patients were not operated on. Furthermore, these variables had predictive value for the risk of sudden cardiac death in the natural history of the disease (3). In the present study, pre-operative EF rest was found to be significantly correlated to EF max, separately both pre- and post-operatively, which was in concordance with previous studies (7,11,25,26). However, pre-operative EF rest was not connected to post-operative EF increase upon exercise and was, therefore, not found to be informative for LV performance during exercise post-operatively.

Furthermore, we found that pre-operative exercise response was not only a predictor of post-operative exercise response but also that pre-operative ∆EF predicted which type of exercise response the patient was going to have post-operatively. This finding is an extension of results in accordance with earlier studies of cardiac catheterization (23) and echocardiography at rest and after surgery.
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in spite of normal EF rest. That the left ventricular obviously deteriorated at the time of the operation operated on earlier to preserve LVF, which had least patients with decreasing EF should have been preserved it. This finding might indicate that at /H9004 whereas patients who had had normal sponded to exercise normally after operation of patients with unaltered EF pre-operatively re-follow-up. The general pattern was that the group /H11002∆EF had EF had diminished post-operatively in the whole study group, testing. Left ventricular volumes significantly di-
radionuclide ventriculography has high reproduc-
ability, even during exercise, and therefore adds valuable information in borderline cases.

**CONCLUSIONS**

The present study demonstrates that the pre-operative exercise response measured with radionu-
clude ventriculography can identify patients at risk for an abnormal post-operative LVF response dur-
ing exercise. Moreover, it can predict what kind of exercise response (increasing, unaltered, or increas-
ing EF during exercise) to expect after surgery. An abnormal EF response to exercise might also occur in patients who do not fulfill the criteria for surgery based on LV dimensions by echocardiography or EF at rest. We conclude that patients with signif-
ificant chronic AR could benefit from follow-up of LV function at exercise and by considering surgery when the character of the exercise response is abnormal.

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**Table 4. Pre-Operative Diastolic Function in the Subgroups, Based on EF Reaction Upon Exercise**

<table>
<thead>
<tr>
<th>Diastolic Function, No. of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbed</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Relaxation</td>
</tr>
<tr>
<td>Pseudonormal</td>
</tr>
<tr>
<td>Restrictive</td>
</tr>
<tr>
<td>∆EF &lt; −5%</td>
</tr>
<tr>
<td>−5% &lt; ∆EF &lt; 5%</td>
</tr>
<tr>
<td>∆EF &gt; 5%</td>
</tr>
</tbody>
</table>

*Only patients with sinus rhythm are indicated. Abbreviations as in Table 1.

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vascular Angiography and Interven-


atic or minimally symptomatic pa-
tients with chronic aortic regurgita-


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5. Klocke FJ, Baird MG, Lorette BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide im-


Key Words: radionuclide ventriculography n ejection fraction n exercise testing n aortic regurgitation n cardiac surgery.