Effects of pericardiectomy on left ventricular muscle mass and hemodynamic parameters

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Abstract
Aim: It has been shown in many experimental animal studies that increased myocardial tension and ventricular filling after cardiac pericardiectomy leads to increased myocardial protein synthesis and increased left ventricular muscle mass. In this study, we aimed to show left ventricular muscle mass changes, left ventricular end-systolic-end-diastolic volume changes, significant changes in systolic-diastolic blood pressure and wall stress after pericardiectomy performed in patients with normal ejection fraction undergoing coronary artery bypass graft (CABG) operation.

Material and Methods: Echocardiographic ventricular mass, end-diastolic volumes, end-systolic volumes, ejection fraction values were measured in the preoperative 1st day, postoperative 6th weeks and post operative 6th months in our 32 patients with normal ejection fraction who underwent elective coronary artery bypass operation in our clinic.

Results: According to the preoperative values, echocardiographic evaluations showed that left ventricular muscle mass index (LVMMI) increased 15% at 6 weeks, %18 at 6 month after CABG operation (p<0.05). The mean left ventricular end diastolic volume index (LVEDVI) was 55 ±8 ml/m2 preoperatively , 67 ±10 ml/m2 at the 6th week and 70 ±12 ml/m2 at 6th month; this increase was significant respectively (p<0.05). This enlargement occurred with no changes in systolic and diastolic blood pressure and did not lead to significant changes in end-systolic volume and end-systolic circumferential wall stress.

Conclusion: In conclusion, in patients undergoing coronary artery bypass graft surgery, pericardiectomy may lead to a partial increase in left ventricular end-diastolic volume and left ventricular muscle mass with better left ventricular filling.

Keywords: Left ventricular muscle mass; CABG; pericardiectomy

INTRODUCTION
In animal studies it has been shown that intact pericardium has a restrictive effect against volume increase for the heart, prevents dilatation of cardiac chambers and therefore limits stroke volume (1-3). Most of the current information about the functions of the pericardium is obtained from experimental studies in dogs. In these studies, increased myocardial tension and increased ventricular filling lead to an increase in myocardial protein synthesis rate and consequently increased left ventricular muscle mass after pericardiectomy.

However, pericardiectomy effect on physiological ventricular volumes in humans has not been fully elucidated.

In humans undergoing cardiac surgery due to mitral stenosis, small increases in left ventricular end-diastolic volume lead to a marked increase in left ventricular muscle mass, similarly eliminating the suppressive effect of pericardium by pericardiectomy, increasing left ventricular end-diastolic volume, increasing myocardial growth and increasing left ventricular muscle mass. (4-6).

Although the pericardium does not seem to contribute much to the relationship of ventricles during normal systolic filling pressure levels, it affects systolic function in cases of acute dilation of the heart (7-9). It is stated that pericardiectomy may lead to increased concentric left ventricular muscle mass in patients with heart failure with preserved ejection fraction values and this may show a significant improvement in the symptoms of the patients (10,11).

MATERIAL and METHODS
This study was performed with 36 patients who underwent elective CABG surgery with LVEF over 50%. Myocardial infarction developed in 2 cases, 1 patient underwent multiple revisions due to postoperative bleeding, 1 case developed mediastinitis as a complication of surgery.
and these 4 cases in total were excluded from the study. Patients with unstable angina, undergoing emergency coronary surgery, previous myocardial infarction, additional cardiac pathology other than coronary artery disease, systemic diseases such as kidney or liver disease were not included in the study. The mean age was 59 ± 11 years and male/female ratio was 20/12. None of the patients received intravenous heparin and nitroglycerin treatment before the operation. Characteristics of the patients are shown in Table 1.

**Table 1. Characteristics and of the patients**

<table>
<thead>
<tr>
<th>Age (average/range)</th>
<th>59±11 years / 37-68 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male/Female)</td>
<td>20/12 patients</td>
</tr>
<tr>
<td>Diabetes Mellitus n (%)</td>
<td>8 (%21)</td>
</tr>
<tr>
<td>Carotid artery disease n (%)</td>
<td>2 (%5)</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>11 (%28)</td>
</tr>
<tr>
<td>1 artery disease n (%)</td>
<td>5 (%13)</td>
</tr>
<tr>
<td>2 artery disease n (%)</td>
<td>10 (%26)</td>
</tr>
<tr>
<td>3 or more artery disease n (%)</td>
<td>23 (%60)</td>
</tr>
<tr>
<td>Preoperative drug usage n (%)</td>
<td></td>
</tr>
<tr>
<td>- Beta blockers</td>
<td>11 (%29)</td>
</tr>
<tr>
<td>- Calcium channel blockers</td>
<td>2 (%5)</td>
</tr>
<tr>
<td>- Nitrate</td>
<td>1 (%2)</td>
</tr>
</tbody>
</table>

EF, LVESV, LVESVI, LVEDV, LVEDVI, LV muscle mass index, left ventricular circumferential wall stress were measured echocardiographically preoperatively (1 day before the operation) and postoperatively (6 weeks and 6 months after the operation).

\[
\begin{align*}
LVESV &= \frac{5}{6} \times A_{vs} \times L_s \\
LVEDV &= \frac{5}{6} \times A_{vd} \times L_d \\
Mass &= 1.055 \times \frac{5}{6} (A_{tL} - A_{cL}) \\
A_{vs} &= \text{End systolic cavity volume} \\
A_{vd} &= \text{End diastol cavity volume} \\
L_s &= \text{Left ventricular end systolic length} \\
L_d &= \text{Left ventricular end diastolic length}
\end{align*}
\]

Blood pressures of patients were also measured by noninvasive method simultaneously with echocardiography.

**Surgical Technique**

Median sternotomy was applied to all cases. The pericardium was opened wide from the apex to the base and excised. It was left open after the operation. Aortocaval cannulation for CPB (Cardiopulmonary bypass), topical and systemic hypothermia (at 30-32 °C for myocardial protection), antegrade cold blood cardioplegia (at baseline and every 20 minutes) were performed. Distal anastomoses were made before the proximal anastomoses under the aortic cross clamp (ACC), and proximal anastomoses were made using the partial aortic clamp after ACC removal. Complete revascularization was achieved in all patients according to their coronary angiographic lesions.

**Statistical Analysis**

All the data were between the mean SD ± and analyzed with the SPSS statistical program. Comparisons between the measurements calculated at different time intervals (before and after the CABG) and were evaluated using variable ANOVA method. In order to evaluate the difference in each variable in cases with significant p values, Student-Newman-Keuls test was applied for multiple comparisons and values below p <0.05 were considered statistically significant.

**RESULTS**

Sixteen patients (50%) were receiving antianginal therapy. Thirteen (40%) were taking nitrate, 2 (6%) were taking Ca ++ antagonist and 1 was taking Ca ++ antagonist + b blocker combination drug. None of the patients included in the study had perioperative mortality. The mean postoperative intensive care unit stay was 3.9 ±1.2 days and the mean postoperative hospital stay was 7.8 ±1.3 days.

**Systolic and Diastolic Blood Pressures**

The mean systolic blood pressure values of the patients were 130 ±18 mmHg preoperatively, 132±25 mmHg at the 6th weeks postoperatively and 141±24mmHg at the 6th months postoperatively. The mean diastolic blood pressure was 75 ±10 mmHg preoperatively, 76 ±10 mmHg at the 6th weeks postoperatively and 77±12 mmHg at the 6th months postoperatively. No statistically significant difference was found between the blood pressure values of the patients at different periods (Table 2).

**Table 2. Hemodynamic and echocardiographic findings**

<table>
<thead>
<tr>
<th>Total number of patients (n=32)</th>
<th>Preoperative</th>
<th>Postoperative at 6th weeks</th>
<th>Postoperative at 6th months</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVESV (ml)</td>
<td>36 ± 11</td>
<td>39 ±15</td>
<td>38 ±13</td>
</tr>
<tr>
<td>LVESVI (ml/m²)</td>
<td>20 ± 6</td>
<td>22 ± 5</td>
<td>21 ± 4</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>99 ± 21</td>
<td>120 ± 25 ±</td>
<td>125 ± 23 ±</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>55 ± 8</td>
<td>67 ± 10 ±</td>
<td>70 ± 12 ±</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>63 ± 7</td>
<td>65 ± 9</td>
<td>68 ±10 ±</td>
</tr>
<tr>
<td>δc ( kdyn/cm²)</td>
<td>175 ± 22</td>
<td>188 ± 18</td>
<td>190 ± 20</td>
</tr>
<tr>
<td>LVMM (gr)</td>
<td>205 ± 56</td>
<td>236 ± 62 ±</td>
<td>242 ± 58 ±</td>
</tr>
<tr>
<td>LVMMI (gr/m²)</td>
<td>115 ± 25</td>
<td>132 ± 21 ±</td>
<td>135 ± 23 ±</td>
</tr>
<tr>
<td>Systolic Pressure (mmHg)</td>
<td>130 ± 18</td>
<td>132 ± 25</td>
<td>141 ± 24</td>
</tr>
<tr>
<td>Diastolic Pressure (mmHg)</td>
<td>75 ± 10</td>
<td>76 ± 10</td>
<td>77 ± 12</td>
</tr>
</tbody>
</table>

LVESV = Left ventricular end-systolic volume, LVESVI = Left ventricular end-systolic volume index, LVEDV = Left ventricular end-diastolic volume; LVEF = Left ventricular ejection fraction, δc = End-systolic circumferential wall stress, LV = Left ventricle, LVMM = Left ventricular muscle mass, LVMMI = Left ventricular muscle mass index, (+) = p <0.05
Echocardiographic values

Preoperative ejection fraction (EF) values measured by two-dimensional echocardiography and were 63 ±7% on average. EF was 65±9% at the 6th weeks postoperative and 68 ±10% at the 6th months. Although the data obtained at the 6th weeks increased slightly compared to the preoperative values, this increase was not statistically significant (p> 0.05). The values obtained at the 6th months showed a statistically significant increase compared to the values at the preoperative and 6th weeks (Table 2, Figure 1) (p <0.05).

Figure 1. LVEF values of the patients

End systolic volume index was 20 ±6 ml/m2 preoperatively, 22 ±5 ml/m2 at 6th weeks postoperatively and 21 ±4 ml/ m2 at 6th months postoperatively. These findings were statistically not significant (p> 0.05) (Figure 2).

Figure 2. End systolic volume index values of patients

The mean end-diastolic left ventricular volume index (LVEDVI) was 55 ±8 ml/m2 preoperatively, 67 ±10 ml/ m2 at 6th weeks and 70 ±12 ml/m2 at 6th months postoperatively (p <0.05). According to preoperative values, there was a statistically significant increase of 20% at 6 weeks and 25% at 6 months (p <0.05). There was a significant increase between LVEDVI values determined at postoperative 6th week and LVEDVI values obtained at 6 months but this increase was not statistically significant (Table 2, Figure 3).

Figure 3. End diastolic left ventricular volume index values of patients

While the mean left ventricular muscle mass index (LVMMI) was 115±25 g/m2 preoperatively, it was found to be 13 2±21 g/m2 at the 6th weeks and 135 ±23 g/ m2 at the 6th months. The left ventricular muscle mass index increased 15% at 6th weeks and 18% at 6th months compared to preoperative values (p <0.05). There was no significant difference between 6th weeks and 6th months (p> 0.05) (Table 2, Figure 4).
End-systolic circumferential wall stress values did not show statistically significant changes in the 6th weeks and 6th months evaluations according to preoperative values (p> 0.05) (Table 2).

**DISCUSSION**

It is known that myocardial tension and increased ventricular filling cause an increase in the synthesis rate of myocardial proteins (12). Studies suggest that the pericardium is an important factor limiting myocardial growth biologically and pericardiectomy can be a stimulating factor for myocardial growth. Crawford et al. (13) observed a significant increase in end-diastolic ventricular volume after pericardiectomy by two-dimensional echocardiography in a study performed in dogs with closed chests. In studies conducted in rats, a significant increase in left ventricular mass has been reported after pericardiectomy (14). In a study with dogs pericardiectomy with closed chest increases cardiac output during exercise and this is the best evidence of limiting role of pericardium (15).

However, a method and measurement that can independently demonstrate the effect of pericardium in humans is unfortunately not fully available. Therefore, to date, the effects of pericardium on cardiac functions in humans have been observed only in the operating room. In our clinical practice, hemodynamic effects under certain conditions such as acute mitral insufficiency and right ventricular myocardial infarction, where the heart is rapidly expanding, are evidence of pericardial restraint. Mangano et al. (16) studied left ventricular systolic and diastolic function compliance by radionuclide angiography and pulmonary capillary wedge pressure measurements in 15 patients during surgery immediately before and after the pericardiectomy. They have shown that the pericardium had no significant effect on systolic function curves, but caused some degree of increase in the end-diastolic volume index.

In this study, it is stated that there is no change in systemic arterial blood pressure, LVES wall stress or LVESV. These effects on the LV mass are likely to occur due to an increase in transmural expansion pressure that occurs following the opening of the pericardium. These observations support the hypothesis that removal of pericardial restriction may be a stimulating factor for myocardial growth and increase in LV mass, and suggests that this hypothesis may be meaningful to humans as well as to animals.

In our study group, although LVEF showed a slight increase in the first 6 weeks postoperatively, the increase in ejection fraction at the 6th months was quite evident and statistically significant compared to the preoperative values and the 6th weeks values. Compared to the ejection fraction measured before the operation, the increase in EF in the 6th weeks after the operation was approximately 4% and in the 6th months was %8, the mechanism of this increase in EF may probably be related to the increase in the intrinsic contractile performance of the left ventricle and changes in the ventricular loading state. However, 6 months after the surgery, existence of neurohumoral changes related to surgery is not expected. Ejection fraction is dependent on preload and afterload state of the heart depending on the changing loading conditions, so the preload (increase in left ventricular diastole volume) was seen as the most important reason for the increase in EF in the late period in our study. In our study, the post-systolic wall tension index did not change in patients after surgery. This suggests that the increase in EF did not affect the changes in the afterload. It is impossible to say that afterload changes are completely ineffective on the changes in EF since it does not have a relatively specific value. Although patients with normal systolic function and no signs of active ischemia were selected in our study; factors related to CABG surgery (such as pharmacological treatment changes, coronary artery pressure changes, effects of healing process of hybernated myocardial cells, neurohumoral changes, exercise habit changes after surgery) other than pericardiectomy existed contributing to ventricular volume and mass. Coronary artery pressures might have an effect on LV mass. Although the relationship between coronary pressures and diastolic enlargement or filling is generally mentioned, experimentally created coronary ischemia leads to acute reductions in left ventricular wall thickness.

It is possible that revascularization in patients with ischemic heart disease may have a stimulating effect on regional myocardial growth in the ventricular mass. However, various studies have shown that angioplasty alone does not cause a regional increase in ventricular mass in patients undergoing percutaneous balloon angioplasty (17). In addition, Tischler et al. indicated that there is an increase in the ventricular mass and volume after revascularization in patients undergoing CABG, but this increase is independent of the number of grafts applied to patients. These findings suggest that the increase in ventricular mass and volume does not depend on revascularization.

It is possible that there is an increase in blood volume in the walls of the heart after the operation and that can lead to a measurable increase in wall thickness and mass calculations (18). However, this type of effect will not explain the increase in post-diastolic volume, or it requires the presence of a significantly reduced flow at resting state before surgery.

Coronary turgor pressures will not increase significantly after surgery in our study due to selection of patients with normal global systolic function and without acute symptoms according to our study method. Reversible ischemic damage and functional impairment due to reduced coronary flow in stunned and hibernated myocardium terms are expressed. Various metabolic disorders occur during ischemia, such as loss of adenine nucleosides and inhibition of the glycolytic pathway (19,20). The genetic expression of some specific proteins
can change due to myocardial ischemia (21,22). As discussed earlier, in in-vitro models, myocardial strain is an important stimulant of hypertrophy. Therefore, even if the global systolic function is not impaired, it cannot be ignored that the blood flow can cause healing of stunned or hybernated myocardium, LV mass increase myocardial hypertrophy due to the metabolic effects of the restoration.

There are several neurohumoral factors that may affect left ventricular mass in the postoperative period. For example, angiotensin II directly causes myocardial hypertrophy in some patients. Similarly, α-adrenergic stimuli has been shown to have a stimulating effect for myocardial growth (23). Significant increases in cell surface area and volume are observed in cardiac myocyte cell cultures without increasing DNA synthesis in response to α-adrenergic stimulation (24,25,26).

Researcher M. LeWinter mentions that pericardiectomy can provide reasonable hemodynamic benefits in addition to pharmacological treatments in heart failure patients with preserved ejection fraction (27). As a result, bypass surgery may cause an increase in left ventricular mass regardless of the mechanical effects of thoracotomy and pericardiectomy, but any neurohumoral changes occurring in the postoperative period should return to normal after a short time after surgery, while the results obtained in the study such as myocardial mass and end diastolic volume increase continued until the 6th month. These findings show that neurohumoral factors may affect the increase in myocardial mass and volume for a short time after the operation, but the increase in myocardial mass and volume in the long term occurred independently of these factors.

Compensatory myocardial hypertrophy may occur due to the increase in the physical activities of the patients after the operation. However, the fact that the marked increase in ventricular muscle mass occurs within the first 6 weeks when patients begin to get rid of the acute effects of surgery and this reduces the likelihood of physical activity to play a role in the increase in ventricular mass.

In our study with echocardiographic evaluations, there was a significant increase and change in left ventricular volume and left ventricular muscle mass, especially at the 6th week and 6th month after CABG operation. These changes in the left ventricle increased significantly at 6 weeks and remained high at 6 months. This expansion occurred without systolic and diastolic blood pressure changes. The end-systolic volume and also the end-systole circumferential wall stress values did not cause significant changes in circular wall stress.

Therefore, there is a need for clinical studies that involve a larger number of cases and different studies to compare such as cardiac valve surgery patients with normal left ventricular mass.

Limitations of the study

In our study, the absence of a comparison group with an exact equivalent to this procedure may be seen as a limiting factor. Although it is considered to be an ideal control group patients undergoing caab without a pericardiectomy, this is not possible in practice. Maybe changes in ventricular muscle mass should be coordinated with echo as well as pathological evaluations of biopsy materials.

CONCLUSION

In conclusion, pericardiectomy may lead to a partial increase in left ventricular end-diastolic volume and left ventricular muscle mass with better left ventricular filling volumes in patients undergoing coronary artery bypass graft surgery. These findings support the fact that left ventricular end diastolic volume increase is associated with myocardial hypertrophy and left ventricular muscle mass increase.

Conflict of interest: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The study protocol was approved by local ethics committee of Bursa Yuksek Ihtisas Training and Research Hospital (BYİHEAH2002/2-17)

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