Analysis Of Cardiac Markers In Pericardial Fluid
T Ege, A Kocailik, E Duran

Citation

Abstract
Introduction and Objective: We aimed to analyze the cardiac markers in patients undergoing cardiac surgery and to compare pericardial fluid and blood concentrations of these markers.

Materials and Methods: A total of 42 patients undergoing cardiac surgery with sufficient amount of pericardial fluid sample collected were enrolled in the study. The patients were classified into four groups: Group 1: SAP (n=11); Group 2: USAP (n=12); Group 3: PMI (n=12); and Group 4: VHD (n=7). cTI, CK-MB and myoglobin levels were determined in pericardial fluid samples and in simultaneously collected blood samples from peripheral arteries.

Results: EF was lower in PMI patients than in other groups (43.8%±12.6%). CK-MB concentration in peripheral blood samples was higher in PMI group compared to VHD group (16.63±3.48 ng/mL and 3.67±0.69 ng/mL, respectively; p=0.032). CK-MB concentration in pericardial fluid was higher in PMI group (11.45±1.80 ng/mL) compared to SAP (1.64±0.30 ng/mL), USAP (3.43±0.75 ng/mL) and VHD (0.37±0.07 ng/mL) groups (p=0.005, p=0.018 and p=0.000, respectively). Also, cTI concentration was higher in pericardial fluid samples from PMI group (19.78±2.81 ng/mL) than in SAP (0.24±0.06 ng/mL), USAP (1.91±0.32 ng/mL) and VHD (0.00±0.00 ng/mL) groups (p=0.000, p=0.011 and p=0.000, respectively).

Conclusion: In patients with coronary artery disease, pericardial fluid levels of cTI were higher, and both CK-MB and myoglobin levels were lower compared to blood levels. Muscle breakdown continuing after MI results in a decrease in EF and an increase in pericardial fluid cTI level.

ABBREVIATIONS
SAP= Stable Angina pectoris,
USAP= Unstable angina pectoris,
PMI= post-myocardial infarction,
VHD= Valvular heart disease,
cTI= cardiac troponin I,
CK-MB= creatine kinase MB

INTRODUCTION
Pericardial fluid is present between parietal and visceral layers of pericardium; it has a volume of approximately 15-50 ml, and is responsible from lubrication [1,2]. Pericardial fluid is considered as an ultrafiltrate of plasma, owing to the fact that concentrations of many molecules in this fluid is similar to that of plasma [2,3]. Many factors including systemic diseases, coronary artery disease, malign diseases, connective tissue disorders, infectious diseases, and idiopathic factors can increase the amount of pericardial fluid and change its composition [1,3,4,5,7,8].

Blood concentrations of some molecules that are released upon myocardial injury are used to estimate the degree of myocardial injury. Cardiac troponin I (cTI), myoglobin and creatine kinase MB (CK-MB) are among the most widely used cardiac markers. Their blood levels increase significantly, particularly during conditions that cause myocardial injury, including acute myocardial infarction, and also due to excess load on ventricular muscle [9,10,11,12,13,14,15]. Relative paucity of studies investigating the change in pericardial fluid concentrations of cardiac markers compared to studies on blood concentrations has been the basis of this study.

Our aim was to provide a contribution to literature data by assessing the pericardial fluid concentrations of these markers in patients undergoing cardiac surgery and by comparing them with blood levels.

MATERIALS AND METHODS
A total of 42 patients from whom sufficient amount of
pericardial could be collected during routine cardiac procedures in our unit were enrolled in the study. Patients with a sample volume of less than 5 ml were excluded. Approval from Institutional Ethics Committee and written consent from patients were obtained before the study procedures were commenced. Patients were classified into 4 groups:

- **Group 1:** Patients with clinical manifestations of stable angina pectoris (SAP), but requiring coronary artery bypass grafting (CABG) due to critical lesions detected at coronary angiography (n=11) (SAP = substernal angina precipitated by exertion and relieved by rest or nitroglycerin in <10 min).

- **Group 2:** Patients with a diagnosis of unstable angina pectoris (USAP), undergoing coronary angiography and subsequent CABG (n=12). [USAP = All patients presented with angina pectoris at rest associated with electrocardiographic changes but without myocardial enzymatic alterations (Creatine kinase-MB, aspartate amino transferase, lactate dehydrogenase and Troponine I)].

- **Group 3:** Patients suffering from MI within last 4 weeks of study and (post-myocardial infarction: PMI) undergoing CABG (n=12). [PMI patients = Patients with a diagnosis of transmyocardial infarction within 4 weeks of study, based on enzyme changes (Troponin I, Creatine kinase-MB, aspartate amino transferase, lactate dehydrogenase and electrocardiographic alterations)].

- **Group 4:** Patients who were operated due to rheumatic valvular heart disease (VHD) (n=7)

cTI, myoglobin and CK-MB levels was measured in simultaneously collected pericardial fluid and blood samples.

Following median sternotomy, mediastinal adipose tissue and thymus was displaced away from pericardium, and then pericardium was opened vertically and pericardial fluid sampling was made. Caution was experienced to avoid from contact between pericardial fluid and blood. Simultaneous peripheral arterial sampling was made. The samples were placed in 5 mL sterile tubes (with no anticoagulants added) and immediately transferred to the laboratory, where they were centrifuged and measurements were made as soon as serum was separated.

Cardiac troponin-I (cTn-I), MB-isoenzyme of creatinine kinase (CK-MB) and myoglobin levels were analyzed with the Triage Cardiac System (Biosite Diagnostics, San Diego, California, USA). Analytic sensitivities and normal values of cardiac markers are presented below:

**STATISTICAL ANALYSES**

Results are presented as mean ± standard deviation. All analyses were performed using SPSS software for windows (SPSS Inc, Chigaco, IL, USA) and differences were considered statistically significant at a probability level of less than 0.05.

Results in the three groups were compared with repeated measured analysis of variance (ANOVA) followed by Bonferroni post-hoc test.

**RESULTS**

Overall demographic and operative data are illustrated in Table 1. There were no significant differences between the groups with regard to age and body surface area (BSA). However, EF was lower in PMI group (43.8 ± 12.6%) compared to other groups (vs SAP p=0.007, vs VHD p=0.018) (Table 1).

**Figure 1**

![Figure 1](image)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Analytic Sensitivity</th>
<th>Average Values in Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTn-I</td>
<td>0.19 ng/mL</td>
<td>&lt;0.19 ng/mL</td>
</tr>
<tr>
<td>CK-MB</td>
<td>0.75 ng/mL</td>
<td>1.3 ng/mL</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>2.70 ng/mL</td>
<td>52 ng/mL</td>
</tr>
</tbody>
</table>

**Table 1: Patient characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>SAP (n = 11)</th>
<th>USAP (n = 12)</th>
<th>PMI (n = 12)</th>
<th>VHD (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Year)</td>
<td>65 ± 24±8.8</td>
<td>63.1±5.8</td>
<td>55 ± 8.9</td>
<td>60 ± 12.8</td>
</tr>
<tr>
<td>Gender</td>
<td>11:0</td>
<td>9:3</td>
<td>7:5</td>
<td>4:3</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.78±0.10</td>
<td>1.86±0.20</td>
<td>1.71±0.22</td>
<td>1.72±0.10</td>
</tr>
<tr>
<td>EF (%)</td>
<td>60±2±12.4</td>
<td>57.1±18.6</td>
<td>44.3±12.0</td>
<td>61.3±10.6</td>
</tr>
</tbody>
</table>

* p<0.007, ** p<0.018

SAP = Stable angina pectoris
USAP = Unstable angina pectoris
PMI = Post-myocardial infarction
VHD = Valvular heart disease
Figure 3
Table 2: Concentrations of cardiac markers in pericardial fluid and blood.

<table>
<thead>
<tr>
<th></th>
<th>SAP (n=11)</th>
<th>USAP (n=12)</th>
<th>PMI (n=12)</th>
<th>VHD (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CK-MB (ng/mL)</strong></td>
<td>1.6±0.30</td>
<td>3.4±0.75</td>
<td>11.4±1.80</td>
<td>0.37±0.67</td>
</tr>
<tr>
<td><strong>Troponin I (ng/mL)</strong></td>
<td>0.3±0.06</td>
<td>1.9±0.32</td>
<td>19.7±3.81</td>
<td>0.00±0.00</td>
</tr>
<tr>
<td><strong>Myoglobin (ng/mL)</strong></td>
<td>92.75±17.0</td>
<td>83.8±7.35</td>
<td>142.5±16.25</td>
<td>116.1±18.5</td>
</tr>
<tr>
<td><strong>cTI (ng/mL)</strong></td>
<td>5.3±0.80</td>
<td>43.9±0.40</td>
<td>16.6±3.48</td>
<td>3.6±0.69</td>
</tr>
<tr>
<td><strong>Myoglobin (ng/mL)</strong></td>
<td>0.1±0.01</td>
<td>0.2±0.02</td>
<td>1.4±0.67</td>
<td>0.00±0.00</td>
</tr>
<tr>
<td><strong>CK-MB (ng/mL)</strong></td>
<td>201.6±22.0</td>
<td>282.1±27.25</td>
<td>309.3±19.17</td>
<td>238.7±20.34</td>
</tr>
</tbody>
</table>

*α: SAP, p<0.05; α: USAP, p=0.018; α: VHD, p=0.000; α: USAP, p=0.000; α: VHD, p=0.052 (One way ANOVA test)

CK-MB concentrations were higher in PMI group (16.6±3.48 ng/mL) than in VHD group (3.67±0.69 ng/mL) (p=0.032) (Table 2). CK-MB concentration in pericardial fluid was significantly higher in PMI group (11.4±1.80 ng/mL) than in SAP (1.6±0.30 ng/mL), USAP (3.4±0.75 ng/mL) and VHD groups (0.37±0.07 ng/mL) (p=0.005, p=0.018 and p=0.000, respectively).

Also, cTI concentration was higher in pericardial fluid samples from PMI group (19.7±3.81 ng/mL) than in SAP (1.9±0.32 ng/mL), USAP (3.6±0.69 ng/mL) and VHD groups (0.00±0.00 ng/mL) (p=0.00, p=0.011 and p=0.000, respectively).

**DISCUSSION**

Our findings demonstrate that CK-MB concentrations in pericardial fluid samples from patients with a history of acute MI within the last 4 weeks who have an EF of <50% are higher compared to SAP, USAP and VHD patients. Another observation is that, the increase in cTI levels in pericardial fluid samples is inversely related with EF.

Blood levels of CK-MB, cTI and myoglobin levels give an estimate of myocardial injury. Troponins, which are essential proteins for the functions of skeletal muscle, have three subunits referred to as C, I, and T. Troponin I is a 23 kD protein that has inhibitory role in the contractile functions of heart and that inhibits the contractions in the absence of calcium and troponin C. Abnormally high plasma levels of this protein are observed in acute myocardial infarction, pulmonary embolism, heart failure and pericardial tamponade.

Myoglobin is a protein that is present in muscle tissue and its porphyrin ring binds oxygen; concentration of this protein dramatically increases in case of muscle injury. After MI its levels rise during the first 1-3 hours, reaches a peak between 6-9 hours, and returns to normal values within 24-36 hours.

CK-MB, is a dimeric enzyme, its level is very sensitive even to minute changes. An increase in CK-MB is an important sign.

Myocardial injury is associated with increased blood levels of these three molecules. In our series, all these three markers had lower values in blood and pericardial fluid samples of SAP, USAP and VHD groups compared to PMI group. Higher concentrations of cTI in pericardial fluid compared to blood levels suggest an ongoing process of local muscle breakdown. In the group with higher levels of cTI in pericardial fluid, the left ventricular EF was low. This finding reflects the diminished contractile strength due to myocardial injury. In other groups blood and pericardial fluid levels of cardiac markers, as well as the EF values were comparable.

Nunes et al report increased blood levels of troponin I associated with an increase in left ventricular wall thickness and pulmonary artery pressure in patients with aortic valve disease, in spite of the absence of ischemia. In our series blood and pericardial fluid levels of cTI were low, although further studies with larger patient populations would be appropriate to reach a firm conclusion.

Epicardial diffusion is another factor that is responsible from high pericardial fluid concentrations of cTI following an MI. The epicardial diffusion of molecules into pericardial cavity is dependent on their molecular weight (MW). Molecules with a MW smaller than 40 kD can readily diffuse into pericardial fluid, and hence, cTI with a molecular weight of 23 kD should be easily diffusible. On the other hand, CK-MB cannot be subject to epicardial diffusion, as its MW is 85 kD, explaining the lower values observed in...
pericardial fluid versus blood samples in all groups [6]. Although myoglobin was expected to be able to diffuse into pericardial fluid on the basis of its low MW (17.5 kD), its levels were lower in pericardial fluid samples than in blood samples in all groups. Considering the fact that the blood level of myoglobin is determined by molecules both released from heart and skeletal muscle tissues, we believe that this difference arise from myoglobin released from skeletal muscle.

In conclusion, concentrations of cTNI were higher, and concentrations of CK-MB and myoglobin were lower in pericardial fluid samples from patients with coronary heart disease compared to blood levels. The ongoing breakdown of myocardial tissue is associated with a decrease in EF and an increase in cTNI levels in pericardial fluid.

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