Cardiac Biomarkers and Myocardial Dysfunction in Septicemia

Deep Chandh Raja1*, Sanjay Mehrotra2, Avinash Agrawal2, Abhishek Singh3, Kamlesh Kumar Sawlani3

Abstract

Objectives: Cardiac biomarkers have been studied in sepsis in the past and various mechanisms for their rise have been elucidated. However their association with severity of sepsis, mortality and myocardial dysfunction warrants further studies. We have studied three different cardiac biomarkers- troponin T (trop T), creatine phosphokinase MB isoform (CPK MB) and NT pro brain natriuretic peptide (NT Pro BNP) in patients with septicemia. We have attempted to observe the levels of these biomarkers in sepsis, their individual abilities to predict the severity of sepsis, mortality and association with myocardial dysfunction noted in echocardiography.

Results: There were 54 patients each of septicaemia and controls. The means of the three biomarkers, namely Troponin T, CPK MB and NT Pro BNP, were significantly elevated in patients with sepsis- mean values of 0.23±0.8 ng/ml, 9.9±13.4 ng/ml and 5988.62±13.7 pg/ml respectively. Myocardial dysfunction was observed in 27 cases. There were 13 non-survivors. Troponin T and NT pro BNP were strongly associated with higher mortality. CPK MB had better correlation with myocardial dysfunction.

Conclusion: We conclude that myocardial dysfunction using echocardiography is seen in around half of the patients with sepsis. Cardiac biomarkers can be routinely used in patients of septicemia to suggest the severity of sepsis, to detect myocardial injury and dysfunction and prognostication. CPK MB may be very useful to suspect myocardial dysfunction in such patients.

Introduction

Myocardial dysfunction, which is characterized by transient biventricular impairment of intrinsic myocardial contractility, is a common complication in patients with sepsis.1 Cardiac troponins, creatine phosphokinases and natriuretic peptides are biomarkers that were previously introduced for diagnosis and risk stratification in patients with acute coronary syndrome and congestive heart failure. However, their prognostic and diagnostic impact in critically ill patients of septicemia warrants definition.2,3 In this study we have evaluated the levels of cardiac biomarkers- Troponin T, Creatine phosphokinase MB isoform (CPK MB) and NT Pro Brain natriuretic peptide (BNP) in septicemic patients and their correlation with the stage, severity of sepsis (risk stratification), mortality (prognostication) as well as their correlation with myocardial dysfunction.

Editorial Viewpoint

• Role of cardiac biomarkers in determining severity of myocardial dysfunction in sepsis is questionable.
• This study suggests these markers can detect severity of sepsis and related myocardial dysfunction and its prognostication.

Material and Methods

This study is a single centre hospital-based case-control study conducted in patients admitted to the Medical Intensive Care Unit (MICU) of our institute over a period of 1 year from January 2014 to December 2014.

Inclusion and Exclusion Criteria

All patients aged more than 18 years, admitted with suspected sepsis, were considered for enrolment into the study. The following patients were excluded:

1. The presence of any cardiothoracic event before inclusion (history, clinical, electrocardiography (ECG) or echocardiographic evidence of one of the following- coronary insufficiency, cardiothoracic trauma or surgery,

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patients admitted with suspected sepsis evaluated with a detailed clinical examination and investigations

Exclusion criteria applied

CASEx Patients diagnosed as sepsis, severe sepsis or septic shock

CONTROLS-Non septicemic patients

Patients enrolled into study with consent

APACHE II score given to each patient

SPECIAL INVESTIGATIONS (TROP T, NT PROBNP, CPK MB, ECG, 2D ECHO)

Results pooling & analysis of cases and controls

Fig. 1: Study design

Cardiopulmonary resuscitation, cardioversion, or endocarditis, myocarditis, or pericarditis, rheumatic heart disease, valvular insufficiencies, cor pulmonale or any form of cardiomyopathy

2. The chronic intake of any drug that is known to cause cardiac disease, in the previous 6 months before inclusion (that would include chronic alcoholism, anti-cancer drugs)

3. Patients with proven records of chronic renal disease or history of chronic intake (duration>6 months) of any drug that is known to decrease glomerular filtration rate or with creatine levels ≥ 1.5 mg/dl

4. Patients with systemic diseases that are known to influence cardiac function over a long period of time like diabetes mellitus, hypertension, thyroid disease, HIV disease

5. Patients in fluid overload states like in pregnancy, severe anaemia (Hemoglobin <7 g/dl)

6. Patients with central nervous system (CNS) diseases like haemorrhage, meningitis, encephalitis, brain abscess

7. Patients who have refused consent to the study

All patients were diagnosed with sepsis or severe sepsis or septic shock according to the criteria given by ‘The American College of Chest Physicians and the Society of Critical Care Medicine’ convened in 1991.4,5 Based on the initial clinical evaluation, hematological and biochemical investigations, all the patients who fall under the following categories of sepsis – sepsis, severe sepsis or septic shock were enrolled into the study after applying the exclusion criteria. The patients’ severity of sepsis was graded according to the APACHE II scoring system.6,7 Patients with chronic health diseases were excluded from the study and hence no points were given for this part of APACHE II score. One of the following were performed to isolate the source of infection in cases where it was warranted- sputum culture, cerebrospinal fluid (CSF) routine and culture, pleural fluid routine and culture, ascitic fluid routine and culture, pus culture.

Biochemical Assays

Cut-off values considered indicative of cardiac injury were:
1. ≥ 0.1 ng/ml for troponin T
2. ≥ 500 pg/ml for NT pro BNP
3. ≥ 5.0 ng/ml for CPK-MB mass

Troponin-T, NT pro BNP were determined by means of a third Generation assay (sandwich immune assay) based on electrochemiluminescence (Elecys, Roche Diagnostics) which uses recombinant human cardiac Troponin-T and NT Pro BNP as reference standards. NT pro BNP and CK-MB (mass) was also determined on Elecsys (Roche Diagnostics). The lower detection limits of the test assay kits used were 0.010 ng/ml for Troponin T, 0.1 ng/ml for Troponin I, 0 pg/ml for NT pro BNP, 0.9 ng/ml for CPK MB mass.

Parameters in 2D Echocardiography

The following parameters of left ventricular function were studied on a PHILIPS echocardiography machine, with facilities of M-mode, doppler and 2D-echocardiography: left ventricle (LV) end systolic (ESD) and end diastolic diameters (EDD)-measurements taken by M-mode, LV end systolic volume (ESV) and end diastolic volume (EDV) by Simpson’s biplane method, LV stroke volume (SV) and cardiac output (CO), cardiac index (CI), fractional shortening (FS), and ejection fraction (EF) by biplane Simpson’s method. The reference standards and formulae put up by the European Society of Echocardiography8 were followed.

Study of Controls

All the above mentioned investigations were also carried out in 54 non septicemic patients. After applying the inclusion and exclusion criteria they were subject to echocardiographic examination and estimation of levels of cardiac biomarkers. The results were
Table 1: Echocardiographic parameters in sepsis (n=54)

<table>
<thead>
<tr>
<th>2D echocardiographic parameters</th>
<th>Mean</th>
<th>2D echocardiographic parameters</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume (ml/sq.m)</td>
<td>169.19±32.8</td>
<td>Left ventricular stroke volume (ml)</td>
<td>85.9±27.8</td>
</tr>
<tr>
<td>End-systolic volume (ml/sq.m)</td>
<td>83.28±28.31</td>
<td>Cardiac output (l/mt)</td>
<td>10.48±4</td>
</tr>
<tr>
<td>End-diastolic diameter (mm)</td>
<td>6.22±5.38</td>
<td>Cardiac index (l/mt/sq.m)</td>
<td>5.75±2.22</td>
</tr>
<tr>
<td>End-systolic diameter (mm)</td>
<td>4.3±0.52</td>
<td>Fractional shortening (%)</td>
<td>20.9±7.45</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>50±13.7</td>
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</tbody>
</table>

Table 3: Variables in survivors and non-survivors

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n=41)</th>
<th>Non-survivors (n=13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean APACHE II score</td>
<td>11.95±4.8</td>
<td>17.85±4.8</td>
<td>0.003</td>
</tr>
<tr>
<td>TROPONIN T (ng/ml)</td>
<td>0.05±0.1</td>
<td>0.8±1.5</td>
<td>0.006</td>
</tr>
<tr>
<td>CPK MB (ng/ml)</td>
<td>8.7±13.1</td>
<td>13.58±14.2</td>
<td>0.156</td>
</tr>
<tr>
<td>NT Pro BNP (pg/ml)</td>
<td>3134</td>
<td>14991</td>
<td>0.007</td>
</tr>
<tr>
<td>End-diastolic volume (ml/sq.m)</td>
<td>162</td>
<td>190</td>
<td>0.006</td>
</tr>
<tr>
<td>End-systolic volume (ml/sq.m)</td>
<td>76.6</td>
<td>104.3</td>
<td>0.001</td>
</tr>
<tr>
<td>End-diastolic diameter (mm)</td>
<td>6.39</td>
<td>6.69</td>
<td>0.05</td>
</tr>
<tr>
<td>End-systolic diameter (mm)</td>
<td>4.19</td>
<td>4.7</td>
<td>0.009</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>52.1</td>
<td>43.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>22.06</td>
<td>17.39</td>
<td>0.05</td>
</tr>
<tr>
<td>Left ventricular stroke volume (ml)</td>
<td>85.78</td>
<td>86.31</td>
<td>0.9</td>
</tr>
<tr>
<td>Cardiac index (l/mt/sq.m)</td>
<td>5.7</td>
<td>5.9</td>
<td>0.87</td>
</tr>
<tr>
<td>Low ejection fraction (&lt;55%)</td>
<td>16/41 (39%)</td>
<td>11/13 (84.6%)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Results

The total number of patients enrolled into the study were 108. Those with suspected/proven sepsis based on clinical and biochemical evaluation were 54 in number. An equal number of patients with no suspicion/proven sepsis were the controls.

Statistical Analysis

The data are presented as mean ± standard deviation, or when indicated, in percentage. Statistical analysis was performed using software Stata version 11.1 Texas, US. Comparisons between the groups were made by Mann-Whitney U test/ two sample T-tests for quantitative data and Fisher Exact test for categorical data. P values of less than 0.05 were considered to indicate statistical significance. Coefficient of correlation was used to study the linear relationship between ejection fraction, APACHE II score and each of the cardiac biomarkers. The study design is outlined in Figure 1. With a prevailing incidence of myocardial dysfunction in sepsis between 50 and 60% deciphered from previous studies and a desired confidence interval of 0.05 and confidence level of 95%, the calculated sample size was 44.

Demographic Characteristics

The mean age group of the study group was 45±20.3 years (range 18-96 years). Among the 54 cases enrolled, 29 were males and the rest females. The mean age of controls in 47.5±21.2 years (range 18-95 years). There were 30 males and 24 females in the control group. After applying the appropriate statistical analysis, we found that both the groups-cases and controls were not significantly different from each other with respect to age and sex (p= 0.991 and 0.847 respectively).

The Etiology and Severity of Sepsis

There were 31 patients (57.4%) with pneumonia, 20.37% with urosepsis, 11.1% with intra-abdominal sepsis in form of pancreatitis/peritonitis/appendicitis and the rest (11%) had skin/soft tissue infections/hepatitis. The majority (59.2%) of the cases were in stage 3 of sepsis, where they had at least one organ dysfunction and 24.1% of cases were in septic shock. Mean APACHE II score among cases was 13.37±5.39 (range 12-26), with 85.2% cases having a score ≥10.

Echocardiographic Evaluation of Patients with Sepsis

The mean LV EF was depressed in those patients of sepsis (mean LVEF 50.06±13.7% against 61±12% in controls). The mean fractional shortening was reduced in the cases (20.9±7.45, normal >30%) (Table 1). Myocardial dysfunction, as defined by an ejection fraction below 55% was observed in 27 patients of sepsis (50% of cases). There were 12, 13, 2 patients with mild (EF 40-50%), moderate (EF 30-40%) and severe (<30%) left ventricular systolic dysfunction respectively. There was an increase in the end-systolic and end-diastolic dimensions and volumes (Table 1). We observed that the mean cardiac index was increased 5.75±2.22 l/mt/sq.mt. (Normal=2.6-4.2 l/mt/sq.mt) (Table 2).

Those patients of myocardial dysfunction (LVEF <55%) had a significantly higher mean APACHE II score (15.44±5 vs. 11.30±5, p=0.004) and significantly higher rates of mortality (89.65 vs. 15.4%, p=0.009).

Evaluation of Cardiac Biomarkers in Cases (Table 1)

All the three biomarkers, namely Troponin T, CPK MB and NT Pro BNP, were significantly elevated in patients with sepsis- mean values of 0.23±0.8 ng/ml, 9.9±13.4.
significant P-value <0.05

0.14 0.2033

NT Pro BNP

mg/dl and mean total leucocyte count was 16753.15±11108.13 cells per cubic mm, in the cases. There were 83.3% cases with positive NT Pro BNP according to the cut-offs applied, whereas 50% had positive CPK MB and 27.75% had positive Troponin T.

Study of Variables in Non-Survivors (Table 3)

There were 75.93% of survivors in the cases. Rest of the patients (13/54) expired during the hospital stay. The observed mean APACHE II score was significantly higher in patients with sepsis (17.85±4.8).

Discussion

Myocardial Dysfunction in Septicemia

The classical cardiovascular response to septic shock is
Peripheral vasodilatation manifest as systemic hypotension and hyporesponsiveness to vasopressor agents. Although it is known that intrinsic myocardial dysfunction also occurs, this is commonly masked by the concomitant elevation in cardiac index. Initial studies of 1980s employing pulmonary artery catheterisation (PAC) and radio nucleotide techniques (RNC) were performed in such patients, revealing the changes in cardiac function. Survivors of septic shock were found to have decreased systolic function with an ejection fraction of about 33% and an increase in left ventricular end-diastolic diameter. These changes in left ventricular function were of rapid onset and reversible in survivors within 7 to 10 days.

In our study, myocardial dysfunction was detected in 27 patients (50%), as compared to 50-60% reported in other studies. There were 84.6% of non-survivors with low ejection fraction. The negative predictive value of left ventricular ejection fraction in predicting mortality was 92.6%. Thus an ejection fraction evaluation along with biomarker estimation in patients of sepsis may help in prognostication of patients. Landmark studies by Parker et al. showed that myocardial dysfunction as revealed by left ventricular ejection fraction had a poor correlation with mortality, wherein LV stroke work index (LVSWI) was a better measure of systolic dysfunction. Raper et al. had confirmed the presence of myocardial depression in septic patients without shock.

Septic cardiomyopathy is considered as a state of transient biventricular dilatation. True to this statement, we found that, the mean end-diastolic dimensions were increased- 6.22 mm and mean end-diastolic volume indices were high-170 ml/sq.m.t. There was one patient with as high an end-diastolic volume as 224 ml. There were 27% patients with high end-diastolic volumes. In this study, cardiac output and cardiac index was raised in both survivors and non-survivors, relatively higher in non-survivors, though this difference was not statistically significant. Thus we would add that cardiac index, being a function of stroke volume and heart rate, increases in patients of septicemia, as revealed in other studies.

Cardiac depression during sepsis is probably multifactorial. A vast array of mechanisms, pathways, and disruptions in cellular homeostasis have been examined in septic myocardium, namely global ischemia, myocardial depressant substances, circulating cytokines, free radicals, prostanoids causing myocardial and endothelial cell injury. In our study, the correlation between severity of sepsis (by APACHE II score) and myocardial dysfunction was found to be strong.

**Cardiac Biomarkers in Sepsis**

The three cardiac biomarkers evaluated in this study were Troponin T, CPK MB and NT Pro BNP. There have been enough studies in the past, that validate troponins as markers of risk stratification and prognostication in sepsis. According to a few studies, troponins also correlate strongly with myocardial dysfunction. However the same cannot be said about NT Pro BNP, which has been found to correlate well with severity of sepsis as well as mortality, but poorly with myocardial dysfunction mainly due to the different mechanisms of its rise in sepsis. Cardiac troponins and natriuretic peptides provide different information about myocardial dysfunction. Troponin release indicates myocyte damage and loss of cell membrane integrity, and thus gives structural information, whereas BNP reflects wall stress, and thus provides functional information. In contrast, there is rarely any study to evaluate CPK MB as a marker of any correlation with sepsis or myocardial dysfunction.

We found that the means of troponin T, CPK MB and NT Pro BNP were 0.23 ng/ml, 9.9 ng/ml, respectively. Therefore myocardial injury does occur in sepsis. We could record levels as high as 5.3 ng/ml for Trop T, 55.4 ng/ml for CPK MB, 35000 pg/ml for NT Pro BNP. All these rises were in the absence of any derangements of renal functions, any CNS pathologies or any prior cardiac events as ruled out by the exclusion criteria adopted prior to the case enrolment.

We found that all the three biomarkers studied, have a positive linear correlation with APACHE II score. Therefore it is evident in our study, that in sepsis, the three cardiac biomarkers do increase with the severity of sepsis. However, a positive correlation does not necessarily mean a statistically significant association. In our study only CPK MB had a significant association with APACHE II score and hence the severity of sepsis.

**Characterisation of Non-Survivors**

In the cases enrolled into this study, the mortality was 24%. Nearly one-fourth of the cases were in septic shock at the time of enrolment. Most of the patients among non-survivors had organ dysfunctions, and hence belonged to stage 3 of sepsis. They eventually progressed to septic shock (stage 4) before death.

The means of the three cardiac biomarkers were studied in both the survivors and non-survivors. We found that the means of all the three markers, as observed in the cases in-total, were raised in both survivors and non survivors. However the means observed in the non-survivors were much more than in the survivors. As observed in other studies, Troponin T and NT Pro BNP emerged supreme cardiac biomarkers in correlation with mortality in septicemic patients. Thus we would like to
conclude this part of discussion by validating Troponin T and NT Pro BNP as good prognostic markers in septicemic patients. However the role of CPK MB in prognostication, needs to be evaluated by further studies.

Correlation of Cardiac Biomarkers with Myocardial Dysfunction

While Troponin T is a reliable marker for prediction of myocardial dysfunction, NT Pro BNP has been discarded by many studies as an unreliable marker in the evaluation of myocardial dysfunction in sepsis. There have not been any studies validating the role of CPK MB in septic cardiomyopathy. 25-29 We observed an inverse relation between the cardiac biomarkers and ejection fraction. NT Pro BNP had a weak association with myocardial dysfunction, as observed in other studies. 22-24 However, Troponin T and CPK MB had strong associations with myocardial dysfunction.

The most important observations were in regards to positive CPK MB test with the highest positive predictive value of 89%. A negative CPK MB still has a good negative predictive value of 88.89%. The best test for screening patients of myocardial dysfunction was CPK MB with sensitivity close to 90%. It also had a good specificity with regards to myocardial dysfunction. In our study population, if all the 3 tests of biomarkers were negative, then it rules out (100%) myocardial dysfunction. CPK MB performed superiorly than the other troponins and BNP as it has a strong association with myocardial dysfunction.

Hence we conclude that in hospitals where bed side echocardiography still remains a distant possibility, CPK MB, can be of immense help, not only in predicting myocardial dysfunction, but also in risk stratification of sepsis and predicting the severity of sepsis. However for predicting mortality in sepsis, Troponin T and NT Pro BNP would be of better help.

Limitations of the Study

Systemic vascular resistance was not measured in the study. This parameter has been shown to be an independent predictor of mortality in sepsis. 27 The sample size of the patients with septicemia was 54. A larger sample would have helped in making better conclusions regarding the utilities of the biomarkers. Lastly, a follow-up study of the left ventricular systolic functions and the alterations in the levels of cardiac bio markers during the period of the illness was not done, which would have helped in better understanding of the course of cardiac injury in natural history of sepsis.

Acknowledgement

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References

6. Knaus WA, Draper EA, Wagner DP, et al. Relative myocardial depression in sepsis and predicting the severity of sepsis. 7 The sample size of the study of the left ventricular systolic functions and the alterations in the levels of cardiac bio markers during the period of the illness was not done, which would have helped in better understanding of the course of cardiac injury in natural history of sepsis.
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