

Correlation Level of Cardiac Troponin-I with Total Duration of Oxygen/Ventilator Therapy in the Term New-borns with Respiratory Distress

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Abstract

Background: In spite of its potential clinical prognostic significance, only a small number of studies have been conducted to date involving neonatal cardiac troponin-I as an early indicator of significance respiratory dysfunction.

Objective: Aim of this study was to evaluate the clinical significance cardiac troponin-I as marker of cardio-respiratory failure in term newborns.

Methods: Cardiac troponin-I level was determined in serum (at 24-48 hours after birth) in 55 term neonates with respiratory distress and 36 healthy, term newborns. The cardiac troponin-I level is correlated with the total duration of oxygen and ventilatory therapy (expressed in days) in both groups with (13/55) or without (32/55) deaths.

Results: Newborns with respiratory distress had a significantly higher level of cardiac troponin-I, compared to the control group, with the largest increase in cardiac troponin-I observed in mechanically ventilated patients (31/55). The length of applied respiratory support was positively correlated with the level of cardiac troponin-I in survivors of respondents, while in the group of children who died the level of cardiac troponin-I was negatively correlated with total duration of respiratory support, and the number of days to death.

Conclusions: The increase in cardiac troponin-I could indicate the development of severe respiratory failure in term neonates with respiratory distress.

Keywords: Cardiac troponin I; Newborn; Respiratory distress; Perinatal asphyxia

Abbreviations:

RD: Respiratory Distress; cTnI: Cardiac Troponin-I; GA: Gestational Ages; BW: Body Weight in grams; AS: Appgar score at 5 min; MV: Mechanical Ventilation

Introduction

Markers of myocardial damage are the macromolecules, which after myocardial necrosis diffuse to the cardiac interstitium and microvasculature. The specificity of cardiac markers is reflected in high concentrations in the myocardium and absence in other tissues, while the sensitivity of these markers is reflected in speed of their release into the blood after myocardial damage [1]. Markers of myocardial necrosis, which is now commonly used in clinical practice are: creatine kinase and its isoenzyme creatine kinase-muscle, troponin I and T, lactate dehydrogenase, myoglobin, and others [2-5].

Troponin complex consists of three subunits that regulate the contractile process in muscle interfering calcium ions. The three subunits are: Troponin C (18 kD), which binds to calcium ions, Troponin I (26 kD) that binds to actin and inhibits the reaction between actin and myosin and Troponin T (39 kD), which binds to

tropomyosin. Troponin T and Troponin I are located in the heart and in the skeletal muscle, but are coded to different genes and have a different arrangement of amino acids, which enabled the production of antibodies specific to cardiac troponin form and determination in serum [1,6-8].

Troponin is known to be able to grow in the absence of myocardial infarction, in conditions such as: trauma of myocardium, cardioversion, catheter ablation, cardiac arrest, postoperative myocardial damages, acute pericarditis, acute pulmonary embolism, acute or severe heart failure, myocarditis, cardiomyopathy and some congenital heart disease, toxic effect of drugs during for chemotherapy and others [9,10].

On the other hand, increase in the value of Troponin can occur in other conditions outside of the heart: sepsis, renal or respiratory failure, hemolysis, and amyloidosis and also in situations where the Troponin is a false positive in the presence of rheumatoid factor, heterophile antibodies, fibrin etc. [4].

Determining the value of cardiac troponin I and T, as early diagnostic and prognostic indicators of critically ill term newborns with respiratory failure is the major focus of the scientific community today. The reasons why the poor prognosis associated with increased cardiac troponin is still not fully understood, hence the increase in efforts to shed light on the background of some of the mechanisms of the prognostic role of cardiac troponin [10].

Objective

The main objective of this study was to examine whether the increase in cardiac troponin-I (cTnI) in the first 24-48 hours after birth, can be used as an early screening of critically ill term newborns with cardio-respiratory failure, respectively:

1. Examine whether there is a significant difference in the cTnI level, between the groups of newborns with and without clinical signs of respiratory distress (RD);
2. To determine whether there is a significant difference in the level of cTnI between the ventilated and non-ventilated patients with RD;
3. Examine whether the level of cTnI was correlated with the number of days of oxygen/ventilatory therapy (with special reference to the group of patients with fatal outcome).

Materials and Methods

The study was conducted at the Center of Neonatology, Pediatric Clinic and at the Maternity Gynaecology and Obstetrics Clinic, Clinical Center in Kragujevac, in the period from August 2007 by January 2010 year. In its character study was a retrospective-prospective non-interventional. The diagnostic methods were not applied for the sole purpose of this study, but the diagnosis was carried out within the framework of reference and neonatal protocols that were approved by the parents in the form of written consent, and the decision of the Ethics Committee, the parent institution, and number 01-613.

Based on previously conducted pilot study, where the Fisher and Student t-test was used obtained statistically significant difference in the level of troponin I, as primary variables in the observed groups, (if a power of study is 80%, and a level of statistical significance 0.05) using the statistical program, provided that the required number of subjects in the experimental group is 36 [11].

During the three-year study 108 patients were analyzed. Seventeen subjects were excluded.

Criteria for exclusion from the study were:

1. Congenital heart defect (1 hypoplastic left heart, a ventricular septal defect, pulmonary artery stenosis 1 and 2 atrial septal defect),
2. Chromosomal aberrations (1 and 2 Down Edwards syndrome), or
3. Congenital sepsis (9 patients with positive blood cultures).

Criteria for inclusion of subjects in the study were as follows:

1. Respiratory distress (tachypnea, inspiratory visible indentation of the soft tissues of the chest, cyanosis, and the emergence of expiratory sobbing) [12-14].
2. Apgar score <4 at 1 minute and <7 at 5 minute after birth [15,16];
3. Metabolic acidosis (defined as a lactate level > 3.7 mmol/l in the first 1-12 hours after birth);
4. Absolute indication for conventional ventilation was a hypoxemia PaO <6,65 kPa or 50 mmHg and FiO₂ >0,8; hypercapnia PaCO₂ >8,0 kPa or 60 mmHg; pH <7,2 and apnea longer than 20 seconds, according to the criteria Gligorovic S. from 1995 [17].

5. Maintenance of blood pressure below the tenth percentile for that gestational age and birth weight and / or oliguria <1 ml/kg/hour, despite compensation the volume with colloidal solution, has been indication to use inotropes, according to the criteria from Cruz MA et al. from 2006 years [18].

The level of second-generation of troponin I (cTnI-ultra) in serum was determined in all patients in the first 24-48 hours after birth with enzyme immunoassay method on the device Biomérieux mini Vidas, with technique ELFA ("enzyme- linked fluorescent assay"). In the adult population, the normal level (99th percentile), for this type of apparatus is cTnI-ultra <0.01 µg/l, with the coefficient of variation of 10% (from 0.01-0.11 mg/l) [19]. The reference values for the second generation of troponin I are still not know for the neonatal population, whereas the first generation cTnI reference range varies from 0.01-3 mg/l, depending on the authors (Bader D et al. 2006, Trevisanuto D. et al 2006, Mc Auliffe et al. 2004, Clark SJ et al 2001. and other) [20-24].

Statistical Analysis

For the analysis of basic clinical characteristics of the respondents the descriptive statistics such as arithmetic mean, standard deviation and percentages were used. For comparison of mean values of two variables of the population the Mann-Whitney test-ev was used. The correlation between the two numerical characteristics was studied using Spearman correlation coefficient, and the receiver operating characteristic (ROC) curve for determining cut off values for different markers. The analyses were performed in SPSS 14.0 for Windows. Results were considered statistically significant at the 5% level.

Results

The study included 91 infants born at term. These infants were divided into two main groups (Table 1):

1. First group - 55 patients with clinical signs of respiratory distress, mean gestational age 39.5 ± 1.32 weeks, average Apgar score at 5 minute 4.704 ± 2.186; (median 5) and lactate levels of 8.63 ± 4.43 mmol/l, median 7.6 (4.8-13.3) mmol/l; use of conventional mechanical ventilation required a 31/55 or 56.36%; use of inotropes (dopamine) required 23/55 or 41.82% of respondents; the outcome was fatal in 13/55 or 23.64% of respondents;
2. Second group - 36 healthy, term newborns, mean gestational age 39.8 ± 1.089 weeks, average Apgar score at 5 min 8.94 ± 0.41; (median 9) and the mean lactate levels 1.0388 ± 0.36 mmol/l, median 0.9 (0.8-1.2) mmol/l. All the patients were with normal clinically status.
3. Other clinical characteristics of the respondents surveyed are shown in Table 1.

| Clinical characteristics of (n=91) | New borns with RD (n=55) | Healthy new borns (n=36) |
|--|--------------------------|--------------------------|
| Male (%) | 31/55 (56.36) | 17/36 (47.22) |
| Female (%) | 24/55 (43.64) | 19/36 (52.78) |
| Gestational ages in weeks (x ± SD) | 39.5 ± 1.32 | 39.8 ± 1.089 |
| BW in kilogram (x ± SD) | 3.4298 ± 0.5713 | 3.455 ± 0.352 |
| Appgar score in 5-minute (x ± SD) | 4.704 ± 2.186 | 8.94 ± 0.41 |
| The level of the lactats mmol/l (x ± SD) | 8.63 ± 4.43 | 1.0388 ± 0.36 |

| | | |
|---|---------------|----------|
| O ₂ therapy (>28 days) | 8/55 (14.54) | 0/36 (0) |
| Number of days of O ₂ (x ± SD) | 15.46 ± 17.27 | 0 |
| Application of MV (%) | 31/55 (56.36) | 0/36 (0) |
| Number of days of MV (x ± SD) | 5.679 ± 8.419 | 0 |
| The application of inotropes (%) | 23/55 (41.82) | 0 |
| Died (%) | 13/55 (23.64) | 0/36 (0) |

Table 1: Basic clinical characteristics of respondents in observed groups.

Note: RD-respiratory distress, BW-body weight, O₂- oxygen therapy, MV-conventional mechanical ventilation

- In the group of term neonates with RD, a significant increase in cTnI serum ($p < 0.005$) was observed (median 0.07, with a range from 0.01-0.16 µg/l), compared to the control group: median 0.01 (0.01-0.01) µg/l. Calculated area under the ROC curve for cTnI=0.816; $p < 0.0005$; (cut off 0.045 µg/l; Sensitivity 75% Specificity 84,3%), suggesting that cTnI is a very sensitive marker for prediction of respiratory dysphnction (Figure 1).

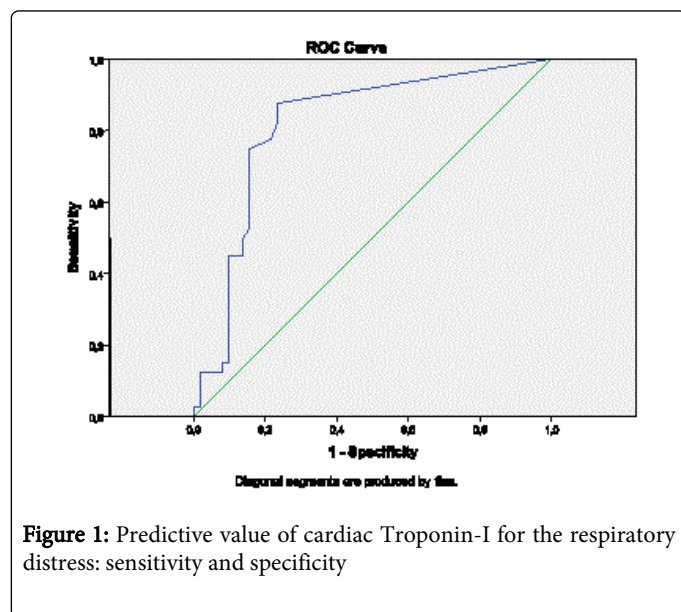


Figure 1: Predictive value of cardiac Troponin-I for the respiratory distress: sensitivity and specificity

- Mann-Whitney test showed that the group of mechanically ventilated infants with RD cTnI level was significantly higher (median 0.11 µg/l; the range of from 0.04-0.18 µg/l; $p = 0.039$), compared to non-ventilated infants with RD (median 0.035 µg/l, with a range of from 0.01-0.135 µg/l). Calculated area under the ROC curve for cTnI=0.800; $p < 0.0005$; cut off level cTnI for conventional mechanical ventilation was 0,055 µg/l; Sensitivity 71% Specificity 87.83% (Figure 2).

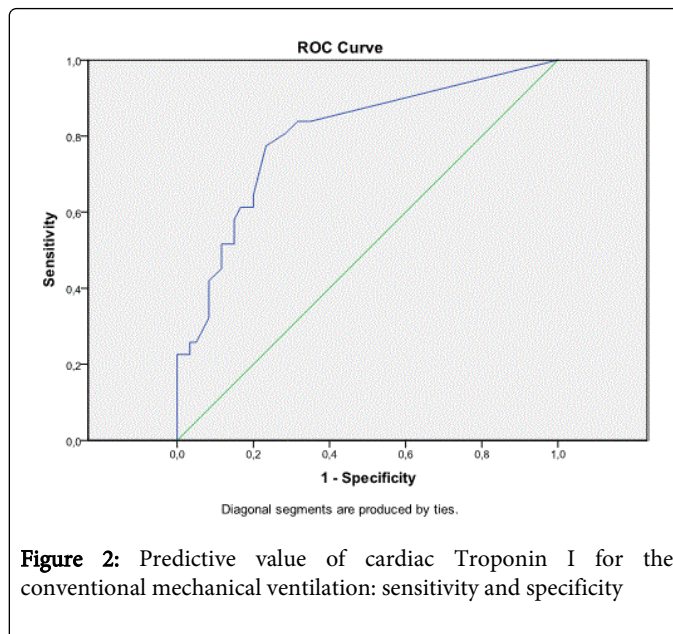


Figure 2: Predictive value of cardiac Troponin I for the conventional mechanical ventilation: sensitivity and specificity

Also, in critically ill infants who were hypotensive requiring inotropic therapy (dopamine in the dose of 5 µg/kg/min) significant increase in cTnI was observed (median 0.15 µg/l; with a range from 0.06-0.56 µg/l; $p = 0.006$) compared to normotensive, infants with RD (0.035 µg/l, with a range from 0.01-0.137 µg/l).

Surviving patients with early growth in cTnI demanded longer useful respiratory support, compared to subjects in which the level cTnI ranged from reference values (Table 2).

| The observed parameter | cTnI (r) | p* |
|-------------------------|----------|---------|
| No. O ₂ days | 0,273 | <0,0005 |
| No. MV days | 0,273 | <0,0005 |

Table 2: Correlation of cardiac troponin I with duration of oxygen therapy/ conventional mechanical ventilation, demonstrated by the correlation coefficients in the group forward asphyxial infants without fatal outcome

Note: p*- significant significance at level $p < 0,01$ (2- degree of freedom); cTnI - cardiac troponin I; r - correlation coefficients; Number of O₂ days - Total duration of oxygen therapy, expressed in days; Number of MV days - total duration of conventional mechanical ventilation in days

On the other hand, the group of patients with fatal cTnI level was negatively correlated with total duration of respiratory support, and the number of days to death (Table 3).

| The observed parameter | cTnI (r) | p* |
|-------------------------|----------|-------|
| No. O ₂ days | -0,316 | 0,132 |
| No. MV days | -0,406 | 0,044 |

Table 3: Correlation of cardiac troponin I with duration of oxygen therapy / conventional mechanical ventilation in the group of patients with fatal outcome, demonstrated by the correlation coefficients

Note: p^{*}: significant correlation at the level of p<0.05; cTnI - cardiac troponin I; r - correlation coefficients

Discussion

Acute hypoxia and/or hypoxemia and decrease in blood pH further reduce surfactant synthesis, and therefore perinatal asphyxia favors the appearance respiratory distress [12,13,17].

In the newborn children with post asphyxial syndrome delayed initiation of respiration leads to respiratory and metabolic acidosis, which results in increased pulmonary vascular resistance preventing the increase of blood flow through the lungs. Hypoxic pulmonary capillary damage causes them to leak and backflow water into the tissues.

Post-asphyctic heart failure can lead to pulmonary edema, which leads to increase of cardiac markers, as shown in studies [9,20,25].

Similar to other authors [10] and our study observed a significant increase of cTnI in patients with postasphyxial syndrome and RD.

Early growth in cTnI (>0,045 µg/l) is significantly correlated with respiratory distress (r=0.326, p=0.04), whereas the level of cardiac troponin was significantly higher in the group of critically ill, mechanical ventilation and / or hypotensive infants [20,26].

Also, the level of cTnI was positively correlated with total duration of oxygen therapy, or No. of days on conventional mechanical ventilation, similar to the results H. Awada and associates [27].

Although it was a somewhat weaker correlations, they still indicated that the early increase in cTnI (>0,055 µg/l) was more pronounced, and asphyxial infants subsequently required longer mechanical ventilation or oxygen therapy.

On the other hand, when we separated the patients with fatal outcome, the cTnI level was negatively correlated with total duration of mechanical ventilation. In the group of infants with fatal outcome, the number of days of conventional mechanical ventilation was the same as days to death. This means that the greater increase in serum cTnI in the first 24-48 hours after birth was observed in the subjects that lived shorter.

These results indirectly suggest that the early rise in serum levels cTnI can be used as an indicator of critically ill children [28-32]. Early detection would enable the timely treatment of newborns with different degrees of respiratory failure and could prevent a fatal outcome.

Conclusion

In the group of term newborns with respiratory distress, the level of cTnI significantly was higher than in the group of healthy, term newborns. Early growth in cTnI levels is significantly correlated with different degrees of respiratory failure, with significantly higher cTnI reported in critically ill, mechanically ventilated newborn infants. Patients with early growth in cTnI required a much longer useful respiratory support, compared to subjects in which the level cTnI ranged from normal values, which indirectly points to the fact that cTnI can be used in the prognosis of cardio-respiratory failure.

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