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Original Article

# Ventricular function and high-sensitivity cardiac troponin T in preterm infants with neonatal sepsis

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## Abstract

***Background*** Hemodynamic instability in sepsis, especially in the neonatal population, is one of the leading causes of death in hospitalized infants. The major contribution for heart dysfunction in neonatal sepsis is the myocardial dysfunction that leads to decreasing of ventricular function. The combination of echocardiography and laboratory findings help us to understand the ventricular condition in preterm infants with sepsis.

***Objective*** To assess for a correlation between ventricular function and serum high-sensitivity cardiac troponin T (hs-cTnT) level in preterm infants with neonatal sepsis.

***Methods*** We prospectively studied 30 preterm infants with neonatal sepsis who were admitted to the neonatal intensive care unit (NICU) of Cipto Mangunkusumo Hospital from June 1 – August 31, 2013. The ventricular functions were measured using 2-dimensional echocardiography. The parameters of right ventricular (RV) function assessment were tricuspid annular plane systolic excursion (TAPSE) and RV myocardial performance index (MPI). For left ventricular (LV) performance, we assessed ejection fraction (EF), fractional shortening (FS), and LV-MPI. Serum hs-cTnT was measured and considered to be a marker of myocardial injury.

***Results*** Subjects had a mean gestational age of 31.5 (SD 2.18) weeks and mean birth weight of 1,525 (SD 437.5) g. The mean LV function measured by MPI was 0.281 (SD 0.075); mean EF was 72.5 (SD 5.09)%; and mean FS was 38.3 (SD 4.29)%. The RV function measured by TAPSE was mean 6.85 (SD 0.94) and that measured by MPI was median 0.255 (range 0.17-0.59). Serum hs-cTnT level was significantly higher in non-survivors than in survivors [282.08 (SD 77.81) pg/mL *vs.* 97.75 (24.2-142.2) pg/mL, respectively P =0.023]. There were moderate correlations between LV-MPI and hs-cTnT concentration (r=0.577; P=0.001), as well as between RV-MPI and hs-cTnT concentration (r=0.502; P=0.005). The positive correlation between LV and RV-MPI in neonatal sepsis was strong (r=0.77; P <0.001).

***Conclusion*** Left and right ventricular MPI show positive correlations with hs-cTnT levels. Serum hs-cTnT is significantly higher in non survivors. As such, this marker may have prognostic value for neonatal sepsis patients. **[Paediatr Indones. 2015;55:203-8]**.

***Keywords****: preterm neonatal sepsis, myocardial performance index, hs-cTnT*

Sepsis has been defined as the presence of the systemic inflammatory response syndrome (SIRS) in response to infection.[1] Significant therapeutic changes have occurred in neonatal intensive care in the last decades to reduce the mortality rate of newborns. A Millenium Development Goal is to reduce the mortality rate of children, including newborns. The main causes of neonatal mortality in developing countries are

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prematurity (30%), neonatal infection (27%), and asphyxia (23%).[2] Successful treatment for neonatal sepsis remains a challenge. Premature neonates are often in critical condition and represent high numbers of neonatal deaths. The heart is one of the major organs that can be affected by sepsis. Myocardial dysfunction contributes to the high mortality associated with sepsis. Studies in patients with severe sepsis revealed the presence of myocardial dysfunction in up to two-thirds of these patients.[3,4] The inflammatory process starts within 24 hours of birth but may be reversible in survivors within 7 to 10 days, as in non-survivors the prolonged inflammation makes the myocardial dysfunction worse.[5]

Echocardiography is an important tool for the diagnosis of cardiac abnormalities. Proper treatment, supported by echocardiography, may influence the outcome of sick newborns in the NICU. The myocardial performance index (MPI) has been widely used as a non-invasive parameter for the assessment of global systolic and diastolic function in children with a variety septic conditions.[4] Cardiac troponin T has been also used as the biochemical marker for myocardial injury. We designed this prospective study to asses for a possible correlation between cardiac dysfunction and neonatal sepsis and to measure the role of hs-cTnT in neonatal sepsis.

## Methods

We prospectively studied 30 preterm infants with neonatal sepsis, with or without positive blood cultures, who were admitted to the NICU of the Perinatal Unit at Cipto Mangunkusumo Hospital, between June 1 and August 31, 2013. Infants with congenital malformations or genetic syndromes confirmed by clinical appearance and tests were excluded from the study.

Echocardiography was performed by two pediatric cardiologists. The echocardiography parameters recorded for right ventricular assessment were TAPSE and MPI. The parameters for left ventricle performance were EF, FS, and MPI. The MPI was defined as the sum of the isovolumetric contraction time and the isovolumetric relaxation time, divided by the ejection time.[4] Blood samples (0.5 mL) were collected and analyzed by *Immunoassay Elecsys Troponin T STAT* (Roche). History of prenatal care, birth weights, first minute Apgar scores and gestational ages were also recorded.

We followed subjects for 7 days to look for neonatal morbidities or mortality. The study was approved by the Ethics Committee Review Board of the University of Indonesia.

## Results

Thirty preterm neonates with sepsis were involved for this study. Their mean gestational age was 31.5 (SD 2.18) weeks and mean birth weight was 1,525 (SD 437.5) g. Subjects' median Apgar score at 1 minute was 6 (range 3-9) and 24 out of 30 subjects required resuscitation in the delivery room as well as ventilation with positive pressure during early life. Subjects' median heart rate was 150 (range 130-162) times per minute, mean hemoglobin level was 12.6 (SD 3.1) g/dL, median leukocyte count was $10.74x10^3$/uL (range $4.08\text{-}46x10^3$/uL), and median platelet count was $13.95x10^3$/uL (range $15\text{-}52.4x10^3$/uL). Neonates with anemia and thrombocytopenia often suffered coagulation problems and gastrointestinal hemorraghage, requiring transfusions of fresh frozen plasma or platelet suspension. **Table 1** shows the characteristics of subjects and septic markers.

Early neonatal sepsis was diagnosed in 24/30 of subjects. Septic marker results were as follows: mean

**Table 1.** Characteristics of subjects

| Characteristics | N=30 |
|---|---|
| Mean gestational age (SD), weeks | 31.5 (2.18) |
| Gender | |
| Male, n | 18 |
| Female, n | 12 |
| Mean birth weight (SD), g | 1,525 (437.5) |
| Median 1-minute Apgar score (range) | 6 (3-9) |
| Median heart rate, x/minute (range) | 150 (130-162) |
| Mean hemoglobin level (SD), g/dL | 12.6 (3.1) |
| Median leukocyte count (range), $10^3$/uL | 10.74 (4.08-46) |
| Median platelet count (range), $10^3$/uL | 13.95 (15-52.4) |
| Onset of sepsis | |
| Early, n | 24 |
| Late, n | 6 |
| Mean IT ratio (SD) | 0.27 (0.12) |
| Mean C-reactive protein (SD), mg/L | 84.5 (61.81) |
| Median procalcitonin (range), ng/mL | 6.44 (1.53-52.86) |

**Table 2.** Cardiac performance and hs-cTnT levels

| Variables | Values |
|---|---|
| Mean left heart performance | |
| FS (SD), % | 38.3 (4.29) |
| EF (SD), % | 72.5 (5.09) |
| Mean LV-MPI (SD) | 0.281 (0.075) |
| Mean right heart performance | |
| TAPSE (SD), mm | 6.85 (0.94) |
| Median RV-MPI (range) | 0.255 (0.17-0.59) |
| Median cardiac index (range) | 2.295 (1.58-4.75) |
| Median hs-cTnT (range), pg/mL | 118.15 (24.2-369.6) |

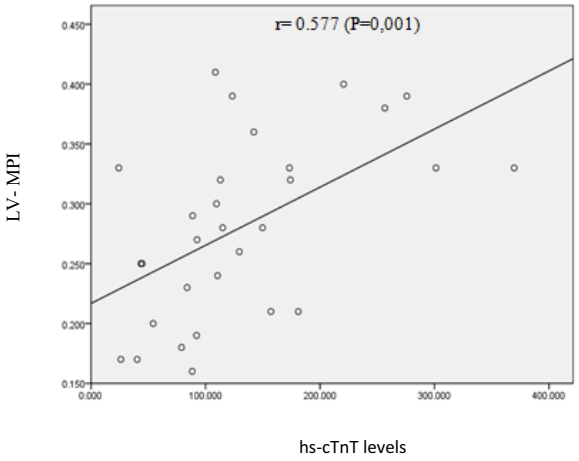


**Figure 1.** Correlation between hs-cTnT levels and LV-MPI

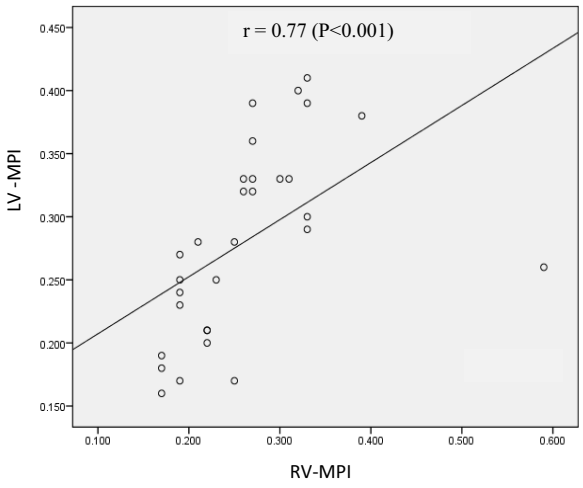


**Figure 2.** Correlation between hs-cTnT and RV-MPI

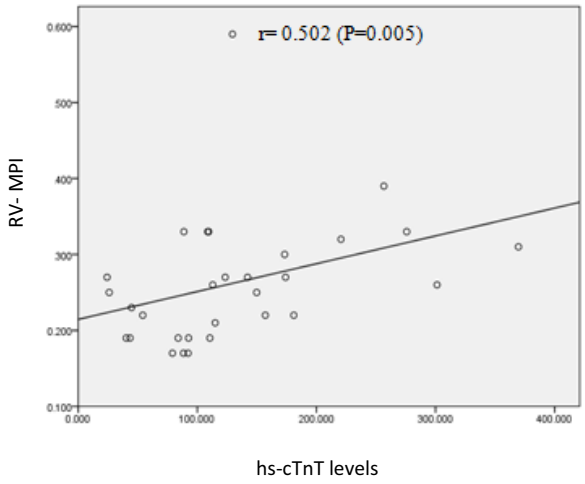


**Figure 3**. Correlation between LV-MPI and RV-MPI

IT ratio 0.27(SD 0.12), mean C-reactive protein 84.5 (SD 61.81) mg/L and median procalcitonin 6.44 (range 1.53-52.86) ng/L. The main maternal morbidities were infection, prolonged rupture of membranes, and meconium-stained amniotic fluid. However, 16 newborns had unknown antenatal care history. Sepsis diagnoses by positive blood culture results were seen in only 12/30 of neonates. *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and Gram positive cocci were seen in 3 neonates each. *Bacillus* sp, *Candida parapsilosis* and *Pseudomonas aeruginosa* were seen in 1 neonate each. Antibitiotics were given selectively depending on the clinical appearance, rather than blood culture results. Antibiotics included piperacillin tazobactam and amikasin in 14 neonates, amoxycillin-clavulanic acid and gentamicin in 7 neonates, meropenem in 5 neonates, and cefepime in 4 neonates.

After 7 days of treatment, we observed intracranial bleeding resulting in seizures in 2 neonates, clinical improvement in 5 neonates, and 4 neonates were death (non-survivors).

The mean left ventricle systolic performance measured by FS was 38.3 (SD 4.29) % and mean EF was 72.5 (SD 5.09)%. The mean myocardial performance index for the left ventricle was 0.281 (SD 0.075). The mean right ventricle systolic performance measured by TAPSE was 6.85 (SD 0.94) mm and the median RV myocardial performance index for was 0.255 (range 0.17-0.59). The median cardiac index was 2.29 (1.58-4.75). The median concentration of

the biomarker for myocardial injury, hs-cTnT, was 118.15 pg/mL (range 24.2-369.6) pg/mL (**Table 2**). The median hs-cTnT concentration of non-survivors within 7 days was 282.08 (range 181.6-369.6) pg/mL, while that of the survivors was 97.75 (range 24.2-142.2) pg/mL (P=0.023).

We conducted bivariate analyses with the MPI as the dependent variable and hs-cTnT as the independent variable. The correlation between LV-MPI and hs-cTnT was moderate (r=0.577; P=0.001) (**Figure 1**), while the correlation between RV-MPI and hs-cTnT was also moderate (r=0.502; P=0.005) (**Figure 2**).

The positive correlation between LV and RV-MPI in neonatal sepsis was strong (r=0.77; P <0.001) (**Figure 3**).

In neonatal sepsis with varying degrees of myocardial injury, we found moderately positive correlations between MPI of both ventricles and serum hs-cTnT concentration.

## Discussion

Sepsis was defined by consensus as the systemic inflammatory response syndrome (SIRS) that occurs during infection. It is generally viewed as a disease aggravated by an inappropiate immune response.[3] The cardiovascular system experiences dysfunction during sepsis. Systolic and diastolic left ventricular functions are critical determinants of sepsis-induced cardiovascular disorders.[6,7] Many cellular pathways of left ventricular systolic function are impeded during sepsis and implicated in the active relaxation of the left ventricle.[8]

In our study, preterm neonates with clinical sepsis had temperature instability, respiratory (grunting, retraction, apnea, tachypnea, or cyanosis), gastrointestinal (feeding intolerance or abdominal distention), neurologic (hypotonia, lethargy, seizures), cardiovascular (bradycardia, tachycardia, poor perfusion, or hypotension), or hematology (thrombocytopenia, prolonged coagulation time, bleeding, or anemia) problems.[9,10] Preterm neonates may be affected by maternal infections. The incidence of neonatal sepsis at the Perinatology Ward Cipto Mangunkusumo Hospital in a recent report was 7.3 per 1,000 live births.[2] In developing countries, the incidence was reported to be 1.8-18/1,000 live births.[2] Sepsis risk is slightly higher in male neonates. In our study, 18/30 of subjects were male.

Early-onset sepsis in neonates is defined as clinical sepsis within 72 hours after birth.[11,12] In our study, maternal vertical infections were not clearly evident, due to the lack of maternal prenatal histories. We found 24/30 neonates diagnosed with early-onset sepsis. Subjects' mean IT ratio was 0.27 (SD 0.12) and mean C-reactive protein concentration was 84.5 (SD 61.81) mg/dL. Polymorphonuclear neutrophils are the first line of innate immunity, with IT ratios able to predict the outcome of sepsis.[10,13] Nevertheless, in our study only 12/30 subjects with sepsis were diagnosed by positive blood cultures, while the remaining subjects had negative blood cultures, despite a clinical appearances in accordance with sepsis conditions. The mortality in our study was caused by septic shock, which led to hypotension and multiorgan failure, despite the administration of inotropic agents.

Cardiac dysfunction can change the course of sepsis. Cardiac index can be normalized in neonatal sepsis, as myocardial insult is frequently reversible. The hemodynamic response to sepsis in neonates is significantly more variable. These changes seem to be reversible because in survivors, cardiac function returns to normal in 7 to 10 days.[14,15] Early recognition and aggressive supportive therapy of sepsis-associated myocardial dysfunction are important to reduce morbidity and mortality.[3,16] In our study, the normal cardiac index was indicative of a possibile stunned myocardium condition.

Detecting left ventricular diseases is a major goal in clinical cardiology. A reduced ejection fraction, commonly the basis for diagnosis of systolic heart failure, is associated with impaired prognosis and is a major determinant of the outcome of neonatal sepsis. In a previous study, systolic functions in preterm neonates with or without sepsis were similar. In preterm neonates with sepsis, the LV systolic function measured by EF was 72.81 (SD 6.79)% and FS was 43.46 (SD 8.47)%, as compared with non-sepsis measurements of EF 70.56 (SD 5.10)% and FS 38.61 (SD 8.14)%.[15,16] In our study, the systolic LV functions were normal [FS 38.3 (SD4.29)% and EF 72.5 (SD 5.09)%]. Symptoms of heart failure have also been ascribed to diastolic disease when ejection fraction is normal. The MPI is used for detecting a prolonged

isovolumic time and a short ejection time, either singly or in combination, indicating diastolic dysfunction of the left ventricle due to the myocardial injury.[17] Systolic and diastolic dysfunction are known to coexist in neonatal sepsis, therefore, an echocardiographic Doppler index that combines measures of systolic and diastolic function is needed.[16]

The MPI is independent of heart rate or arterial pressure, but increases in cardiomyopathy, including myocardial injury and heart failure.[18-20] The MPI has been reported to be simple, reproducible, and independent of heart rate or blood pressure. The MPI is also independent of ventricular geometry.[19] In our study, the LV-MPI was 0.28 (SD 0.075) and RV-MPI was 0.255 (range 0.17-0.59), similar to another study in which Doppler tissue echocardiography revealed a mean LV-MPI of 0.23 (SD 0.02) and mean RV-MPI of 0.29 (SD 0.12).[15] Another study in preterm neonates also had similar results, with mean LV-MPI of 0.27 (SD 0.16).[1] Several studies on neonatal sepsis in different situations have used MPI and hs-cTnT to diagnose cardiovascular dysfunction. Due to the specificity of cTnT to myocardial tissue and its high sensitivity for myocardial injury, hs-cTnT may be used as a biological marker for myocardial injury. Increased cTnT is generally believed to result from inflammatory myocardial injury and is associated with biventricular dilatation and ejection fraction depression.[16] Nevertheless, some patients with increased cTnT do not exhibit reduced ejection fraction. Isolated impairment of ventricular relaxation might be present.

In patients with sepsis, increased cardiac troponin T is generally believed to result from inflammatory myocardial injury and is associated with biventricular dilatation.[16,20] We found a higher hs-cTnT level in non-survivors, compared to that of survivors. Furthermore, a previous study found higher hs-cTnT levels in septic vs. non-septic neonates [190 (120-320) pg/mL vs. 30 (0-7) pg/mL, respectively; ($P < 0.0001$)].[3] Another study also reported that median neonatal cTnT was 44 (27-73) pg/mL, while that in sick infants was 121 (65-238) pg/mL; ($P < 0.0001$).[21] The median hs-cTnT level in our study was 118.15 (24.2-369.6) pg/mL. The non-survivors had higher level results than the survivors. The possibility of myocardial injury was more often observed in non-survivors with higher hs-cTnT. As such, hs-cTnT may be useful to predict outcomes in patients with neonatal sepsis.[22] A previous study reported correlations between LV-MPI and cTnT level ($r=0.80$; $P<0.0001$) and between RV-MPI and cTnT level ($r=0.73$; $P<0.0001$).[4] We also found positive correlations between LV-MPI and hs-cTnT level ($r=0.577$; $P=0.001$) and between RV-MPI and hs-cTnT level ($r=0.502$; $P=0.005$), both of moderate strength. Since our study lacks invasive measurements of left ventricular diastolic function, it is possible that a diagnosis of left ventricular diastolic dysfunction was missed in some patients. Although the MPI is not the reference method for measuring left ventricular contractility, it is accepted for non-invasive assessment of left ventricular function.

Our findings confirm previous observations that neonatal sepsis is associated with myocardial dysfunction. The MPI seems to be a useful parameter in assessing global cardiac function in neonatal sepsis. Myocardial performance index and hs-cTnT may be very useful as early markers of myocardial injury in neonatal sepsis. Furthermore, hs-cTnT concentration could be a marker for mortality in neonatal sepsis.

We suggest that patients with neonatal sepsis undergo cardiovascular evaluation, including echocardiography to assess general cardiovascular performance, MPI to assess myocardial dysfunction, and hs-cTnT measurements to predict outcomes in neonatal sepsis.

## Conflict of interest

None declared.

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