

## Correlation between Troponin-I and Lowering Cardiac Function in Newborn with Respiratory Distress

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### Abstract

**Background:** Respiratory distress is one of common problem found in newborn. Cardiac function probably affected by the problem on respiratory tract. Currently, echocardiography is the best tool to assess myocardial contractility and cardiac function in general, meanwhile its existence still limited. Troponin I is one of predictor of myocard injury in adults population, but not widely use in neonates.

**Objectives:** The objective of this study is to determine the correlation between troponin I and cardiac function in neonates with respiratory distress.

**Method:** We performed a cross sectional study of all neonates admitted to Neonatal ward, Sanglah Hospital between November 2016 to February 2017. We performed examination of cardiac function parameters such as the TAPSE, MV E/A ratio, ejection fraction, cardiac output and stroke volume measured by echocardiography, and troponin I were taken simultaneously. The two ways correlation analysis between troponin I and cardiac function was measured using Spearman correlation test.

**Results:** Fifty two subjects with mean gestational age 32.93 weeks were enrolled in this study. Echocardiography result showed diastolic dysfunction in 88.4% cases, TAPSE dysfunction in 78,8% cases, and ejection fraction in 13.5% cases. There was a significant positive correlation between troponin I and cardiac output ( $r = 0.100$ ,  $p = 0.044$ ) and stroke volume ( $r = 0.076$ ,  $p = 0.049$ ).

**Conclusion:** Troponin I had a very weak significant positive correlation to cardiac output and stroke volume in newborn with respiratory distress. Therefore, troponin I unable to replace the echocardiography to examine cardiac function in newborn with respiratory distress.

**Keywords:** Respiratory Distress; Neonates; Troponin-I; Cardiac Function

### Abbreviations

TAPSE: Trans Annual Plain Systolic Excursion; MV E/A Ratio: Mitral Valve E wave/A wave ratio; EF: Ejection Fraction; CO: Cardiac Output; SV: Stroke Volume; CKMB: Creatinine Kinase M-B; BNP: B-type natriuretic peptide; GE, USA: General Electronic of United States of America; CPAP: Continuous Positive Airway Pressure; PEEP: Positive End Expiratory Pressure; IQR: Inter Quartile Range; SD: Standard Deviation; NICU: Neonatal Intensive Care Unit; TTNB: Transient Tachypnea of Newborn; PPHN: Persistent Pulmonary Hypertension of Newborn; PDA: Patent Ductus Arteriosus; ECG: Electrocardiogram; IRDS: Idiopathic Respiratory Distress Syndrome; SVR: Systemic Venous Return; MAP: Mean Arterial Pressure; NCPAP: Nasal Continuous Positive Airway Pressure (NCPAP) mode; NIPPV: Non Invasive Positive Pressure Ventilation (NIPPV); SIMV: Synchronized Intermittent Mandatory Volume (SIMV); PC-AC: Pressure Control-Assisted Control (PC-AC); pg: Picogram; ml: Millilitre.

### Introduction

Respiratory distress is a very common problem found in the newborns. Respiratory distress syndrome is common in preterm neonates, but is also common in patients with sepsis. Several previous studies have demonstrated relationship between lung disorder and decreased cardiac function. It is based on oxygen perfusion disorders in tissues, including heart muscle [1-6].

Troponin measurements have been used to diagnose heart muscle damage, during routine cardiac catheterization in children, resuscitation in cardiac arrest, or open heart surgery in children with congenital heart disease. Decreased cardiovascular function is common in neonates born prematurely as well as sick neonates. Cardiac contractility disorders and low cardiac output are the complications of respiratory distress syndrome in premature infants. Troponin T and I are useful markers for detecting ischemic damage in cardiac muscle

in adult and children. Troponin T has demonstrated its ability to identify heart muscle damage in neonates born with asphyxia or with respiratory distress. Several studies in neonates have demonstrated the usefulness of creatinine kinase MB isoform (CKMB) as a biomedical indicator of specific hypoxic injury. These markers are not widely used because they are influenced by factors such as gestational age, sex, weight, and delivery [7,8].

Troponin is a part of the inhibiting protein complex that forms the contractile apparatus of the striated muscle, including the heart. The specific forms of the three troponin subunits T, C and I are present in different muscle types. Troponin I has been recognized as a marker of specific biomarkers in cardiac muscle necrosis [9].

Decreased heart function can be initiated from the damage of heart muscle cells, to greater structural damage that leads to interference of cardiac function. Decreased cardiac function can be seen from irregular heart rhythm, decreased ejection fraction, decreased cardiac output, decreased stroke volume, altered cardiac chamber size that can be observed through echocardiography [10-15].

Echocardiography examination is one of the noninvasive supporting examinations that can clearly describe a person's heart condition. The limited availability of echocardiography examination, cost that is quite expensive, and the need for skilled user to perform this examination, are the obstacles that will be faced when providing services in limited facilities. Given the need for early detection of heart damage in neonatal sepsis, more preliminary markers that more readily available are needed. In the state of necrosis of the heart muscle cells, there are also release of cardiac damage markers, including CKMB, B-type natriuretic peptide (BNP), myoglobin and troponin [16,17].

Troponin I is one component of the complex of 3 separate proteins, together with tropomyosin altering the sensitivity of calcium to process the formation of cross bridge actin myosin in heart muscle cells. Troponin I is found only in myocardial cells, and is a potent inhibitor of this reaction. Troponin I is sensitive and specific in describing heart damage, and there is no cross-reaction with troponin from the striated muscle of the heart found. Cardiac Troponin I levels more sensitive to show cellular damage than CKMB fraction or myoglobin level [18]. Biochemical markers of functional decline and ischemic deterioration may play an important role in replacing the role of echocardiography at health service centers where echocardiography and equipment operators are not available [1].

Increased troponin I levels in the neonate with respiratory distress, may be an early marker of further damage from heart cells that may provide a poorer prognosis in patients [19]. Early administration of heart drugs in neonates with respiratory distress is expected to maintain the contractility and function of cardiac muscle cells so they work well. However its use still has not become a routine protocol in infants with respiratory distress [20]. This study was conducted in the hope of early detection of heart damage in infants with respiratory distress through examination of troponin I levels in the blood.

## Materials and Methods

This was a cross-sectional study to analyze the two-way correlation between troponin I and declining cardiac function. Subjects of this study were neonates with respiratory distress. The inclusion criteria in this study were neonates with respiratory distress whose parents had agreed to participate and signed the informed consent. Subjects with major congenital anomaly, musculoskeletal, congenital heart disease, inotropes use such as dopamine, dobutamine and epinephrine; perinatal history: maternal smoking, preeclampsia, tocolytic use, chorioamnionitis, incompatibility blood were excluded [21-23]. The number of sample was calculated using formula for single group sample based on the correlation values from previous study [24,25].

$$n = \left( \frac{(Z\alpha + Z\beta)}{0,5 \ln \left( \frac{(1+r)}{(1-r)} \right)} \right)^2 + 3$$

Z $\alpha$ : 1,960

Z $\beta$ : 1,645

n: Sample size

r: Previous study reference value for correlation of troponin and cardiac function is 0,4 [17].

According to formula, the minimum number of samples required were 46 neonates with respiratory distress.

All eligible subjects had questionnaires, blood measurement and echocardiography examination at Sanglah Hospital Denpasar. Echocardiography evaluation included the measurement of systolic and diastolic function. The measurement of systolic and diastolic function consisted of ejection fraction (EF), cardiac output (CO), stroke volume (SV), E/A ratio, and tricuspid annular plane systolic excursion (TAPSE). Transthoracic echocardiographic examinations were performed by one experienced pediatric cardiologist to exclude intra-examiner and extra-examiner bias. Echocardiographic measurements were performed with a Vivid 7 ultrasound machine (GE, USA) with pediatric probe. Troponin I was measured with 5 ml blood vein. The measurement troponin I was within 12 hours from echocardiographic measurement.

## Results and Discussion

The median age of subjects was 1 day old. The mean gestational age were 32.93 weeks. Normality test was performed using Kolmogorov-Smirnov test where data distribution of age, were not normal. General characteristic of the subjects were shown in table 1. The most common ventilator support used is CPAP of 61.6%. The oxygen fraction of < 40% was used when subjected to the study with the proportion of 82.6%. Forty-four percent of the PEEP used during the examination was 6.

Subject Characteristic	n = 52
Gender, male, n (%)	23 (44,2)
<b>Gestational age, week, n (%)</b>	
< 30 weeks	11 (21.1)
30 - 33 weeks	16 (30.8)
34 - 36 weeks	16 (30.8)
≥ 37 weeks	9 (17.3)
<b>Age at the time of examination, hour, n (%)</b>	
< 24 hour	7 (13.5)
24 - 48 hour	14 (26.9)
48 - 72 hour	10 (19.2)
≥ 72 hour	21 (40.9)
<b>Birth weight, gram, median (IQR)</b>	
< 1000g	3 (5.7)
1000 - 1500g	22 (42.3)
1500 - 2500g	18 (34.6)
> 2500g	9 (17.4)
<b>Diagnosis of the mother, n, (%)</b>	
Hypertension	13 (7.7)
Antepartum bleeding	2 (3.8)
Others*	47 (90.4)
<b>Diagnosis at the time of hospitalization, n (%)</b>	
Hyaline Membrane Disease	27 (52.0)
Neonatal pneumonia	22 (42.3)
Early-onset neonatal sepsis	1 (1.9)
Transient tachypnea of newborn	1 (1.9)
Persistent Pulmonary Hypertension	1 (1.9)
<b>Method of delivery, n (%)</b>	
Spontaneous	30 (57.7)
Sectio Caesaeran	22 (42.3)
<b>APGAR score on minute 5, n (%)</b>	
Not asphyxia	22 (42.3)
Moderate asphyxia	17 (32.7)
Severe asphyxia	13 (25.0)
<b>Downe's score</b>	
< 3	9 (17.3)
4 - 6	20 (42.3)
> 6	23 (50.4)
<b>Diagnosis of heart abnormalities, n (%)</b>	
PDA	23 (44.2)
No PDA	29 (55.8)
<b>Outcome, n (%)</b>	
Survive	39 (75)
Death	13 (25)

**Table 1:** General subjects characteristics.

\*Diagnosis of the mother: premature rupture of membranes, fever, urinary tract infection, no complications during pregnancy and delivery. Abbreviations: APGAR: Appearance, Pulse, Grimace, Activity, Respiration; PDA: Patent Ductus Arterioses.

Cardiac function in patients with respiratory distress in this study was assessed by TAPSE evaluation, cardiac output, ejection fraction, stroke volume and mitral valve E/A ratio. Diastolic dysfunction characterized by decreased E/A ratio of the mitral valve was obtained in 88.4% of subjects. The condition of asphyxia was found in 57.7% of subjects. The analysis of differences in troponin levels based on the condition at birth with the results: severe asphyxia (IQR) 18.0 (103) pg/ml, moderate asphyxia (IQR) 12.0 (11) pg/ml, and no asphyxia 34.5 (67) pg/dl with p = 0.013.

Analysis of the declining heart function was assessed using 5 parameters. We found weak correlation between troponin I levels with cardiac output and stroke volume in neonates with respiratory distress. The results of cardiac function analysis with troponin I levels in neonates with respiratory distress were included in table 3.

Characteristics	n (%)
<b>Ventilatory support, n (%)</b>	
Ventilator	20 (38.4)
CPAP	32 (61.6)
<b>Ventilation mode, n (%)</b>	
PC AC	14 (26.9)
SIMV	5 (9.6)
HFO	1 (1.9)
CPAP	27 (51.9)
High Flow	5 (9.6)
<b>FiO<sub>2</sub> upon examination, n (%)</b>	
50 - 60 %	4 (7.7)
40 - < 50%	5 (9.6)
30 - < 40%	20 (38.4)
20 - 30 %	23 (44.2)
<b>PEEP upon examination, n (%)</b>	
8	2 (3.8)
7	17 (32.7)
6	23 (44.2)
5	10 (19.2)

**Table 2:** Characteristics of breathing apparatus on neonates with respiratory distress.

Abbreviations: CPAP: Continuous Positive Airway Pressure; PC-AC: Pressure Control - Assisted Control; SIMV: Synchronized Intermittent Mechanical Ventilation; HFO: High Frequency Oscillation; PEEP: Positive End Expiratory Pressure.

	Correlation coefficient	p value
TAPSE	0.045	0.584
The mitral valve E/A ratio	0.223	0.527
Ejection fraction	-0.058	0.408
Cardiac output	0.100	0.044
Stroke volume	0.076	0.049

**Table 3:** Correlation between troponin I and decreased heart function on neonates with respiratory distress.

In this study there was a significant weak positive correlation between the troponin I levels with cardiac output and stroke volume. An overview of troponin I levels with cardiac output and stroke volume is shown in figures 1 and 2.

**Discussion**

Subjects of this study consist of 52 neonates. Twenty-three males, with the average gestational age is 32 weeks. The mean age (SD) of the subject when subjected was 72 (48) hours. Subjects hospitalized at the NICU with the most diagnosis were hyaline membrane disease, followed by neonatal pneumonia, early-onset neonatal sepsis, transient tachypnea of the newborn and persistent pulmonary hyperten-

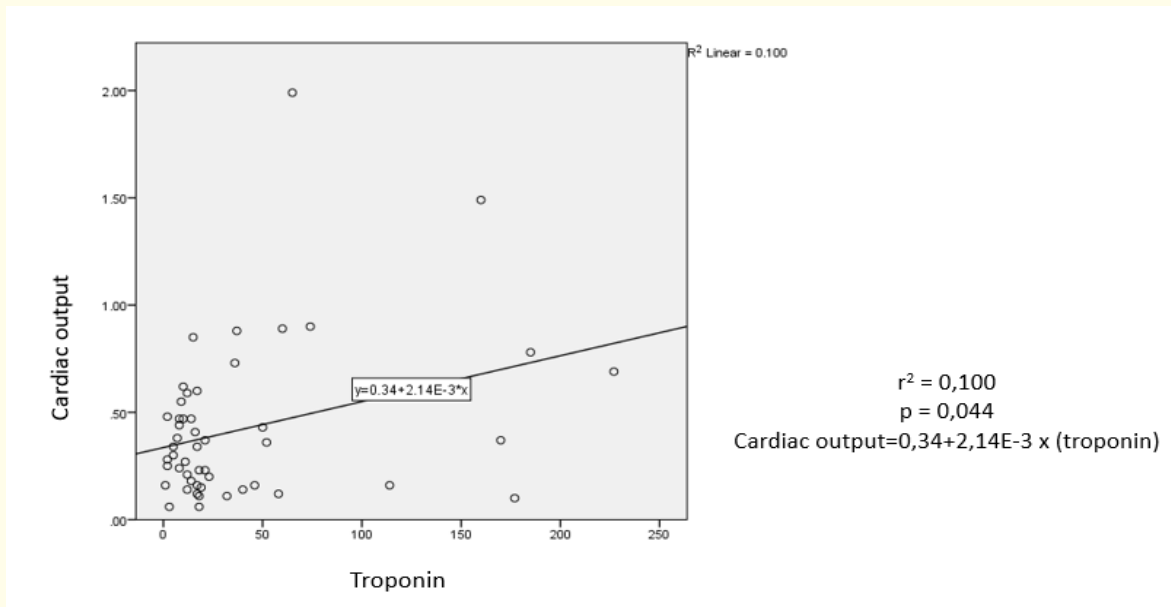


Figure 1: Overview of cardiac output based on the levels of troponin I in neonates with respiratory distress.

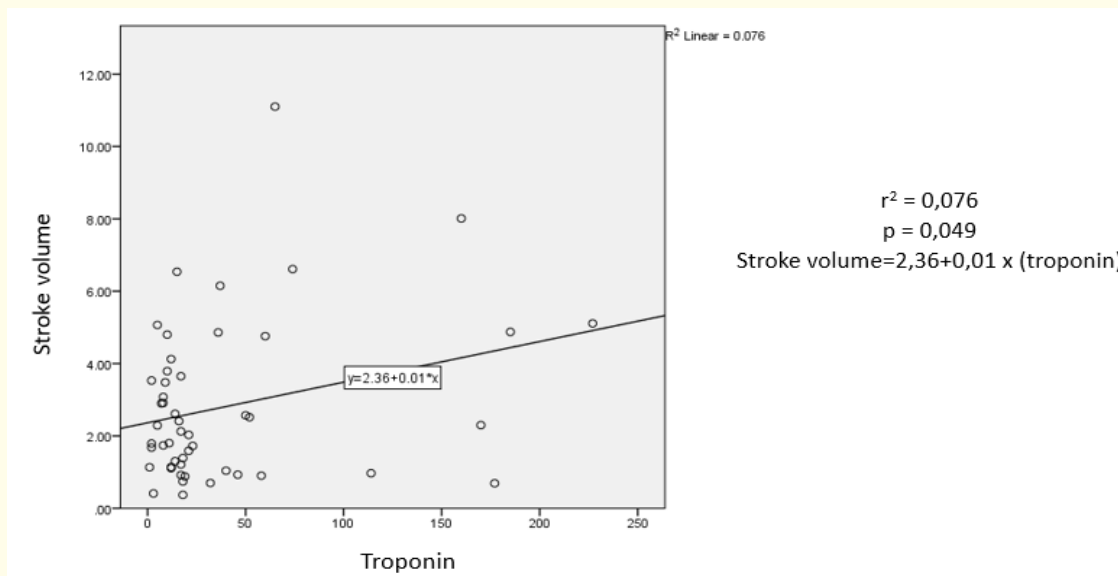


Figure 2: Overview of the stroke volume based on troponin I level on neonates with respiratory distress

sion. The case of patent ductus arteriosus was also found in this study. This condition is especially found in premature infants and this is due to the absence of ductus arteriosus closure. Forty-eight percent of subjects in this study were born with very low birth weight below 1500 grams. This study found that 57.7% of subjects had normal labor, 42.3% through a cesarean section, none via vacuum or forceps.

Cardiac function in this study was assessed through several parameters, namely right ventricular function (TAPSE), as well as several left ventricular functions including diastolic function (mitral valve E/A ratio), and systolic function (ejection fraction, cardiac output, and stroke volume). The results of echocardiography examination showed 88.4% of neonates with respiratory distress experienced diastolic dysfunction. The decline in TAPSE was 78.8%, cardiac output was found in 40.4% of subjects, ejection fraction decreased by 13.5%, and stroke contents by 40.4%. This is in accordance with research by Distefano., *et al.* which found a significant association between respiratory distress and decreased cardiac function in neonates, as well as troponin I (all  $p < 0.05$ ). Cardiac function evaluated is the left and right

ventricular ejection fraction, right and left ventricular cardiac output, and the right and left ventricular stroke volume. Hypoxic conditions that occur due to respiratory distress, resulting in impaired filling of chambers in the heart. Research by Hirsch., *et al.* obtained similar results, that was elevated levels of troponin I under conditions of respiratory distress, but only by inotropic score, not echocardiographic parameters [26].

Our study showed respiratory distress associated with impaired right ventricular function and decreased diastolic function. The state of pulmonary hypertension characterized by increased pulmonary pressure in the condition of respiratory distress leads to high resistance in the lung. This causes the blood flow from the right ventricle through the pulmonary artery experiencing resistance. This continuous condition results in a impairment of the right heart. This is illustrated by the decrease in TAPSE in 78.8% of the subjects of this study. Pulmonary dysfunction in respiratory distress also results in left ventricular filling disruption seen in the diastolic phase. However, ventricular emptying occurring in the systolic phase has not been impaired. It is seen in this research that 88,4% show representation of diastolic dysfunction.

The decrease in diastolic function in this study was not followed by a decrease in systolic function. This is because in the initial phase of respiratory distress, there is a compensation effort to maintain homeostasis in the form of endogenous catecholamines releases such as dopamine and epinephrine which aims to maintain the stroke volume and cardiac output. This will lead to increased cardiac contractility and increased heart rate, so there has been no systolic dysfunction. This is similar to the study by Khufassh., *et al.* who obtained an illustration of systolic function characterized by a weak correlation between the right and left ventricular stroke volume, and the right and left cardiac output with troponin T levels ( $r = -0.34$ ,  $p = 0.013$ ;  $r = -0.43$ ,  $p = 0.001$ ;  $r = -0.16$ ,  $p = 0.26$ ;  $r = -0.21$ ,  $p = 0.14$ ) [1].

Our study used troponin I parameters, that capable of assessing reversible myocard damage, while troponin T only assessed irreversible damage and troponin C was not specific to myocardial damage [9,27]. The bivariate analysis in our study found that troponin I levels had a significantly weak correlation with cardiac output and stroke volume ( $r = 0.100$ ,  $p = 0.049$ ,  $r = 0.076$ ,  $p = 0.044$ ).

The examination of troponin levels in our study was conducted 1 time, and examined in the time adjacent to echocardiography examination. High troponin yields but not accompanied by decreased cardiac function in this study may be due to examination only in the initial phase of respiratory distress, and no reexamination of the advanced phase of respiratory distress. Different results may be obtained when the troponin examination is performed in the advanced phase of respiratory distress, when the body is no longer able to compensate and decreased tissue perfusion happens. Serum troponin I serial examination in the study by Hirsch., *et al.* obtained a strong correlation between troponin I levels and decreased heart function in the advanced phase of respiratory distress ( $r = 0.83$ ,  $p < 0.05$ ), although at the beginning the correlation was weak ( $r = 0.4$ ,  $p < 0,05$ ) [1].

Troponin is a protein inhibitor complex that forms the contractile apparatus of all striated muscles, including the heart. In adult patients, troponin I measurements show the definitive diagnostic tool of a myocardial infarction condition. Troponin I is detected in the circulation immediately after ischemic damage and persisted to increase within 5 - 7 days after the incident [9,28]. Hirsch., *et al.* showed that pediatric patients had cardiac troponin levels similar to those of adults, and indicated the specificity of these markers in conditions of heart failure in children and neonates [26]. The study by Way., *et al.* demonstrated ECG abnormalities during mechanical ventilation, which showed subendocardial ischemia in premature neonates with respiratory distress [29]. Our study did not observe the incidence of myocardial infarction, because no electrocardiographic examination was performed on the subject.

The normal troponin I concentration according to Bader., *et al.* is  $0.58 \pm 0.63$  ng/ml [8]. The level of 1.80 ng/ml is the upper limit of troponin levels in full term neonates [8]. The troponin levels in our study varied, from  $< 4$  pg/ml, to over 4000 pg/ml. One subject with severe respiratory distress, had a very high troponin I level of 4076 pg/ml. This high yield is also accompanied by poor cardiac representation, i.e. decreased cardiac function characterized by decreased TAPSE value, shortening fraction, ejection fraction, cardiac output and stroke volume. Mortality in this patient occurred within 1 x 24 hours after troponin I examination. Troponin I examination on this subject was performed after a respiratory distress of more than 72 hours. This indicates that troponin I examination to assess cardiac function should be performed in the advanced phase of respiratory distress.

The degree of severity of respiratory distress has an important role in increasing troponin I serum concentrations, and is associated with an increased mechanism of myocardial injury. Immature destruction from myocardium may be due to hypoxemia, acidosis due to IRDS, or the negative impact of mechanical ventilation [17].

Damage to myocardial contractility and low cardiac output is often a complication of conditions such as respiratory distress and perinatal asphyxia. Cardiac dysfunction may occur secondary to myocardial ischemia and/or necrosis [30]. The asphyxia condition stimulates the release of troponin from the myocardium [31]. In some subjects who had asphyxia at birth, good cardiac function was found despite high troponin levels. This can be explained because troponin physiologically persists in the circulation for 5 - 7 days after release. Severe asphyxia was obtained in 25% of our study subjects, 27.7% had moderate asphyxia and 42.3% had no asphyxia. Our study also found significantly different levels of troponin I between asphyxia and non-asphyxia neonates. Severe asphyxia (IQR) of 18.0 (103) pg/ml, moderate asphyxia (IQR) 12.0 (11) pg/ml, and not asphyxia 34.5 (67) pg/ml with  $p = 0.013$ . It is estimated that the impact of elevated levels of troponin I when asphyxia lasted until the time of data collection on our subjects, thus affecting levels of troponin I remain high when the heart function is still normal. This is similar to a study by Rajakumar, *et al.* that acquiring asphyxia is one of the conditions associated with decreased cardiovascular function due to impaired mechanical ventilation [32].

Cardiac function is affected by the degree of severity of respiratory distress and ventilation management. The release of troponin I into circulation is associated with the increase of cardiac filling pressure, which is affected by mechanical ventilation [33,34]. This increased troponin I is not known whether it is caused by the use of mechanical ventilation, or the high levels of troponin I that make the patient require mechanical ventilation.

Research by Kluckow, *et al.* found systemic venous return (SVR) and cardiac output interrelated with each other, seen in neonates using mechanical ventilation [35]. Although an increase in SVR increases blood pressure, it seems that the increase in the long afterload pressure actually decreases cardiac output and systemic flow. Intermittent positive pressure or distended airway pressure may increase pulmonary pressure and alveolar volume [36]. Alveolar expansion can increase pulmonary vascular resistance, and high pulmonary pressure. This increase in pressure will lead to similar increased pressure to the heart and large blood vessels, which can affect the venous return to the heart. This will decrease cardiac contractility and cardiac output. Previous studies by Noori, *et al.* also showed a high Mean Airway Pressure (MAP) associated with low SVC in preterm neonates [37]. Whether this is a direct result of PPV effects lowering SVR, or indicating the severity of lung disease, is unknown. Based on the pathophysiology, it is predicted that mechanical ventilation contributes to changes in troponin I levels.

The use of mechanical ventilation in our study varied, from the use of Nasal Continuous Positive Airway Pressure (NCPAP) mode, Non-Invasive Positive Pressure Ventilation (NIPPV), Synchronized Intermittent Mandatory Volume (SIMV), and Pressure Control-Assisted Control (PC-AC). The pressure given during mechanical ventilation differs in this study, with variations from 5 - 8. The possible differences in mechanical ventilation mode and the pressure used in our study subjects will affect troponin I levels.

Another factor that also affects cardiac function is inotropic use [20]. All of our study subjects did not get inotropic so that the inotropic effect on cardiac function excluded.

The parameters of cardiac function in our study were recorded in 3 times of measurements and the mean was taken to reduce intra-examiner bias. Echocardiographic measurements were performed by one pediatric cardiologist consultant, to reduce inter-examiner bias variation. Congenital heart disease such as hemodynamically significant PDA is said to have an effect on levels of troponin T in neonates with respiratory distress [38]. The role of primary heart disease to the decline in cardiac function has been excluded, since exclusion of two large PDA cases and no other congenital heart disease have been found.

Our study found no statistically significant association between troponin I levels with sex, weight, delivery method, and prenatal condition. Research by Quivers, *et al.* showed the opposite, i.e. gestational age and birth weight significantly have a role against troponin I levels in neonate patients [7,39,40]. Premature infants had significantly higher levels of troponin I than a term infants ( $p = 0.008$ ) and body weight had a significant association with troponin I levels ( $p = 0.005$ ), but study by Quivers, *et al.* performed on subjects with no respiratory distress.

Although not designed to evaluate the association between troponin I levels with mortality, we found no significant difference in troponin I levels between living and dead groups. This is in contrast to research by Hirsch, *et al.* who found significant increases between troponin I levels in the Pediatric Intensive Care Unit (PICU) setting and were used as poor outcome indicators [26]. This difference is caused by examination of troponin I levels in this study was performed only once, on the initial phase of respiratory distress. Based on these results, troponin I cannot be used as an outcome predictor of neonates with respiratory distress.

Some of the limitations of this study are the portable echocardiography device used in this study is less suitable for use in neonates and needs probe adjustment to obtain better results; Troponin I was evaluated once in this study, at the early stage of respiratory distress, asphyxia condition not in uniform way, that it needs to reduce bias and different mechanical ventilation mode in every subject [41].

### Conclusion

There is a weak positive correlation between troponin I with cardiac output and stroke volume in neonates with respiratory distress.

### Conflict of Interest

I declare no conflict of interest in this study.

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