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## **Correlation of cardiac troponin T level, clinical parameters and myocardial ischaemia in perinatal asphyxia**

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**Abstract Introduction:** Resource limitation in developing countries may preclude access to cardiac troponin-T assay thereby necessitating reliance on clinical judgment for identification of hypoxic myocardial cellular injury.

**Objectives:** To relate selected clinical signs with elevated serum cardiac troponin-T in asphyxiated term neonates.

**Methods:** Asphyxia was identified by low umbilical arterial blood pH  $\leq 7.20$  and low five minute Apgar score  $\leq 6$  while controls were term, non-asphyxiated neonates. All babies were examined for heart rate, heart rhythm irregularities, peripheral pulse volume, respiratory rate,

pallor, cyanosis, heart murmur and sensorium.

**Results:** Thirty term, asphyxiated neonates and their matched controls were studied. Central cyanosis, reduced pulse volume, pallor, depressed sensorium; tachycardia and tachypnea were all associated with increased odds ratios for abnormal cardiac troponin-T levels.

**Conclusion:** Clinicians working in resource-limited health facilities should have a high index of suspicion for myocardial cellular injury when these signs are elicited.

**Keywords:** neonates, asphyxia, troponin-T, myocardial injury

### **Introduction**

Perinatal asphyxia is one of the leading causes of neonatal deaths in Nigeria where up to 100 – 180 per thousand live births are affected.<sup>1-3</sup> Severe perinatal asphyxia has been known to cause ischaemic myocardial injury with potentially fatal outcomes.<sup>4-6</sup> Serum cardiac troponin T (cTnT) is a reliable marker of myocardial injury.<sup>7</sup> In spite of the significant burden of perinatal asphyxia in our practice, many health facilities cannot afford the necessary equipment for assessment of serum cTnT.

Following an asphyxia event, the dive reflex preferentially sustains vital organ perfusion (heart, brain and adrenals) but as asphyxia progresses, these vital organs including the heart eventually become compromised.<sup>8</sup> The cardiovascular damage that ensues is related to cerebral damage as well as neonatal death.<sup>4-6</sup> Some of the clinical features of cardiovascular injury include atrioventricular valve regurgitation, hypotension, bradycardia, tachycardia and shock.<sup>9</sup> Troponin is an inhibitory protein complex located on the actin filament of the cardiac muscle and is elaborated in cardiac damage.<sup>10</sup> Troponin-T (cTnT) is specific for myocardial injury and is unaffected by, mode of delivery, birth weight and gender.<sup>11</sup> Previous studies have noted a significant relationship of troponin T levels with the use of vasopressors.<sup>12-14</sup> This may not be unconnected to the various

degrees of shock that necessitated the use of the vasopressors in the studied neonates. However studies that relate cTnT directly to signs such as pallor, cyanosis, tachypnoea, tachycardia, low pulse volume and depressed sensorium could not be found by our search.

The authors have previously reported the serum levels of serum cardiac troponin T in term newborns and demonstrated that myocardial damage does occur perinatal asphyxia.<sup>6</sup> However, we are aware that resource limitation may preclude access to cardiac troponin assay in many of our practice settings. It is therefore important to examine the inter-relationship of cardiovascular signs with serum cardiac troponin levels. Hence we set out to correlate the occurrence of elevated serum cTnT (and hence myocardial injury) with selected clinical parameters including the heart rate, respiratory rate, peripheral pulse volume, heart rhythm irregularities, pallor, cyanosis, heart murmur and sensorium. Of particular interest was to identify high risk clinical pointers for elevated serum cTnT that could be used to enhance the diagnosis of asphyxia related myocardial injury in resource limited health facilities.

### **Subjects and methods**

Cases and controls were recruited from the delivery

rooms and neonatal intensive care units (NICU) of the Lagos University Teaching Hospital (LUTH) and the Lagos State University Hospital, Lagos (LASUTH).

Full term asphyxiated neonates with gestational age  $\geq 37$  weeks were consecutively recruited. Asphyxia was defined based on double criteria of five minute Apgar score  $\leq 6$  and umbilical arterial blood pH  $< 7.2$ . The controls were normal non-asphyxiated term neonates matched for age, birth weight and sex. Echocardiogram was done to exclude congenital heart disease in all cases and controls. All babies were examined between 1–6 hours of life for heart rate, heart rhythm irregularities, peripheral pulse volume, respiratory rate, pallor, cyanosis, heart murmur and sensorium. Written and verbal consent was obtained from at least one parent. Approval was gotten from the Research and Ethics Committees of both institutions.

#### Laboratory procedures

pH: was measured using Ion Selective Electrode (ISE) electrolyte analyser 6000 manufactured by SFRI France.

#### Cardiac Troponin-T test

The bedside kit, Cobas h232 ® system manufactured by ROCHE, England was used. The result of cTnT analysis is stratified by the Cobas h232 system manufacturer as low risk ( $< 0.03\text{ng/ml}$ ), medium risk ( $0.03$  to  $0.1\text{ng/ml}$ ) and high risk ( $> 0.1\text{ng/ml}$ ). For high risk results ( $> 0.1\text{ng/ml}$ ), absolute values were displayed on the equipment while for low and medium risk values, results were displayed as ' $< 0.03\text{ng/ml}$ ' or ' $0.03$  to  $0.1\text{ng/ml}$ ' respectively. A high risk result is synonymous with a positive test indicative of myocardial cell damage.

#### Echocardiography

ALOKA Prosound 4000 ® ultrasound diagnostic equipment was used with the multi frequency paediatric phased array transducer. (Frequency range of  $3.0 - 7.5$  MHz)

#### Data collection

A pre-designed proforma was used to record both clinical and laboratory data for all eligible newborns. Data was analyzed using EPI info 2008 version 3.5.1. Chi square test (Pearson) and odds ratios with 95% confidence intervals were used to test for statistical significance with respect to discrete data while Student t- test was used for continuous data. Probability value less than 0.05 was considered statistically significant.

## Results

A total of thirty asphyxiated and thirty non asphyxiated babies who met the study criteria were recruited from December 2009 to May 2010.

## General description of study population

Subjects and controls were similar in distribution of gender, mode of delivery, and birth weight (table 1). Chi-square analysis of mode of delivery has been limited to caesarean section and spontaneous vertex delivery because of the small number of patients in the other two groups. Also chi-square analysis for birth weight was limited to the first two groups ( $1500-2499\text{g}$  and  $2500-3499\text{g}$ ) because of the small number of patients in the third group. The mean gestational age of primary subjects was similar to that of controls ( $39.0 \pm 1.5$  weeks Vs  $38.4 \pm 1.2$  weeks,  $t = 1.65$ ,  $p = 0.1$ ). The mean birth weight was  $3168 \pm 628.5\text{g}$  and  $3143 \pm 574.1\text{g}$ , respectively for subjects and controls ( $p = 0.87$ ).

**Table 1:** Selected general characteristics of subjects and Controls

Variable	Subjects n = 30	Controls n = 30	Total n = 60
<i>Gender*</i>			
Male	17 (56.7)	17 (56.7)	34 (56.7)
Female	13 (43.3)	13 (43.3)	26 (43.3)
<i>Mode of delivery**</i>			
Spontaneous vertex	16 (53.3)	10 (33.3)	26 (43.3)
Caesarean section	12 (40.0)	20 (66.7)	32 (53.3)
Breech	1 (3.3)	0 (0.0)	1 (1.7)
Vacuum extraction	1 (3.3)	0 (0.0)	1 (1.7)
<i>Birth weight (gm) ***</i>			
1500- 2499	6 (20.0)	6 (20.0)	12 (20.0)
2500-3999	22 (73.3)	22 (73.3)	44 (73.7)
$\geq 4000$	2 (6.7)	2 (6.7)	4 (13.3)

\*  $\chi^2 = 0.00$ ,  $p = 1.00$  (degrees of freedom=1)

\*\*  $\chi^2 = 3.32$ ,  $p = 0.07$  (degrees of freedom=1)

\*\*\*  $\chi^2 = 0.00$ ,  $p = 1.00$  (degrees of freedom=1)

Figures in brackets are percentages of n.

#### pH:

The mean level of pH for the subjects and controls were  $7.11 \pm 0.08$  and  $7.26 \pm 0.04$  respectively.

#### Serum cTnT:

Asphyxiated subjects were significantly more likely to have high risk test results than controls ( $p = 0.00$ , table 2). The association between the Apgar score and the serum cTnT level is depicted in figures 1 and 2. All thirty subjects had Apgar scores in the range of 4 – 6 at five minutes.

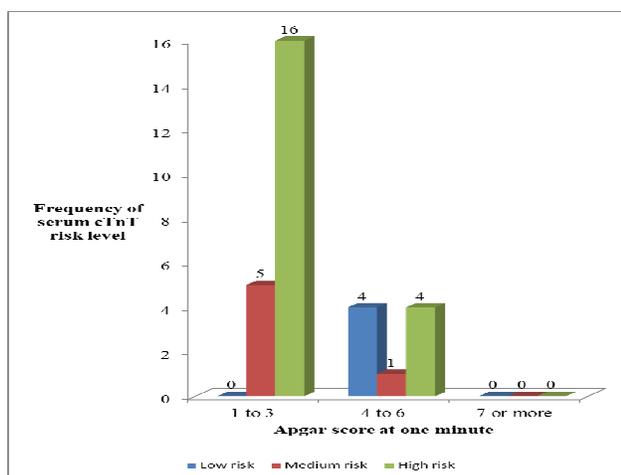
**Table 2:** Distribution of Serum cTnT test results

Serum cTnT (ng/ml)	Subjects	Controls
$< 0.03$	4 (13.3)	26 (86.7)
$0.03 - 0.10$	6 (20.0)	4 (13.3)
$> 0.10$	20 (66.7)	0 (0.0)
Total	30 (100.0)	30(100.0)

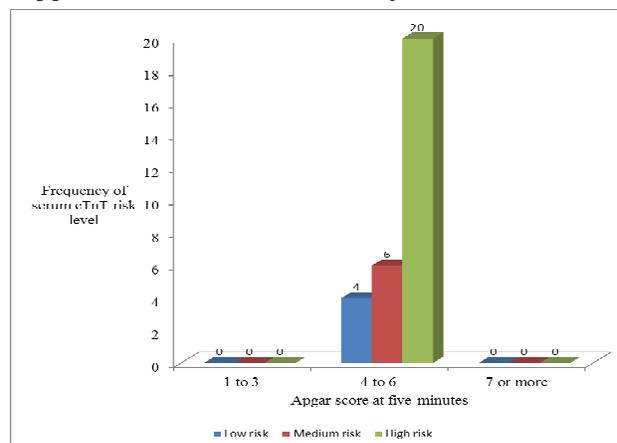
\* $\chi^2 = 30.0$ ,  $p = 0.00$  (degrees of freedom = 2)

Figures in brackets are percentages of column total

**Fig 1:** Association between serum cTnT risk level and Apgar score at one minute for subjects



**Fig 2:** Association between serum cTnT risk level and Apgar score at five minutes for subjects



### Clinical findings and serum level of cTnT

For ease of analysis, two groups of study population were recognised; those with abnormal cTnT test result (cTnT > 0.1ng/ml) and those with cTnT ≤ 0.1ng/ml.

Central cyanosis, reduced pulse volume, pallor, depressed sensorium; tachycardia and tachypnea were all associated with increased odds ratios for abnormal cardiac troponin T levels. (OR=0.0, 0.0, 107, 0.0, 0.11 and 0.24 respectively: table 3)

**Table 3:** Associations between clinical findings and troponin level

	Present No (%)	Elevated serum cTnT level Absent No (%)	Odds ratio	95% confidence limit
<i>Heart rate (beats/min)</i>				
<120	2(50.0)	0 (0.0)	undefined	
120 – 160	9 (20.0)	36 (80.0)	reference group	
>160	9 (69.2)	4 (30.8)	0.11*	0.02 – 0.53
<i>Regularity of heart rate</i>				
Regular	19 (32.2)	40 (67.8)		
Irregular	1 (100.0)	0 (0.00)	0.00	0.00 - 8.81
<i>Pulse volume</i>				
Full	2 (5.6)	34 (94.4)	reference group	
Moderate	15 (71.4)	6 (28.6)	0.02*	0.00 – 0.15
Small	3 (100.0)	0 (100.0)	0.00*	0.00 – 0.24
<i>Murmur</i>				
Present	1 (50.0)	1 (50.0)		
Absent	19 (32.8)	39 (67.2)	0.49	0.01 – 19.05
<i>Respiratory rate (cycles/min)</i>				
<30	1 (100.0)	0 (100.0)	undefined	
30 – 60	10 (23.3)	33 (76.7)	reference group	
>60	9 (56.3)	7 (43.7)	0.24*	0.06 – 0.92
<i>Pallor</i>				
Present	19 (76.0)	6 (24.0)	107.67*	11.0 – 2611.25
Absent	2 (2.9)	34 (97.1)		
<i>Central Cyanosis</i>				
Present	20 (74.1)	7 (25.9)	0.00*	0.00 – 0.07
Absent	0 (0)	33 (100.0)		
<i>Sensorium</i>				
Alert	(0)	28 (100)		
Depressed	20 (62.5)	12 (37.5)	0.00*	0.00 – 0.13

Figures in brackets are percentages of row total

\* Significant

## Discussion

Myocardial ischaemia does occur in perinatal asphyxia. Serum cTnT is a biochemical marker of myocardial cell death.<sup>6, 10 and 11.</sup> The current study focused on correlating selected physical findings with presence of elevated cTnT as a means of enhancing the diagnosis of asphyxia related myocardial ischaemia in resource poor health facilities where equipment for estimation of serum cTnT may not be available routinely.

The physical findings which were of high clinical interest include tachypnoea, tachycardia, cyanosis, low pulse volume, pallor and depressed sensorium. All these features had significant odds of elevated cTnT. This may be explained by varying severities of circulatory failure (shock) in affected neonates. This finds support in the report of Clarke and colleagues<sup>12</sup> that hypotensive sick infants had significantly higher troponin T concentrations than the normotensive sick counterparts. Myocardial ischaemia causes shock which manifests with low pulse volume, tachycardia, tachypnoea, cyanosis, pallor.<sup>9</sup> Depressed sensorium is an indication that hypoxic ischaemic encephalopathy has occurred.<sup>8</sup> Therefore, even though the initial dive reflex preferentially sustains perfusion of the brain, the heart and adrenals, as asphyxia progresses, these vital organs eventually become compromised with consequent organ damage.

It is striking to also note that while there are guidelines for the evaluation of hypoxic ischaemic encephalopathy in perinatal asphyxia, there is no similar guideline for myocardial ischaemia in perinatal asphyxia. Meanwhile, such guidelines could be derived from simple but

focused physical examination which is very cost effective. The predominant profile associated with an increased cTnT in our study is that of a term baby with perinatal asphyxia who develops pallor, cyanosis, tachypnoea, tachycardia, low volume peripheral pulses and depressed sensorium within the first few hours of delivery. This profile is not uncommon in most practice settings in developing countries and without doubt, it is beneficial that physicians begin to include myocardial ischaemia in the assessment of asphyxiated newborns. Future studies may derive scoring or grading systems that will form a guideline for assessment of perinatal asphyxia related myocardial infarction. There is no doubt that adequate cardiovascular monitoring as well as adequate fluid and shock management could reduce morbidity and improve asphyxia related mortality in affected babies. Overall, tackling neonatal mortality related to asphyxia could go a long way in meeting the nation's Millennium Development Goal (MDG- 4) which focuses on reducing childhood mortality.<sup>15</sup>

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