

Cardiac troponin T in cord blood

S J Clark, P Newland, C W Yoxall, N V Subhedar

Abstract

Background—Perinatal asphyxia is associated with cardiac dysfunction. This may be secondary to myocardial ischaemia. Cardiac troponin T is the ideal marker for myocardial necrosis. Elevated levels in cord blood may be associated with intra-uterine hypoxia and increased perinatal morbidity.

Aims—To establish an upper limit of normal for cardiac troponin T concentration in the cord blood of infants. Relations between cardiac troponin T levels and other variables were investigated.

Methods—Cord blood samples were collected from 242 infants and analysed. Data on gestation, birth weight, sex, Apgar scores, respiratory status, and mode of delivery were recorded.

Results—A total of 242 samples were collected, and 215 samples from infants without respiratory distress were used to establish the 95th percentile of 0.050 ng/ml. The gestation of these infants ranged from 31 to 42 weeks and birth weight ranged from 1.4 to 5 kg. There were no relations between cardiac troponin T levels and the other variables in these healthy infants. Twenty seven infants developed respiratory symptoms requiring oxygen and/or ventilation. These infants had significantly higher cord cardiac troponin T levels than their healthy counterparts (median (interquartile range) 0.031 (0.010–0.084) *v* 0.010 (0.010–0.014) ng/ml respectively; *p* < 0.001).

Conclusions—Cardiac troponin T levels in the cord blood are unaffected by gestation, birth weight, sex, or mode of delivery. Infants with respiratory distress had significantly higher cord cardiac troponin T levels, suggesting that cardiac troponin T may be a useful marker for myocardial damage in neonates.

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neonates have used creatine kinase isoforms as biochemical indices of myocardial injury.⁷ However, these markers have been largely discarded because gestation, sex, birth weight, and mode of delivery all affect creatine kinase levels.^{7, 8}

Troponin is an inhibitory protein complex located on the actin filament in all striated muscle and consists of three subunits T, C, and I. Cardiac troponin T concentration has now become the yardstick for myocardial infarction in adults.⁸ In sick infants, myocardial stunning may be responsible for some of the cardiovascular insufficiency seen in the neonatal period.⁶ If this stunning is due to myocardial ischaemia, it may be reflected in elevated cardiac troponin T levels.

The aims of this study were to (a) establish a reference range for cardiac troponin T in the cord blood of healthy infants, and (b) investigate levels of cord cardiac troponin T in sick infants.

Subjects and methods

SAMPLE COLLECTION AND ANALYSIS

A cord blood gas analysis is performed on all infants at Liverpool Women's Hospital, if a sample can be obtained from the umbilical remnant. Any excess blood from these samples was collected during routine laboratory hours over a ten month period, January to October 1999. The local paediatric research ethics committee approved this study, without the requirement for parental consent. Blood was collected in lithium heparin sample bottles and transported to the laboratory where it was separated and frozen within three hours of sampling. We performed biochemical analysis with an Elecsys 1010/2010 Systems analyser using the Elecsys Troponin T STAT Immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). This has a lower limit of detection of 0.010 ng/ml, with minimal cross reactivity with cardiac troponin I (0.002%) and skeletal troponin T (0.001%).⁹ Precision and repeatability studies were performed.

SUBJECTS

We collected data on gestation, birth weight, sex, Apgar scores, mode of delivery, intrapartum cardiotocograph, and cord acid/base status from maternal and/or infant hospital records. We intended to establish a reference range in healthy infants, but a number of samples were collected from infants who went on to develop respiratory distress. Therefore infants were divided into two groups: (1) "healthy" (without requirement for respiratory support); (2) "respiratory distress" (requirement for supplemental oxygen or mechanical ventilation).

University of
Liverpool, Liverpool,
UK
S J Clark

Royal Liverpool
Children's Hospital,
Liverpool
P Newland

Liverpool Women's
Hospital
C W Yoxall
N V Subhedar

Correspondence to:
Dr Clark, Neonatal Unit,
Liverpool Women's Hospital,
Crown Street, Liverpool
L8 7SS, UK
rvecho@yahoo.com

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Cardiovascular compromise is common in sick term and preterm newborn infants.¹⁻³ Impaired myocardial contractility and low cardiac output are common complications of conditions such as respiratory distress syndrome and perinatal asphyxia.¹⁻³ This reduced cardiovascular reserve may present clinically with hypotension, which is associated with increased mortality and adverse neurological outcomes.^{4, 5} It has been suggested that this cardiac dysfunction, or stunning, may be secondary to myocardial ischaemia and/or necrosis.⁶ Previous studies in

Table 1 Population characteristics

	Healthy	Infants with respiratory distress
Total number of infants	215	27
Males	121 (56%)	23 (85%)
Gestation (completed weeks)	39 (37–41)	32 (28–35)
Birth weight (kg)	3.34 (2.89–3.63)	1.88 (1.06–2.15)
Normal intrapartum cardiotocograph	167 (78%)	15 (55%)
Caesarean section	85 (39%)	17 (63%)
Apgar at 5 minutes	10 (9–10)	9 (9–10)
Cord pH	7.32 (7.28–7.36)	7.35 (7.32–7.39)
Cord base excess	-4.0 (-5.8 to -2.2)	-2.1 (-2.9 to -0.9)
Cardiac troponin T (ng/ml)	0.010 (0.010–0.014)	0.031 (0.010–0.084)*

Values expressed as number (%) or median (interquartile range).

* $p < 0.0001$ compared with healthy infants.

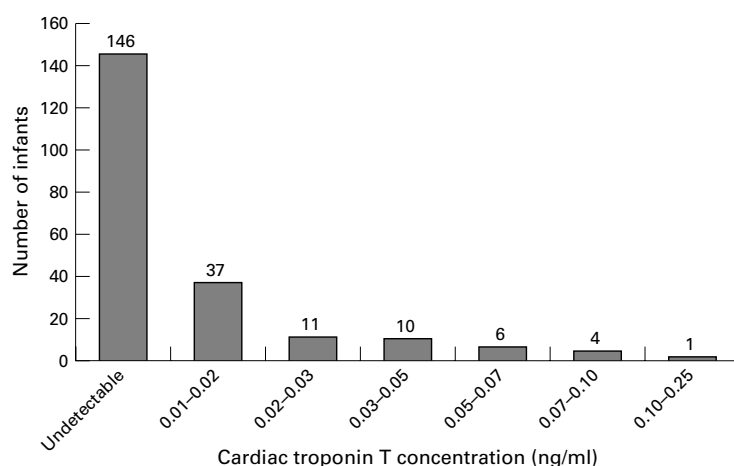


Figure 1 Distribution of cardiac troponin T concentration in healthy infants. The number of infants are given at the top of each column.

STATISTICAL ANALYSIS

In healthy neonates, the relation between cord cardiac troponin T levels and various variables was investigated using Spearman's rank correlation coefficient for continuous variables, and the Mann-Whitney U test for categorical variables. We constructed a reference range of cardiac troponin T values and calculated the upper limit in this population (95th percentile). Cardiac troponin T levels in infants with respiratory distress were compared with those from our reference group of healthy infants (Mann-Whitney U test). We examined the effects of cardiac troponin T level on the development of respiratory distress in the entire study population, using multiple logistic regression analysis, with the presence of respiratory distress as the dependent variable. We controlled for the effect of potential confounding variables such as gestation, birth weight, sex, cord acid base status, mode of delivery, intrapartum cardiotocography results, neonatal sepsis, and Apgar scores. Statistical analysis was performed using SPSS for Windows, Release 8.0

Results

A total of 242 cord blood cardiac troponin T samples were analysed; 27 of these were collected from infants who were subsequently categorised as developing respiratory distress. Table 1 shows the patient characteristics and cardiac troponin T levels for healthy infants and those who developed respiratory distress.

HEALTHY INFANTS

In healthy infants, there was no significant relation between cardiac troponin T level and gestation ($r = -0.03$, $p = 0.70$), birth weight ($r = -0.12$, $p = 0.08$), cord pH ($r = -0.12$, $p = 0.07$), and Apgar score at one minute ($r = -0.08$, $p = 0.26$) or five minutes ($r = -0.03$, $p = 0.65$). Similarly, there was no significant difference in cardiac troponin T levels when boys were compared with girls (median (interquartile range) 0.010 (0.010–0.013) *v* 0.010 (0.010–0.015) ng/ml respectively; $p = 0.58$) or when vaginal delivery was compared with caesarean section (median (interquartile range) 0.010 (0.010–0.010) *v* 0.010 (0.01–0.015) ng/ml respectively; $p = 0.10$). The overall median (interquartile range) of cardiac troponin T levels in these healthy infants was 0.010 (0.010–0.014) ng/ml. The 95th percentile for this population was 0.050 ng/ml. Figure 1 shows a distribution histogram for this population.

INFANTS WITH RESPIRATORY DISTRESS

The 27 infants who developed respiratory distress had cardiac troponin T levels that were significantly higher than those of the healthy infants (median (interquartile range) 0.031 (0.010–0.084) *v* 0.010 (0.010–0.014) ng/ml in the healthy infants). Figure 2 shows the distribution of values of cardiac troponin T levels in the healthy and sick infants. All infants with respiratory distress received supplemental oxygen treatment for a median (interquartile range) of 5 (3–9) days. Seventeen of these infants received mechanical ventilation for a median (interquartile range) of 1 (0–2) day. Four infants died from respiratory failure related to extreme prematurity, three of whom had cord cardiac troponin T levels in excess of the 95th percentile in healthy infants. The other infant, born at 27 weeks with prolonged rupture of membranes from 19 weeks, died from hypoxaemic respiratory failure and had undetectable cord blood levels of cardiac troponin T. However, by 4 hours of age, this had risen to 0.175 ng/ml. All four infants who

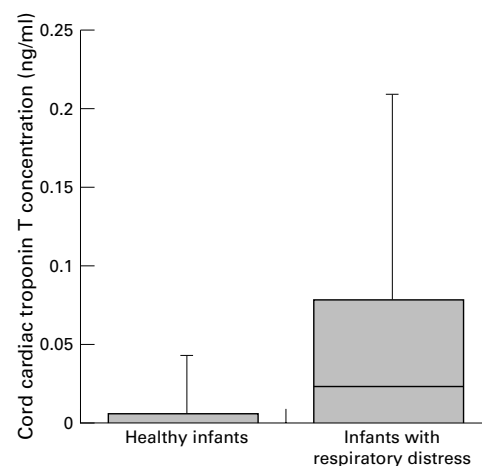


Figure 2 Box and whisker plots for cord blood cardiac troponin T concentration in the healthy infants and those with respiratory distress. Whiskers give 5th (in grey) to 95th percentiles, the box is the interquartile range, and the line within the box is the median.

Table 2 Independent predictors of developing respiratory distress

	R	p Value
Gestation	-0.34	<0.001
Cord cardiac troponin T	0.20	0.003
Apgar at 1 minute	-0.19	0.003
Cord pH	0.18	0.004
Male sex	0.19	0.005

Variables rejected: birth weight, cord base excess, Apgar at 5 minutes, mode of delivery, medical attendance at delivery, intrapartum cardiotocograph, result of first blood culture.

died required inotropic support; only one other infant had a requirement for inotropic support of cardiovascular instability during the neonatal period. The median (interquartile range) cardiac troponin T concentration for these five infants was 0.096 (0.013–0.098) ng/ml, but this was not significantly higher than the other infants who did not receive inotropic support (median (interquartile range) 0.028 (0.010–0.049) ng/ml; $p = 0.36$).

LOGISTIC REGRESSION

Across all 242 infants, after controlling for potential confounding factors, cord cardiac troponin T levels remained significantly and independently associated with the development of respiratory distress ($r = 0.20$, $p = 0.003$) (table 2).

REPEATABILITY AND PRECISION

The coefficient of repeatability for 21 individual samples run in duplicate was 9.8%. The coefficient of variance for repeated samples at a known concentration of 0.014 ng/ml was 6.7%.

Discussion

Most of the healthy infants had an undetectable level of cardiac troponin T in cord blood, and there was no variation with gestation, birth weight, sex, or mode of delivery. The 95th percentile for cardiac troponin T in healthy infants was 0.050 ng/ml. Cord cardiac troponin T levels were significantly higher in infants with respiratory distress, an association that was independent of confounding variables.

The values of cardiac troponin T reported in this study are comparable with those in previously published studies.^{10 11} However, unlike other workers, we have used a third generation assay which is unaffected by haemolysis, renal insufficiency, and icterus.⁹ Furthermore, our measurement technique has minimal cross reactivity with skeletal troponin T,⁹ a potential source of error in previous studies. The present study also represents a much larger cohort of infants than has been studied previously, and includes many preterm infants. Adamcova *et al*¹⁰ published a reference range in 15 healthy term infants from 38 to 41 weeks gestation, but used an assay affected by haemolysis, which gave falsely high values in five of the infants. Adamcova *et al*¹¹ also addressed potential placental transfer of maternal cardiac troponin T. This is unlikely to occur, as the T subunit has a molecular mass of 37 kDa and is therefore too large to diffuse freely across the placenta.¹¹ In their study 22 women between 32 and 36 weeks gestation received tocolytic treatment. The level of car-

diac troponin T in the cord blood of eight infants born during the study showed no relation to maternal values.¹¹

Infants with respiratory distress did not all have elevated cardiac troponin T levels; three infants born at 27, 28, and 30 weeks had undetectable levels. Only five infants developed systemic hypotension requiring treatment with inotropes, of whom four died. There is a suggestion that the infants who required inotropes had higher cardiac troponin T concentration, although this did not reach significance, perhaps because of the small numbers. It is therefore possible that most of these infants, despite needing respiratory support, had negligible myocardial damage. However, the main aim of this study was to assess cardiac troponin T concentrations in healthy infants, and therefore no formal assessment of cardiovascular function was included in the study design.

Cardiac troponin T levels were undetectable at birth but had risen to 0.175 ng/ml by 4 hours of age in one infant who ultimately died of hypoxaemic respiratory failure complicated by systemic hypotension. In adults, cardiac troponin T begins to rise two hours after a cardiac insult.⁸ Cardiac troponin T levels in cord blood will inevitably only reflect preceding antenatal cardiac injury. It is probable that, after an acute insult at birth or shortly afterwards, cord cardiac troponin T levels will not be elevated, despite evidence of cardiac dysfunction. Serial measurements of cardiac troponin T may prove to be of greater value in such situations. Cardiac dysfunction has been shown not only in shocked very low birthweight infants, but also in mature newborn infants who are asphyxiated or have profound sepsis.^{1–3} We speculate that in these conditions cardiac troponin T levels may be more strikingly elevated.

The main limitation of our study is that the reference population of healthy infants contained no extremely preterm babies below 31 weeks gestation. Relatively few babies below this threshold have no signs of respiratory distress. However, there were three infants born at 27, 28, and 30 weeks with low levels of cardiac troponin T, who needed minimal respiratory support for less than 24 hours. In addition, as there was no significant overall correlation between cardiac troponin T levels and gestation in healthy infants, we believe that it is justified to extend our reference range to include the most preterm babies, but we acknowledge that interpretation of cardiac troponin T levels in this group of immature babies is problematic.

The number of infants who went on to develop respiratory distress in this study was relatively small, with only eight infants dying or developing chronic lung disease. The principal purpose of this study was to establish a reference range in healthy infants, which is essential before levels in sick infants can be interpreted. Nevertheless, we have provided some preliminary information showing that cord cardiac troponin T levels are elevated in sick infants. We propose to continue this work by studying serial postnatal cardiac troponin T samples in a larger cohort of sick infants. We

speculate that cardiac troponin T measurements may be useful in early identification of infants with myocardial ischaemia, secondary to severe perinatal asphyxia or in association with hypoxaemic respiratory failure.

In summary, we have established a reference range for cardiac troponin T in cord blood of newborn infants that is unrelated to other important variables, and shown that infants who develop respiratory distress have higher than normal levels of cardiac troponin T.

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