ORIGINAL ARTICLE

Concentrations of cardiac troponin T in neonates with and without respiratory distress

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Arch Dis Child Fetal Neonatal Ed 2004;**89**:F348–F352. doi: 10.1136/adc.2002.025478

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Accepted 22 April 2003

Aims: To establish a practical postnatal reference range for cardiac troponin T in neonates and to investigate concentrations in neonates with respiratory distress.

Methods: Prospective investigation in a tertiary neonatal unit, recruiting infants with and without respiratory distress (sick and healthy infants respectively). Concentrations of cardiac troponin T were compared between sick and healthy infants, accounting for confounding variables.

Results: A total of 162 neonates (113 healthy and 49 sick infants) had samples taken. The median (interquartile range) cardiac troponin T concentration in the healthy infants was 0.025 (0.01–0.062) ng/ml, and the 95th centile was 0.153 ng/ml. There were no significant relations between cardiac troponin T and various variables. The median (interquartile range) cardiac troponin T concentration in the sick infants was 0.159 (0.075–0.308) ng/ml. This was significantly higher ($p < 0.0001$) than in the healthy infants. In a linear regression model, the use of inotropes and oxygen requirement were significant associations independent of other basic and clinical variables in explaining the variation in cardiac troponin T concentrations.

Conclusions: Cardiac troponin T is detectable in the blood of many healthy neonates, but no relation with important basic and clinical variables was found. Sick infants have significantly higher concentrations than healthy infants. The variations in cardiac troponin T concentration were significantly associated with oxygen requirement or the use of inotropic support in a regression model. Cardiac troponin T may be a useful marker of neonatal and cardiorespiratory morbidity.

Cardiovascular compromise is common in sick term and preterm infants.[1–3] Impaired myocardial contractility and low cardiac output are common complications of such conditions 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 myocardial dysfunction, or stunning, is due to ischaemia and/or necrosis.[6] Previous studies in neonates have used creatine kinase isoforms as biochemical markers of myocardial injury.[7] However, these markers have been largely discarded because gestation, sex, mode of delivery, and birth weight all affect creatine kinase activity.[7 8]

Troponin is an inhibitory protein complex forming part of the contractile apparatus of all striated muscle, including the heart. Specific forms of the three troponin subunits T, C, and I exist in different muscle types. Cardiac specific troponins T and I have become established as the best biochemical markers for myocardial necrosis.[8 9] They start to increase two hours after myocardial infarction, and concentrations can remain raised for up to two weeks after a full thickness infarct.[8 9] Indeed the assays for cardiac troponin T are now so sensitive and specific, mainly because of the use of the latest third generation assays, that a concept of minimal myocardial damage has arisen in adult medicine. These marginal increases in cardiac troponin T are associated with worse outcomes in adult patients after admission to hospital.[10 11] Previous studies in children and neonates have used older first or second generation assays and have referred to adult reference ranges.[12–16]

We have previously reported that cardiac troponin T concentration in the cord blood of neonates is unaffected by gestation, birth weight, and sex.[17] Furthermore, increases in cardiac troponin T in the cord blood were found to independently predict the development of respiratory distress syndrome.[17]

To establish a postnatal reference range in healthy infants, we conducted a prospective controlled investigation, using the latest third generation assay, of the postnatal concentrations of cardiac troponin T in healthy infants without respiratory distress. We also investigated postnatal cardiac troponin T concentrations in sick infants.

METHODS

Subjects

Two groups of infants were studied. Healthy infants were defined as those who did not have respiratory distress. They were recruited from the postnatal and neonatal wards of Liverpool Women's Hospital. Sick infants were defined as those with respiratory distress requiring supplemental oxygen or ventilation. They were recruited from the neonatal unit of Liverpool Women's Hospital. Liverpool Women's Hospital is a large tertiary neonatal unit that has approximately 6000 deliveries per annum and around 800 admissions to the neonatal unit, of which about 250 require ventilation. Informed parental consent was obtained. Postnatal blood samples were collected at the time of routine phlebotomy for bilirubin estimation or blood group ascertainment. Therefore recruitment of the postnatal infants depended on them having a blood sample taken for clinical reasons. Neonatal unit blood samples were collected at the time of routine phlebotomy or arterial line sampling, and recruitment of these infants was mainly when the main investigator, SJC, was present on the neonatal unit. Patient recruitment ran from June 1999 to July 2000. Sex, gestation, birth weight, mode of delivery, Apgar scores, cord acid-base status, computerised intrapartum cardiotocograph assessment, age at blood sampling, need for ventilation, duration of respiratory support, and inotropic requirements were recorded. The study

protocol had been approved by the local research ethics committee. As this was an observational study, the standard unit policies for cardiorespiratory support were followed—that is, respiratory support for arterial saturations in air < 94% and inotropic support with dopamine, dobutamine, and hydrocortisone as first, second, and third line treatment for mean arterial blood pressure less than the 10th centile[18] for birth weight despite volume expansion.

Sample analysis

Samples were spun, separated, and frozen at –20°C until batch analysis was performed. We performed biochemical analysis with an Elecsys 1010 System analyser using the Elecsys Troponin T STAT Immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). This electrochemiluminescent sandwich enzyme linked immunosorbent assay has a lower limit of detection of 0.01 ng/ml, with minimal cross reactivity with cardiac troponin I (0.002%) and skeletal troponin T (0.001%).[19] The coefficient of repeatability for paired samples was less than 10%, and the coefficient of variation for precision analysis was 6.4%.

Statistical analysis

In healthy infants, cardiac troponin T concentrations were not normally distributed (fig 1) and therefore medians and interquartile ranges are reported and non-parametric comparisons were made. The relation between cardiac troponin T concentration 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 concentrations and calculated the upper limit in this population (95th centile). Cardiac troponin T concentrations in sick infants were compared with those from our reference group of healthy infants (Mann-Whitney U test).

The sick infants were subdivided into those who required inotropic support and those who did not. We compared the concentrations of cardiac troponin T between these two subgroups. We further divided the group of sick infants who received inotropic support into those who survived and those who died and compared the concentrations of cardiac troponin T between these two subgroups.

We used backward multiple linear regression to investigate which factors from gestation, birth weight, sex, cord acid-base status, mode of delivery, abnormal intrapartum cardiotocograph by computerised assessment, Apgar scores, age at blood sampling, and admission to the neonatal unit independently predicted the cardiac troponin T concentrations.

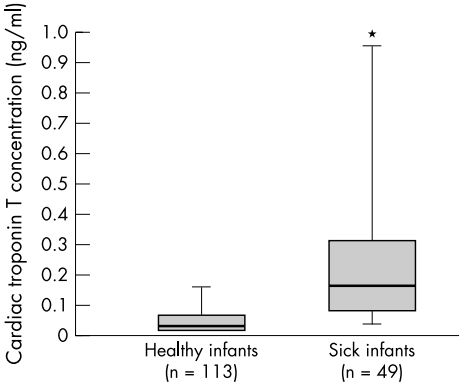

Figure 1 Distribution of postnatal cardiac troponin T concentrations for sick and healthy infants. Whiskers are 5th and 95th centiles. The grey box is the interquartile range, and the dark line in the middle of the grey box is the median value. *p < 0.0001 compared with healthy infants.

Statistical analysis was performed using SPSS for Windows, release 10.0 (SPSS Inc).

RESULTS

Healthy infants

Samples were taken from 113 healthy infants at a median (interquartile range) age of 68 (40–96) hours. Cardiac troponin T was undetectable in 36 infants (32%); they were assigned a value of 0.01 ng/ml. The median (interquartile range) cardiac troponin T concentration in the healthy infants was 0.025 (0.01–0.062) ng/ml. Table 1 gives the basic details for these infants.

Most healthy infants were recruited from the postnatal ward. However, some healthy infants were admitted to the neonatal unit for thermal and nutritional support (but not for cardiorespiratory support), mainly as there were 18 infants born at less than 2000 g and 12 infants of 33 weeks gestation and less in this group overall. The most premature infant born without respiratory distress and therefore included in the healthy group was 29 weeks gestation, and the lightest infant was 1035 g. The 95th centile for cardiac troponin T in healthy infants was 0.153 ng/ml. There were no significant correlations between cardiac troponin T and age at sampling, gestation, birth weight, cord acid-base status, or Apgar scores (table 2). There was no significant difference in concentrations of cardiac troponin T between the sexes, modes of delivery, or abnormal computerised intrapartum cardiotocography results (table 3).

Sick infants

Samples were taken from 49 sick infants at a median (interquartile range) age of 26 (20–43) hours. The sick infants were significantly ($p < 0.0001$) younger at the time of sampling. None of these infants had undetectable concentrations of cardiac troponin T. The median (interquartile range) cardiac troponin T concentration was 0.159 (0.075–0.308) ng/ml. Table 1 also gives the basic and clinical details for the sick infants. All but eight infants had a primary diagnosis of respiratory distress syndrome. The sick infants had significantly ($p < 0.0001$) higher cardiac troponin T concentrations than the healthy infants (fig 1).

Twenty two of the sick infants received inotropic support for hypotension. These hypotensive sick infants had significantly higher cardiac troponin T concentrations than the normotensive sick infants (0.258 (0.163–0.514) *v* 0.105 (0.069–0.174) ng/ml, $p < 0.0001$).

Eleven of the hypotensive sick infants died. The infants who died had higher cardiac troponin T concentrations than the hypotensive sick infants who survived but the difference was not significant (0.410 (0.237–0.600) *v* 0.205 (0.098–0.279) ng/ml, $p = 0.17$).

A linear regression model was constructed using backward stepwise regression to explain the variation in cardiac troponin T for all of the 162 infants studied. Only two variables were retained in the model, the use of inotropes and requirement for supplemental oxygen (table 4).

DISCUSSION

Cardiac troponin T was detectable in many of the healthy infants studied. In the sick infants, the cardiac troponin T concentration was significantly higher, and in those who were hypotensive there was a further significant increase. None of the variables assessed explained this change in cardiac troponin T concentration except for the presence of respiratory distress needing supplemental oxygen and a requirement for inotropes. In particular, cardiac troponin T was independent of all basic variables and postnatal age.

Table 1 Basic and clinical data for healthy and sick infants

Variable	Healthy infants (n = 113)	Sick infants (n = 49)
Gestation (weeks)	38 (35–39)	29 (27–31)
Birth weight (g)	2990 (2380–3560)	1130 (910–1930)
Male	64 (57%)	33 (67%)
Age at time of sampling (hours)	68 (40–96)	26 (20–43)
Apgar at 5 minutes	10 (9–10)	8 (7–9)
Cord pH	7.33 (7.29–7.36)	7.33 (7.24–7.37)
Cord base excess	−3.4 (−5.9 to −1.1)	−3.0 (−6.5 to −1.6)
Delivered by caesarean section	58 (51%)	20 (41%)
Normal intrapartum cardiotocograph	85 (75%)	31 (63%)
Admitted to neonatal unit	20 (18%)	49 (100%)
Total duration of respiratory support (days)	None	5 (2–32)
Number ventilated	None	44 (90%)
Total duration of ventilation (days)	None	3 (1–7)
Use of inotropes	None	22 (45%)
Oxygen requirement at 28 days of age	None	23 (47%)
Died	None	11 (22%)
Cardiac troponin T concentration (ng/ml)	0.025 (0.010–0.062)	0.159 (0.075–0.308)*

Values are median (interquartile range) or number (percentage).
*$p < 0.0001$ compared with healthy infants.

Sick infants

The finding of increased cardiac troponin T in sick infants with respiratory distress may be explained in several ways. Firstly, myocardial injury with cardiac dysfunction may result in impaired gas exchange requiring treatment with supplemental oxygen and/or mechanical ventilation. Alternatively, primary respiratory disease may lead to myocardial injury either directly because of a defect in arterial oxygenation or indirectly through the reduction in cardiac output associated with mechanical ventilation. Finally, respiratory and cardiac compromise may have a common cause such as perinatal asphyxia or sepsis.[20 21]

Cardiac troponin T concentration was higher in hypotensive sick infants receiving inotropic support than in normotensive infants. This finding is in keeping with previous studies that have shown cardiac dysfunction in shocked very low birthweight infants and infants with perinatal asphyxia or profound sepsis.[1–3] As cardiac function was not formally assessed in this study, we can only speculate that a raised cardiac troponin T concentration reflects myocardial injury sufficiently severe to cause myocardial stunning with impaired contractility and low cardiac output. Nevertheless, our observations of raised cardiac troponin T concentrations in sick hypotensive infants receiving inotropes, and the independent association between inotropic treatment and cardiac troponin T both support this view. However, there is a potentially worrying speculation that inotropic support may be the cause of the raised cardiac troponin T concentration. The first line inotrope in this centre is dopamine, a potent vasoconstrictor as well as a positive chronotrope. Coronary artery perfusion is dependent on diastolic pressure and cardiac diastolic time. Although diastolic pressure will rise with a dopamine infusion, it is possible that the vasoconstriction and reduced diastolic time interval could have a synergistically negative effect on the myocardial oxygenation, leading to higher cardiac troponin T concentrations. All the samples were taken once the infants were on dopamine and not before. A study in which samples are taken before and after the start of dopamine may answer this. However, there are no time series data available yet on cardiac troponin T in children. In adults, concentrations start to rise within two hours of the onset of myocardial chest pain. Concentrations peak about 12 hours after this and can remain raised for two weeks after a myocardial infarction, but this is due to cardiac troponin T leaching out of the necrotic myocardium.[8] This is a different mechanism of injury from that seen in neonates, and the rate of clearance of cardiac troponin T from the blood of a neonate is not known.

The sick hypotensive infants who died tended to have higher cardiac troponin T concentrations than the sick hypotensive infants who survived. This difference did not reach significance, but this may well be due to the small sample size. Other poor outcomes such as necrotising enterocolitis and cranial ultrasound abnormalities were not investigated because of their low incidence in this study.

The study by Trevisanuto *et al*[22] also found a significant difference between infants with and without respiratory distress, although the median values of 0.38 ng/ml and 0.13 ng/ml respectively are much higher than those reported here. This may be because of our use of the third generation assay which has minimal cross reactivity with other contractile proteins and it is not affected by renal insufficiency, haemolysis, and icterus, all of which may be common in sick neonates.

Table 2 Correlation coefficients between cardiac troponin T and various variables for the 113 healthy infants

Variable	Spearman's ρ	p Value
Gestation (weeks)	−0.01	0.93
Birth weight (g)	−0.01	0.97
Age (hours)	0.08	0.38
Apgar at 5 minutes	0.12	0.22
Cord pH	−0.12	0.23
Cord base excess	0.02	0.87

Table 3 Comparison of cardiac troponin T concentrations (ng/ml) in the different subgroups within the 113 healthy infants and their p values

Grouping variable	Group	Median	Interquartile range	p Value
Sex	Boy	0.021	0.01–0.047	0.10
	Girl	0.036	0.01–0.086	
Mode of delivery	Vaginal	0.020	0.011–0.059	0.41
	Caesarean	0.026	0.01–0.074	
Normal computerised intrapartum cardiotocograph result	Yes	0.024	0.01–0.065	0.66
	No	0.025	0.01–0.058	
Admitted to neonatal unit	Yes	0.026	0.018–0.048	0.41
	No	0.024	0.01–0.068	

Table 4 Data for all 162 infants entered into backward multiple linear regression with cardiac troponin T as the dependent variable

Variable in multiple linear regression	Partial correlation coefficient	p Value
Gestation (weeks)	0.05	0.52
Birth weight (g)	0.06	0.49
Sex	0.06	0.44
Age at time of sampling (hours)	0.05	0.51
Apgar at 5 minutes	−0.08	0.30
Cord pH	0.03	0.69
Cord base excess	0.08	0.32
Mode of delivery	−0.03	0.76
Intrapartum cardiotocograph	−0.02	0.84
Admission to neonatal unit	−0.02	0.84
Need for respiratory support	0.23*	0.004
Use of inotropes	0.45*	0.0001

*Variables found to be independently significantly related to cardiac troponin T concentration.

Healthy infants

Our cohort of healthy babies encompasses a wider gestational age and birth weight span than other studies published to date.[12 23] Despite this broad pragmatic definition of healthy, cardiac troponin T concentrations seem to be unaffected by the variables that made creatine kinase an unreliable biochemical marker of myocardial ischaemia.[7 8] However, there are very few infants born at less than 29 weeks or 1000 g who do not have some degree of cardiorespiratory insufficiency, and this is a limitation in our study. We must consider the possibility that cardiac troponin T is higher in the more premature infants because of the effect of their lower gestational age. There is no simple answer to this as most extremely preterm infants are sick. However, the only factors associated with increased cardiac troponin T concentrations were the presence of respiratory distress needing supplemental oxygen and a requirement for inotropes and not gestational age. Therefore it does not seem unreasonable to use the reference range from healthy infants for those born more prematurely. In addition, in our study on cord cardiac troponin T concentrations, there was no relation with gestational age.[17]

Another possible concern is the ontogeny of troponins. Bodor *et al*[23] showed expression of cardiac troponin T in fetal skeletal muscle up to 20 weeks of gestation. However, they could not show cardiac troponin T in healthy mature human skeletal muscle by Western blot. We chose to measure cardiac troponin T rather than cardiac troponin I because Sasse *et al*[24] showed that, at 38 weeks gestation, 75% of the troponin I in the human myocardium may be the slow twitch skeletal type. This falls to 50% by about 12 weeks of postnatal age, and by 8 months of postnatal age only cardiac troponin I is expressed in the human myocardium. This underexpression of cardiac troponin I combined with the higher lower limit of detection for this relatively new assay may result in a lack of sensitivity of cardiac troponin I in detecting neonatal myocardial injury.

The concentrations of postnatal cardiac troponin T in healthy infants reported in this study are significantly higher than those from our previous study,[17] in which the median (interquartile range) of cord blood cardiac troponin T in healthy infants was 0.01 (0.01–0.014) ng/ml ($p < 0.0001$, fig 2). The reason for this apparent postnatal rise in cardiac troponin T is not entirely clear nor is its timing. We speculate that the process of birth itself may lead to functional hypoxaemia, and that, despite an apparently uncomplicated delivery, some healthy newborn infants may sustain minimal myocardial injury resulting in a small and probably transient rise in cardiac troponin T. However, the degree of any cardiac dysfunction (if any) is likely to be very mild, without any associated clinical signs or appreciable neonatal morbidity. As healthy newborn infants rarely have repeated blood samples, it is unlikely that a time series for cardiac troponin T will be produced in the same babies. Indeed the most common reason for blood sampling in healthy infants is bilirubin estimation at 3–4 days of age. This partly explains the excess of babies born by operative delivery in this study, as they will still be in hospital with their mothers, whereas babies born by normal vaginal delivery are often discharged much earlier, before the development of jaundice.

Study limitations

It is possible that recruitment bias may have had an effect on the outcomes observed in this study. In the healthy infant group (no oxygen requirement), the vast majority of samples were taken from infants from the postnatal wards who remained in hospital long enough to have a bilirubin concentration check. Therefore, no early discharges were included in this group. However, the assay is unaffected by icteric concentrations up to exchange values,[19] and so this reference range should be reasonably representative. It is more likely that selection bias was present in the sick group of babies. The sicker the baby, the more likely the parents were to be present at any given time, making recruitment more convenient. Also the sicker the baby, the more likely the staff would think about cardiovascular compromise. These infants therefore have multiple blood samples taken, giving more opportunity to enrol them into the study. These factors may have led to the high numbers of infants receiving inotropes recruited to this study.

The definition of sick babies was purposely broad. This was a pragmatic approach, as a baby with an oxygen requirement receives more intensive observation and monitoring. It is also usually the defining characteristic that causes other interventions such as initiation of antibiotics, regular blood gas assessment, etc. Administration of oxygen was started if the arterial saturations in air were below 94%. This is a clearly defined cut off and therefore more generalisable, unlike requirement for ventilation, continuous positive airways pressure, or high frequency oscillation, each of which are used as primary, secondary, or rescue methods of respiratory support depending on which unit or country the baby is born in. However, we recognise that there are multiple pathways to needing supplemental oxygen.[20 21] All but eight babies in

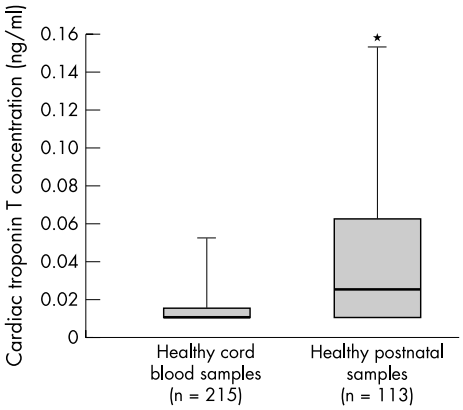

Figure 2 Distribution of cardiac troponin T concentrations for healthy infants with cord blood samples on the left and healthy postnatal samples on the right. Whiskers are 5th and 95th centiles. The grey box is the interquartile range and the dark line in the middle of the grey box is the median value. *$p < 0.0001$ compared with healthy cord blood samples.

the sick group had respiratory distress syndrome as a primary diagnosis.

While this study was under way, publications[13 14] suggested that both maternal tocolytics and pre-eclampsia may raise neonatal troponin concentrations. However, we had not collected data on either of these potentially confounding factors. The study of Narin *et al*[14] on pre-eclampsia found a median cardiac troponin T concentration of 0.1 ng/ml in 17 healthy controls, four times higher than the median value in our healthy infants (who would probably have included some pre-eclamptic mothers). In their study group of 15 babies, the concentrations of cardiac troponin T were 0.7 ng/ml, three times higher than in our hypotensive infants. In the study of Adamacova *et al*,[13] of eight cord blood samples in infants exposed to 72 hours of tocolytics, the concentration of cardiac troponin T was 0.13 ng/ml. The 95th centile from our cord blood study was only 0.05 ng/ml.[17] Adamacova *et al* also studied the effect of haemolysis on the early generation assay.[16] In 10 unhaemolysed samples, concentrations were 0.05 ng/ml compared with 0.19 ng/ml in five haemolysed samples, a fourfold rise. Earlier assays were also known to have higher cross reactivity with contractile components and suffered from interference from renal insufficiency, as well as haemolysis.[19] It is possible that the raised concentrations seen in the above studies were reflections of the earlier assay limitations and their small numbers. However, future studies of cardiac troponin T in neonates need to control for these maternal factors.

There was an association with the requirement for inotropes, but we have no other data on myocardial performance in this study. Future studies of cardiac troponin T in the neonate need to link cardiac troponin T concentrations with myocardial function.

Summary and speculation

We have established concentrations of cardiac troponin T in the blood of postnatal healthy infants. Sick neonates with respiratory distress, especially those requiring inotropic support for hypotension, have raised concentrations of cardiac troponin T. This leads us to speculate that cardiac troponin T may prove to be a useful early marker of cardiac dysfunction in newborn infants. However, myocardial dysfunction needs to be linked with raised cardiac troponin T concentration. If future studies can do this, then measurements of cardiac troponin T may be helpful in the management and assessment of infants with circulatory compromise.

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