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Frequency of Elevations in Markers of Cardiomyocyte Damage in Otherwise Healthy Newborns

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Abstract

Myocardial damage in infancy is a risk factor for eventual cardiac disease. Given that myocardial stress is greatest during the perinatal period and that the neonatal period is when the majority of pediatric heart failure occurs, we sought to determine whether even otherwise healthy neonates might have sub-clinical myocardial damage, and if so, what characteristics might identify them. We assayed umbilical cord and neonatal serum samples from 32 normal neonates for biomarkers of myocardial injury. No neonate had clinical evidence of cardiac or other abnormalities. Serum cardiac troponin T (cTnT) was elevated in 19 of 25 (76%) cords and in 16 of 17 (94%) neonates; levels indicating myocardial infarction (≥ 0.2 ng/mL) were found in 2 patients (1 umbilical cord and 1 neonatal sample). Creatine kinase-MB was elevated in 6 of 16 (38%) cords and in 8 of 15 (53%) neonates. Cardiac troponin I was elevated in 11% and 17% of samples; myoglobin in 4% and 17%; and high-sensitivity C-reactive protein in 9% and 40%. Measures of myocardial injury were associated with longer hospitalization ($r = 0.50$, $P = 0.04$), non-Caucasian race ($P = 0.012$), lower birth weights ($P = 0.014$), positive maternal cervical cultures ($r = 0.41$, $P = 0.046$), and elevated high sensitivity C-reactive protein ($r = 0.66$, $P = 0.005$). In conclusion, clinically occult myocardial injury appears to occur in some healthy newborns, although whether it is pathologic or not remains to be determined.

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Keywords

neonates; cardiac disease; troponin; myoglobin; C-reactive protein; creatine kinase-MB

Myocardial damage in infancy is a risk factor for eventual cardiac disease.^{1,2} Pediatric cTnT levels correlate with myocardial damage and provide prognostic information.^{3,4} Since myocardial stress is greatest during the perinatal period and that neonates have the majority of pediatric heart failure,⁵ in this prospective, exploratory study, we sought to determine whether even otherwise healthy neonates might have sub-clinical myocardial damage, and if so, what characteristics might identify them. We hypothesized a priori, based on prior studies,¹⁻³ that there would be a relationship between measurable cTnT and gestational age, birth weight, Ballard score,⁶ sex, ethnicity, maternal cervical cultures, length of stage 2 labor, type of delivery, Apgar scores, and length of stay.

Methods

The institutional review board of the University of Rochester Medical Center (URMC) approved this study. Parents gave written informed consent. We enrolled a convenience sample of healthy newborns at the URMC between 1999 and 2002. Umbilical cord and neonatal serum samples were obtained as close to 48 hours of age as possible and stored at -70°C . We abstracted perinatal data from maternal and neonatal medical records (Table 1 and Table 2).

Stored sera samples were assayed at an off-site reference laboratory blinded to clinical data. High-sensitivity C-reactive protein (hsCRP) was assayed by the N High Sensitivity CRP assay (Dade Behring). The Elecsys Troponin T STAT test (Roche Diagnostics) was used to assay cTnT. Cardiac troponin I (cTnI) was measured by the Stratus II analyzer (Dade Behring). Creatine kinase MB fraction (CK-MB) was assayed by the ACS:180 CKMB assay (Bayer). Myoglobin was measured using the Myoglobin STAT immunoassay (Roche Diagnostics).

Medians of 2 groups were compared with Wilcoxon rank sum tests. Associations between pairs of continuous variables were assessed with Spearman's correlation coefficients. The C-statistic measured how well 1 marker can discriminate between those neonates who had cTnT measurements above the limit of detection (>0.01 ng/mL) and those who did not.⁷ We report markers with excellent (C-statistic: 0.8–0.9) or outstanding (C-statistic >0.9) discrimination.⁷ Alpha was set at 0.05, all P-values were 2-sided, and SAS version 9.1 was used.

Results

We enrolled 32 clinically healthy, full-term neonates whose size was mostly (91%) appropriate for gestational age and who had normal lengths of hospitalization (Table 1 and Table 2). None had known or suspected cardiac disease, symptoms, or medications; maternal inflammatory events; severe congenital anomalies; reduced intravascular volume; renal dysfunction; postnatal infections; treatment with cardiotoxic medications; or glucocorticoid or thyroid supplementation. There was insufficient blood volume to measure all markers for all neonates. We expect no biases since neonates with and without each marker had similar baseline characteristics (Table 1 and Table 2). Unreported missing data analyses indicated that the data appeared to be a random sample of all data.⁸ Markers were elevated in most cord and neonatal samples (Table 2 and Table 3). Two neonates (1 umbilical cord and 1 neonatal sample) had cTnT levels at acute infarction levels (≥ 0.2 ng/mL).

Neonatal serum cTnT levels had outstanding discrimination (C-statistic = 0.99, 95% CI: 0.93 to 0.99) between fetuses that did and did not have measurable cTnT in their umbilical cord blood. Similarly, neonatal CK-MB had excellent discrimination (C-statistic = 0.83, 95% CI:

0.66 to 0.97) for the presence or absence of elevated umbilical cord cTnT. Umbilical cord blood and neonatal serum myoglobin levels had outstanding discrimination (C-statistic for umbilical cord myoglobin = 0.92, 95% CI: 0.67 to 0.99; C-statistic for neonatal serum myoglobin = 0.91, 95% CI: 0.65 to 0.99) for the presence or absence of neonatal serum cTnT.

Non-Caucasian maternal race was associated with elevated umbilical cord cTnT levels. Neonatal cTnT elevations correlated strongly with neonatal hsCRP and length of hospitalization (Table 3). Umbilical cord blood cTnI, CK-MB, and myoglobin levels were directly correlated to each other and were inversely related to umbilical cord hsCRP levels (Table 3). Using partial correlation coefficients, cTnI confounded the relationships of hsCRP with umbilical cord myoglobin and umbilical cord CK-MB. Controlling for cTnI using partial correlations, hsCRP was no longer significantly associated with umbilical cord myoglobin or CK-MB, indicating that cTnI drives the first three negative associations in Table 3.

At these levels of elevations, umbilical cord cTnT values were not correlated with umbilical cord cTnI, CK-MB, myoglobin or hsCRP values, but they were higher in non-Caucasians (cTnT was not significantly correlated with birth weight, but $P = 0.09$) (Table 4). However, non-Caucasian mothers had newborns with significantly lower birth weights than Caucasian mothers ($P = 0.014$). Elevated neonatal myoglobin, CK-MB, and hsCRP were related to Cesarean-section, female sex, and increased hospital length of stay. Serum cTnT correlated with increased serum hsCRP and lengths of hospitalization (Table 4). When type of delivery was controlled for there was no association between serum cTnT and length of stay ($P = 0.77$), but newborns delivered by Cesarean-section tended to have higher serum cTnT ($P = 0.07$) and longer lengths of stay ($P < .001$).

Discussion

The proportion of neonates with elevated cTnT levels was higher than that in ill infants, children, and adolescents and in healthy adults in the literature,^{2,9} suggesting that myocardial injury, although clinically occult, is common in this young age group. This conclusion is supported by elevations in the other markers of cardiomyocyte injury. It remains unclear whether these increased levels represent normal neonatal values associated with physiologic myocardial remodeling, occult myocardial injury, or both, and whether these may be associated with morbidity.

Evidence of myocardial injury based on cTnT elevations in pediatric populations identifies patients at-risk for subsequent cardiomyopathy years later.^{3,4} These elevated markers have a very high prevalence in newborns, but the incidence of known cardiomyopathy and related diseases in children remains low.⁵ However, cardiomyopathy incidence is more than 10-fold higher in the first year of life than later in childhood.⁵

Other human^{2,10-19} and animal²⁰ studies support the finding that detectable troponin levels are more common in neonates than in older-aged children. In the newly hatched chick, cTnT elevations are frequent, often severe, and identify a population at high risk for eventual cardiomyopathy as part of the broiler ascites syndrome.²⁰ Our finding that elevated serum troponin levels at 48-hours of age were more common and higher in neonatal blood than in umbilical cord blood is consistent with other studies reporting that troponin concentrations peaked during the 2nd to 4th postnatal days.^{2,11-14} This period of elevation of neonatal troponin levels is consistent with peaks observed in older children with anthracycline cardiotoxicity.⁴ These findings are not restricted to a single assay, troponin, or other myocardial injury marker.

These consistent findings suggest that neonatal myocardial injury is a perinatal-related phenomenon. Our C-statistic data support that elevated neonatal serum cTnT levels reflect

events that began in the prenatal maternal and fetal milieu (antenatal-intrapartum origin). Current fetal monitoring may be insufficient to capture prenatal stresses that result in neonatal myocardial injury. Neonatal cTnT values are unlikely to be influenced by maternal levels since cTnT is too large to cross the placenta.² Troponin elevations in our sample did not correlate with gestational age, birth weight, Apgar score, or sex. Others have noted this lack of relationship; it may reflect a limited sample size and that only two of our study patients had Apgar scores under 7.^{11,13–19}

Children with acute myocarditis have higher cTnT levels than do children with dilated cardiomyopathy, a fact supporting our findings of myocardial injury in young children with generalized inflammation.^{21,22} In other studies, the median cTnT level was 0.088 ng/mL (range: 0.04 to 3.11 ng/mL) in children with myocarditis and 0.010 ng/mL (range: 0.010 to 0.990 ng/mL) in children with dilated cardiomyopathy.²¹ The cTnT level used to diagnose acute myocarditis was 0.052 ng/mL, which has a sensitivity of 71% and a specificity of 86%).²² Our study had a median cTnT of 0.080 ng/mL, and we also detected hsCRP values consistent with inflammation. Both of our findings are consistent with the myocarditis data. Our association of elevated cTnT with positive maternal cervical cultures supports a relationship between neonatal myocardial injury and prenatal infection with inflammation.

Non-Caucasian race was associated with increased cTnT and lower birth weights, and in other studies was associated with increased pediatric cardiomyopathy, suggesting genetic susceptibility.⁵ Girls are more likely to develop cardiomyopathy than boys are after equal exposures of the cardiotoxin, doxorubicin.²³ Study girls had greater elevations of myoglobin and CK-MB than did boys, consistent with an increased vulnerability of the female myocardium to injury.

Cesarean-section had major effects on umbilical cord and serum markers in our study and in others.² The relationship between study cTnT and hsCRP elevations suggests that myocardial injury and generalized inflammation are intertwined. We have also observed this relationship in otherwise healthy older children and in children with heart failure where elevated hsCRP levels are associated with increased clinical severity and worsening dilated cardiomyopathy.²⁴ Elevated hsCRP is associated with subsequent clinically important cardiovascular events.²⁴ Elevated hsCRP levels in early pregnancy are associated with increased risk of spontaneous preterm delivery, suggesting that chronic low-grade inflammation raises hsCRP levels, leading to spontaneous preterm delivery.²⁵ Others have described the fetal inflammatory response syndrome where maternal and fetal inflammation are associated with increased neonatal morbidity.²⁶ Inflammation-mediated over-expression of cTnT has been implicated in the development of cardiomyopathy.²

Two study patients had cardiac troponin levels consistent with acute myocardial infarction. Once damage occurs, the loss of cardiomyocytes limits the potential for myocardial growth.²³ The result may be progressive left ventricular systolic and diastolic dysfunction.^{3,4,23} Troponin elevations in children specifically at risk for myocardial injury predict morbidity and mortality later in life.^{1,3,4,23} That relationship may differ in a well or low-risk population.

Differences between significant associations with cTnT and with cTnI may be caused by antibodies that interfere with the cTnI immunoassay, falsely affecting the results.²⁷ Patients with idiopathic dilated and ischemic cardiomyopathy have cTnI autoantibodies,²⁸ and cTnT is measurable in fetal life in pregnancies with signs of fetal chronic hypoxia.²⁹ Fetal myocardial injury could result in interfering cTnI autoantibodies that impair perinatal myocardial injury detection. Different cTnI immunoassays do not necessarily detect the minor cardiac injuries that indicate increased short- and long-term risks for adverse cardiac events.²⁷ Umbilical cTnI does not correlate with 2 validated cardiomyopathy biomarkers, heart rate and NT-proBNP,

supporting that cTnI may not detect myocardial injury in this setting.³⁰ cTnI assays use different antibodies directed to different cTnI domains resulting in up to a 100-fold value variation.² cTnI is not fully expressed within the neonatal myocardium until 9 months of age, limiting its applicability as a neonatal injury marker.² For these reasons, we focused on cTnT but report results for both cTnT and cTnI.

Serum markers are surrogate endpoints and were not compared with endomyocardial biopsy, echocardiograms, or electrocardiograms. However, low cTnT elevations correlate significantly with histologic evidence of myocardial injury but not with echocardiographic measurements in young children because cTnT levels are more sensitive and specific for active myocardial injury than are echocardiographic measurements.⁴ The fact that several markers of myocardial injury were elevated in this study and that other studies report similar elevations supports the conclusion that elevated cTnT levels represent myocardial injury in neonates.

Follow-up of patients like those in this study could determine whether cTnT elevations are related 1) to adaptive responses to birth and its sequelae as part of normal development, with perinatal remodeling and accelerated apoptosis (3 examples are the hemodynamic changes that occur after birth including the sudden exposure to a high resistance system and the loss of the low pressure placental circulation, a coronary artery diastolic steal with a left-to-right shunting from a patent ductus arteriosus, and the pulmonary vascular changes at birth that likely result in right ventricular remodeling);^{2,10} 2) to maladaptive changes from perinatal ischemia resulting in persistent abnormal left ventricular structure and function;^{1,2,5,23} or 3) to cardiomyopathy.^{1,3–5,23}

Our study raises the possibility that clinically occult myocardial injury occurs in healthy newborns without cardiac symptoms. The elevation of myocardial injury markers may represent normal neonatal values related to myocardial remodeling rather than to pathologic myocardial injury. These findings should prompt prospective studies with additional cardiac assessments to identify the true prevalence of sub-clinical myocardial injury in neonates and the long-term clinical implications of such injury.

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Table 1

Demographic and Birth Characteristics of 32 Otherwise Healthy Neonates Assessed Markers of Cardiomyocyte Injury Within 2 Days of Birth

Characteristic	Patients
Male/Female	16 (50%)/16 (50%)
Maternal race or ethnicity	
African American	10 (31%)
Caucasian	12 (38%)
Hispanic	7 (22%)
Other	3 (9%)
Birth weight for gestational age	
Small	1 (3%)
Appropriate	29 (91%)
Large	2 (6%)
Type of birth delivery	
Vaginal	22 (69%)
Cesarean-section	10 (31%)

Table 2

Clinical Characteristics of 32 Otherwise Healthy Neonates Assessed for Markers of Cardiomyocyte Injury within 2 Days of Birth

Characteristic	Neonates, N	Median	Range	Percent abnormal ^I
Birth weight (grams)	32	3405	2555 to 4625	
Gestational age (weeks)	32	39.5	37.4 to 41.7	
One-minute Apgar score	32	20	3 to 9	
3	1 (3%)			
4	1 (3%)			
7	1 (3%)			
8	9 (28%)			
9	20 (63%)			
Days of hospitalization	32	3	2 to 5	
2	4 (12.5%)			
3	17 (53%)			
4	4 (12.5%)			
5	7 (22%)			
Umbilical cord cardiac troponin T (ng/mL)	25	0.03	0 to 0.42	76.0
Neonatal serum cardiac troponin T (ng/mL)	17	0.08	0 to 0.44	94.1
Umbilical cord cardiac troponin I (ng/mL)	18	0.02	0 to 0.19	17.4
Neonatal serum cardiac troponin I (ng/mL)	18	0.05	0 to 0.13	11.1
Umbilical cord creatine kinase-MB (ng/mL)	16	4.54	0.44 to 9.47	37.5
Neonatal serum creatine kinase-MB (ng/mL)	15	5.57	2.25 to 17.35	53.3
Umbilical cord myoglobin (ng/mL)	23	30.15	12.83 to 87.43	4.3
Neonatal serum myoglobin (ng/mL)	18	43.97	13.08 to 169.27	16.7
Umbilical cord high sensitivity C-reactive protein (mg/dL)	22	0.01	0 to 0.06	9.1
Neonatal serum high sensitivity C-reactive protein (mg/dL)	20	0.03	0.01 to 0.22	40.0

^I Abnormal cardiac troponin T = a level > 0.01 ng/mL, abnormal cardiac troponin I = a level > 0.1 ng/mL, abnormal creatine kinase-MB = a level > 5.5 ng/mL, abnormal myoglobin = a level = 83 ng/mL, abnormal his sensitivity C-reactive protein = a level = 0.04 mg/dL.

Table 3
Statistically Significant Correlations between Markers for Cardiomyocyte Injury
and Birth Characteristics in 32 Otherwise Healthy Neonates

Variable 1	Variable 2	N	Spearman's rho	p ¹
Umbilical Cord Blood				
High sensitivity C-reactive protein	Umbilical cord myoglobin	22	−0.56	0.006
High sensitivity C-reactive protein	Umbilical cord cardiac troponin I	22	−0.67	< 0.001
High sensitivity C-reactive protein	Umbilical cord creatine kinase-MB	16	−0.65	0.007
Cardiac troponin I	Umbilical cord myoglobin	23	0.41	0.053
Cardiac troponin I	Umbilical cord creatine kinase-MB	16	0.58	0.019
Cardiac troponin T	Positive cervical culture	24	0.41	0.046
Creatine kinase-MB	Umbilical cord myoglobin	16	0.81	< 0.001
Neonatal Serum				
Myoglobin	Neonatal creatine kinase-MB	15	0.65	0.009
Creatine kinase-MB	Neonatal high sensitivity C-reactive protein	13	0.58	0.040
High sensitivity C-reactive protein	Length of stay	20	0.67	0.001
Cardiac troponin T	Neonatal high sensitivity C-reactive protein	16	0.66	0.005
Cardiac troponin T	Length of stay	17	0.50	0.040
Other Variables				
Birth weight	Gestational age	32	0.51	0.003
Birth weight	Ballard score ²	32	0.50	0.004
Birth weight	Weight for gestational age	32	0.50	0.004
Ballard score ²	Gestational age	32	0.67	< 0.001
Length of stay	Stage 2 labor	30	−0.43	0.019

¹ P-value for the null hypothesis that Spearman's correlation = 0.

² The Ballard score is a valid and accurate gestational assessment tool comprised of multiple assessments of neuromuscular and physical maturity for the entire newborn infant population.⁶

Table 4

Statistically Significant Differences between Categorical Birth Characteristics on Markers for Cardiomyocyte Injury in 32 Otherwise Healthy Neonates

Variable 1	Variable 2	N	Median for Variable 1	p ^I
Umbilical cord cardiac troponin T (ng/mL)	Race = Caucasian	10	0.022	0.012
	Non-Caucasian	15	0.041	
Birth weight (grams)	Race = Caucasian	12	3525	0.014
	Non-Caucasian	20	3165	
Umbilical cord cardiac troponin I (ng/mL)	Cesarean-section = Yes	8	0.04	0.013
	No	15	0.00	
Length of stay (days)	Cesarean-section = Yes	10	5	0.000
	No	22	3	
Neonatal creatine kinase-MB (ng/mL)	Cesarean-section = Yes	5	8.6	0.028
	No	10	4.0	
Neonatal high sensitivity C-reactive protein (mg/dL)	Cesarean-section = Yes	8	0.12	0.002
	No	12	0.01	
Umbilical cord myoglobin (ng/mL)	Cesarean-section = Yes	8	43.8	0.033
	No	15	28.0	
Stage 2 labor (hours)	Cesarean-section = Yes	9	0	0.007
	No	21	30	
Neonatal myoglobin (ng/mL)	Sex = Female	7	52.6	0.048
	Male	11	33.4	
Neonatal creatine kinase-MB (ng/mL)	Sex = Female	5	8.6	0.037
	Male	10	4.04	

^I Wilcoxon P-value for testing of the medians of variable 1 to determine if they are the same in the two levels of variable 2.