Neonate Gender and Gestational Age are Independent Determinants of Cord Blood Troponin I

Yenidoğan Cinsiyeti ve Gebelik Yaşı Kord Kanı Troponin I Seviyesinin Bağımsız Belirleyicileridir

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ABSTRACT Objective: Troponin is an inhibitory protein complex located on the actin flament in all striated muscles. Cardiac Troponin I is found only in the heart and has been used as a sensitive and specific marker of myocardial injury. Our aim was to investigate the different percentile limits and determinants of cord blood cardiac Troponin I (Tn I) concentrations. **Material and Methods:** A total of 378 consecutive healthy neonates were included in the study. Umbilical cord arterial and venous blood samples were obtained at the time of delivery. Concentrations and determinants of cardiac Tn I were analyzed using multivariate analysis, and percentile values were calculated. **Results:** Multivariate analyses showed that gestational age in weeks (B= -0.17, p= 0.02, t= -2.3) and fetal gender (B= -0.11, p=0.03, t= -2.08) were independent determinants of cord blood cardiac Tn I concentrations. The cases were divided into term (≥37 weeks of gestation) and pretem (<37 weeks of gestation) subgroups for the ease of clinical evaluation. The demographic variables of mothers of term and preterm infants were similar (p> 0.05) except for gestational age (p< 0.01). Mothers of preterm cases had significantly more frequent tocolytic therapy, early rupture of membranes, hypertension and cesarean delivery (p< 0.01). Term infants had more frequent labor induction and labor augmentation (p< 0.01). The 99th percentile limits of cardiac Tn I were 3.8 ng/ml in male (n= 47) and 0.8 ng/ml in female (n= 32) for pre-terms. In term neonates, these values were 2.7 ng/ml in males (n= 166) and 3.1 ng/ml in females (n= 133). **Conclusion:** This study reports the different cardiac Tn I percentile limits in a neonatal population. Our results suggested that the upper reference limits for cardiac Tn I may vary according to gestational age and gender.

Key Words: Troponin I; fetal blood; gender identity; epidemiologic factors

ÖZET Amaç: Troponin tüm çizgili kasların aktin iğciği üzerinde bulunan engelleyici bir proteindir. Kalp kaynaklı Troponin I (Tn I) sadece kalpte bulunur ve kalp kası hasarının duyarlı ve özgül bir belirteci olarak kullanılmıştır. Çalışmamızın amacı göbek bağı kanında kalp kaynaklı troponin I seviyesinin belirleyicilerini araştırmak ve persentillerini belirlemektir. **Gereç ve Yöntemler:** Sağlıklı oldukları kanıtlanmış 378 ardışık yenidoğan çalışmaya alındı. Doğum sırasında göbek bağı kanından arterial ve venöz kan örnekleri alındı. Göbek bağı kanı kalp kaynaklı Tn I konsantrasyonları, belirleyicileri analiz edildi ve persentil değerleri hesaplandı. **Bulgular:** Çok değişkenli analizde gebelik haftasının (B= -0.17, p= 0.02, t= -2.3) ve yenidoğan cinsiyetinin (B= -0.11, p= 0.03, t= -2.08) göbek bağı kanında kalp kaynaklı TnI değerlerinin bağımsız belirleyicileri olduğu bulundu. Olgular pratik klinik değerlendirme için preterm (<37. haftalık gebelik) ve term (≥37 haftalık gebelik) olarak ayrıldı. Preterm ve term bebek annelerinin demografik verileri benzerdi (p> 0.05) ancak gebelik yaşı iki grup arasında anlamlı olarak farklıydı (p< 0.001). Preterm yenidoğan annelerinin doğum sırasındaki özellikleri term yenidoğan anneleri ile karşılaştırıldığında preterm anneleri anlamlı olarak daha fazla tokolitik tedavi almış, daha fazla erken membran rüptürüne sahip, daha fazla hipertansiyonu olan ve daha fazla sezaryen ile doğum yapmış kişilerdi (p< 0.01). Term bebek anneleri ise daha fazla doğum indüksiyon ve augmentasyonu almıştı (p< 0.01). Pretermlerde kalp kaynaklı Tn I'nın 99. persentilleri erkeklerde (n= 47) 3.8 ng/ml, kızlarda (n= 33) 0.8 ng/ml idi. Yine kalp kaynaklı Tn I'nın 99. persentil değerleri term yenidoğan kord kanında erkeklerde (n= 166) 2.7 ng/ml ve kızlarda (n= 133) 3.1 ng/ml idi. **Sonuç:** Bu çalışma yenidoğan topluluğunda farklı kord Tn I persentillerini bildirmektedir. Çalışmamızın sonucunda kalp kaynaklı Tn I seviyelerinin gebelik yaşı ve yenidoğan cisiyetine göre değişebildiğini gösterdik.

Anahtar Kelimeler: Troponin I; fetal kan; cinsiyet kimliği; epidemiyolojik etkenler

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Ischemia and myocardial necrosis are often related to perinatal hypoxia and associated with adverse outcomes in the neonatal period.[1-4] In vitro studies showed that prolonged prenatal hypoxia can cause myocardial infarction (MI) and a persistent decrease in postischemic recovery of left ventricular function.[5,6] Measurements of cardiac enzymes and cardiac specific proteins represent a definite advance in the diagnosis of myocardial damage in the adult population. One of the definitive criteria of MI in adults is increased cardiac enzyme and protein levels above the 99th percentile reference limits.[7,8] However, biochemical markers especially cardiac proteins have not been used routinely in neonates and children for the diagnosis of MI. Moreover, the upper reference limits of these specific markers in the neonatal population have not been definitely clarified.

Troponin is an inhibitory protein complex located on the actin flament in all striated muscles and consists of three subunits as T, C, and I. Cardiac troponin I is the subunit that inhibits actomyosin ATPase activity, preventing muscle contraction in the absence of Ca^{+2} in the human myocardium and released into the bloodstream after myocardial damage. For this reason, cardiac Troponin I has been used as a sensitive and specific marker of myocardial injury.[9,10]

A number of investigators including our group have used cardiac troponins to detect myocardial damage in neonates under various pathological conditions.[11-21] However, in most of these studies, different cut-off values of cardiac Troponin I were determined for prediction of pathological situations. As these cut-off values are affected by the number of cases with pathological conditions, they may not reflect the normal population values or may not coincide with 95th and 99th percentiles of the general population. Moreover, a normal reference limit of cardiac Troponin I assay in neonates has still not yet been established by the American National Committee for Clinical and Laboratory Standarts procedures.[22] In addition, relatively few studies investigated the upper reference limits, especially the 99th percentile values of cardiac Troponin I in healthy neonates.[23-27] The aim of this study is to examine the different percentile limits, especially the 99th percentile values of cord blood cardiac Troponin I, in healthy term and preterm neonates and to investigate the major determinants of cardiac Troponin I levels.

MATERIAL AND METHODS

PATIENTS

The study was performed between February 2004 and February 2007 in Kocaeli University, Department of Obstetrics and Gynecology. A total of 446 consecutive pregnancies gestational ages confirmed according to the date of the last menstrual period or the first trimester ultrasonographic examination were enrolled in the study. Cord arterial blood samples were collected immediately at delivery for blood gas analysis, and cord venous blood samples were collected for Troponin I and cardiac-specific creatine kinase (CK-MB) assays after cord clamping prior to placental separation. Among these, newborns with evidence of congenital infection or sepsis, fetal distress, intrauterine growth restriction (≤5th percentile of growth), intrauterine hypoxia, and icteric, lipemic or hemolyzed serum were not included to the study (n=47). Intrauterine hypoxia was determined as the cord arterial blood pH<7, base excess <-8 and presence of hypoxic ischemic encephalopathy. Additionally, newborns with major congenital anomalies (n= 13) and eight cases of early neonatal deaths were excluded from the study. All newborns were examined by a pediatrician immediately after birth and the healthy neonates were defined as newborns that survive the early neonatal period without the need for resuscitation or intensive care unit admission, staying by their mothers with normal oral feeding. The neonates born to women that had high risk pregnancies were included in the study only if they had normal blood glucose, calcium and C-reactive protein levels. In case of early rupture of the membranes, neonates with normal C-reactive protein, without evidence of microbial pathogen in blood cultures and without leucocyte in the gastric aspirates were included in the study. For the final analysis, 378 healthy term (37 to 42 weeks of gestation, n=299) and preterm newborns (≥30, <37

weeks, n= 79), constituted the study population. The study was approved by the local ethics committee according to Helsinki declaration on human studies, and all parents gave their written informed consent to participate in the study.

LABORATORY ANALYSIS

Cardiac troponin I (TnI) levels were analyzed in 3 ml aliquot from arterial cord blood samples with an AxSYM System analyzer using the second generation Abbott cardiac Troponin I microparticle enzyme immunoassay (Abbott Park, IL. USA). For this assay, the within-run coefficient of variation (CV) was 6.6%, and the manufacturer claims minimal cross-reactivity with cardiac troponin C (0.01%), cardiac troponin T (0.34%), and skeletal troponin I (0.04%) at a concentration of 1000 ng/ml. The lower limit of detection for cardiac Troponin I in this assay was 0.1 ng/mL.

STATISTICAL ANALYSIS

SPSS 11.5 statistical software package program was used for statistical analysis of the study. The percentile values of cord blood cardiac Troponin I were classified according to the variables which were found to predict their levels according to the multivariate linear regression analysis using backward method. Variables evaluated in the model were the presence or absence of tocolytic theraphy (ritodrine and magnesium), intrauterine growth restriction (6 to 10th growth percentile), early rupture of the membranes, maternal age, maternal body mass index, mode of delivery, maternal preeclampsia and hypertension, gestational age in weeks, fetal weight, male or female fetal gender. In the multivariate linear regression model, male fetal gender (B= -0.11, p= 0.03, t= -2.08) and gestational age in weeks (B= -0.17, p= 0.02, t= -2.3) were independent predictors of increased cardiac Troponin I levels and the percentile values of cardiac Troponin I were categorized consistent with these two variables.

RESULTS

Baseline clinical characteristics of the mothers of 378 healthy term and preterm neonates and intrapartum variables are shown in Table 1 and Table 2. Maternal age, nulliparity, body mass index, education status, anemia and prevalence of maternal systemic disease were similar in the two groups. Tobacco use was significantly more frequent among mothers of preterm neonates (p=0.01, Table 1).

Induction of labor using misoprostol and oxytocin augmentation of labor was more frequent among term pregnancies compared to preterm deliveries (p= 0.003 and p< 0.001 respectively, Table 2). On the other hand, tocolytic therapy (p< 0.001), hypertension (p= 0.003), early rupture of the membranes (p< 0.001) and Cesarean delivery (p< 0.001) were more frequent in preterm deliveries compared to term deliveries (Table 2).

The mean gestational age of preterm females was similar to the gestational age of preterm males. (34.6 ± 2.4 weeks versus 34.6 ± 1.9 weeks, p= 0.9). Table 3 reports the different percentile values of

TABLE 1: Demographic characteristics of the pregnant women in the study population (n= 378). The values are presented as mean ± standart deviation or numbers and percentages.

Risk factor	Mothers of Preterms (n=79)	Mothers of Terms (n=299)	p
Age (years)	27.2 ± 5.7	28.8 ± 5	0.1
Gestational age (weeks)	34.7 ± 2	39 ± 1	<0.001
Nulliparity (%)	43 (54.4)	139 (46.5)	0.2
Body mass index (kg/m^2)	27.2 ± 5.2	28.2 ± 4.2	0.3
Tobacco use (%)	16 (20.2)	31 (10.3)	0.01
Education >8 years (%)	29 (36.7)	106 (35.4)	0.8
Anemia (%)	10 (12.7)	23 (7.7)	0.1
Systemic disease* (%)	7 (8.8)	25 (8.3)	0.8

* Includes maternal cardiac and pulmonary disease, thyroid disease, epilepsy, cirrhosis of the liver, chronic renal failure and ulcerative colitis.

TABLE 2: Intra-partum variables of the mothers of healty term and preterm neonates (n=378). The values are presented as mean ± standart deviation or numbers and percentages.

Variable	Mothers of Preterms (n=79)	Mothers of Terms (n=299)	p
Tocolytic ritodrine therapy	16 (20.2)	3 (1)	<0.001*
Misoprostol induction	7 (8.9)	72 (24.1)	0.003*
Oxytocin induction	2 (2.5)	7 (2.3)	0.9
Oxytocin augmentation	26 (32.9)	180 (60.2)	<0.001*
Diabetes mellitus	8 (10.2)	25 (8.4)	0.6
Hypertension	9 (11.3)	10 (3.3)	0.003*
Intrauterine growth restriction (6-10th growth percentile)	8 (10.1)	22 (7.4)	0.4
Oligohydramnios	12 (15.2)	33 (11)	0.3
Polyhydramnios	3 (3.8)	10 (3.3)	0.8
Early rupture of the membranes	22 (27.8)	30 (10)	<0.001*
Meconium stained amniotic fluid	4 (5.1)	27 (9)	0.2
Epidural anesthesia	3 (3.8)	26 (8.7)	0.1
Cesarean delivery	45 (57)	95 (31.8)	<0.001*

* Statistically significant (p<0.05), chi-square test.

cardiac Troponin I in the study population. The 99th percentile value of cardiac Troponin I was 3.8 ng/ml in male and 0.8 ng/ml in female preterm neonates (Table 3). However, this value was 3.1 ng/ml in term female neonates and 2.7 ng/ml in term male newborns (Table 3). The histogram of cord blood cardiac Troponin I values in 378 newborns is presented in Figure 1.

TABLE 3: Different percentile values of cardiac Troponin I in the healthy term and preterm neonates.

Percentile	Preterm		Term	
	Female (n= 32)	Male (n= 47)	Female (n= 133)	Male (n= 166)
5th	0	0	0	0
10th	0	0	0	0
25th	0	0	0	0
50th	0	0.3	0	0
75th	0.2	0.9	0.6	0.6
90th	0.47	2.2	1.1	1.23
95th	0.67	3.1	1.6	1.83
99th	0.80	3.8	3.1	2.7

DISCUSSION

The present study demonstrated different percentile values of cord blood cardiac Troponin I in a neonatal population including healthy term and preterm newborns. Level of cardiac Troponin I was strongly associated with gestational age in weeks and fetal gender.

The first studies investigated reference ranges of cardiac Troponin I levels in a non-adult population was conducted by Hirsch et al. in 1997 and Soldin et al. in 1999.[23,28] Although these studies were performed in heterogeneous populations including children, two distinct results appeared. Hirsch et al. underlined that cardiac Troponin I values were generally not elevated in children with stable cardiac disease.[28] Nevertheless, Soldin et al. reported a new and exciting data: Cardiac Troponin I values were higher during the first year of life.[23] Simultaneously, Quivers et al. underlined the effect of gestational age, birth weight and disease on cardiac Troponin I levels.[29] They found that cardiac Troponin I fractions were greatest in the preterm infants, decreased with increasing gestational age and birth weight.[29] Both Soldin et al. and Quivers et al. speculated that apoptosis which could occur after birth and to a greater degree in the preterm infant might be a possible explanation for the elevated cardiac Troponin I in this age range.[23,29] After these first observations, a brief communication about the cardiac Troponin I levels in

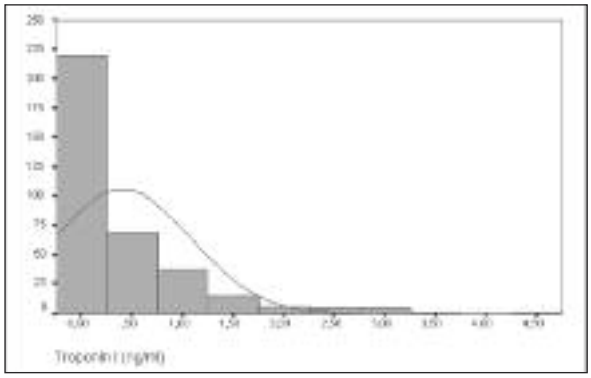

FIGURE 1: Histogram of cord blood cardiac Troponin I values in 378 healthy newborns.

umblical cord blood was reported by Engin et al.[24] They found increased cardiac Troponin I levels in hypertensive disorders and preterm deliveries. However, their study population consisted of non-healthy neonates.[24] Fleming et al. investigated cardiac Troponin I levels in umbilical artery blood in relation to fetal heart rate abnormalities and reported low cardiac Troponin I concentrations in 16 healthy term newborns.[30] Similarly, Trevisanuto et al. found low cardiac Troponin I concentrations in the cord blood of 90 healthy term neonates.[31]

During these observations, one of the other interests about cardiac biomarkers in the neonatal period was emerged regarding the relation between cord blood troponin level and poor outcome. Several investigators including our group studied cord blood cardiac Troponin I as a prognostic or predictive marker under various pathological conditions.[11-16] However suggesting an upper limit for the reference interval of cardiac Troponin I was seemed essential especially for the interpretation of these measurements in sick newborns. Unfortunately, relatively few studies investigated the upper reference limits, especially the 99th percentile values of cardiac Troponin I in healthy neonates.[25-27] Araujo et al. reported plasma cardiac Troponin I concentrations and different percentile limits in 206 healthy newborns.[26] The investigators found that plasma cardiac Troponin I levels were higher in newborns compared to adults. One important finding of their study was lower concentrations of cardiac Troponin I in newborns in the first 48 hours of life than those found 48 hours later.[26] The most important and the largest study on the reference values for cord blood cardiac Troponin I in healthy neonates was performed by Baum et al.[27] Compared to the adult values, the newborn upper limit for cardiac Troponin I was double in cord blood of 869 healthy newborns. The investigators especially underlined that higher reference values for cardiac troponins in neonates do not seem to be restricted to one single assay of troponin, but instead may represent a neonate-related phenomenon.[27] Similar to Soldin et al. and Quivers et al., they explained this elevation by apoptosis. Finally, they concluded that for clinical purposes, it is necessary to establish reference values for neonates for each single troponin assay.[23,27,29]

Similar to the results of Baum et al.,[25] we found higher reference values by using a different troponin assay in healthy neonates. However, our study has some important differences. First, their study included only healthy term neonates. Nevertheless, we found significant differences for the different percentile limits of cardiac Troponin I in terms and pre-terms. Second, we used multivariate analysis to investigate the parameters which could affect the levels of cardiac Troponin I. Baum et al. only used *t* test and found no significant differences for cardiac Troponin I levels in males and females.[25] However, we found statistically significant differences between the values of males and females. Moreover, gender was appeared as one of the important determinants of cardiac Troponin I levels in our multivariate analyses. Third, their study population characteristics only included the type of delivery, birth weight and height. However, a large demographic characteristics and intra-partum variables which could affect levels of cardiac Troponin I levels were employed in the present study.

The most important finding of the present study is on the results of the multivariate analysis for the determinants of cord blood cardiac Troponin I levels. Both fetal gender and gestational age were the strongest determinants of cord blood cardiac Troponin I concentrations. Quivers et al. were the first who reported the effect of gestational age on cardiac Troponin I levels. In their small neonatal group (12 premature infants, gestational age <37

weeks and 6 term infants), comparison of cardiac Troponin I levels between preterms and terms showed that higher levels of cardiac Troponin I was observed in preterms and the value decreased with increasing gestational age.[29] This situation was also observed in the study of Araujo et al.[26] Our findings confirmed this result in a larger population. These findings suggested the same and the most favored opinion of other investigators that the higher cardiac Troponin I levels during the first months of life may be a sign of apoptosis. It is well known that myocardial apoptosis is a part of normal fetal and postnatal maturation.[32] It has also been shown that neonatal myocardium is more vulnerable to myocardial apoptosis than mature myocardium after various stimuli.[32,33] Chandrashekhar et al. showed that caspase inhibition reduced myocardial caspase 3 activation, and this was accompanied by less cleavage of troponin-I and fewer apoptotic cardiomyocytes.[34] All these observations suggested that the apoptotic process of preterm human myocardium can lead to elevation of cardiac Troponin I levels. Thus, gestational age in weeks and different reference limits of cardiac Troponin I especially in the preterm period should be taken into account during interpretation of cardiac Troponin I levels in neonates.

The other determinant of cord blood cardiac Troponin I levels in the study population was gender. In the study of Baum et al., the investigators found a statistically significant difference for cardiac troponin T levels in males and females. However, a significant difference for cardiac Troponin I was only found between natural childbirth and Caesarean section.[25] A recent study of Clerico et al. showed that cut-off values, based on the 99th percentile of cardiac Troponin I distribution in apparently healthy adults, can significantly vary according to age and gender of the reference population.[35] Our results also demonstrated this important point in a neonatal population.[35] Gender was found to be affecting normal reference limits of cardiomyocyte damage both in the adult and newborn populations.[25,35,36] Myocardial apoptosis is an important component of fetal and postnatal heart maturation. Neonatal myocard was shown to be more sensitive than adult myocard to external stimuli that induced apoptozis.[37] Some investigators claimed that healthy term female newborns have higher levels of markers of myocardial damage which might either be due to more subclinical myocardial damage in the female population or higher levels of cathecolamines in the pretem female newborns that increased their survival rate.[36,38] Moreover, gender was found as the most important independent determinant of myocardial apoptozis in human.[38] This difference was also evidenced by the different survival rates of female and male pediatric population in different cardiovascular diseases and this shows differential effect of sex steroids on myocardial gene co-activator and co-repressors and posttranslational modifications.[40,41]

In conclusion, the present study reports different percentile limits and independent determinants of cardiac Troponin I in a neonatal population including healthy preterm and term newborns. Our results suggested that the upper reference limits for cardiac Troponin I in healthy neonates may vary according to gestational age in weeks and gender. Further studies are required to confirm these results.

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