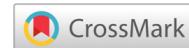


Research Article

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Correlation of cord blood cardiac troponin-t to echocardiographic and tissue doppler variables in infants of diabetics mothers with and without hypertrophic cardiomyopathy

Abstract

Objective: The objective was to evaluate the value of cord blood cardiac troponin-T levels and tissue Doppler echocardiography in evaluation of hypertrophic cardiomyopathy in infants of diabetic mothers.

Methods: A prospective study involved 60 infants of diabetic mothers and 60 healthy neonates.

Cord blood level of cardiac troponin-T was measured and conventional and tissue Doppler echocardiographies were performed for all infants.

Results: Hypertrophic cardiomyopathy was present in 19 cases (31.6%) of infants of diabetic mothers. There were significant increase in the cord blood cardiac troponin-T levels ($P<0.0001$) and more significant systolic and diastolic dysfunction in infants of diabetic mothers than in control group. Infants of diabetic mothers with hypertrophic cardiomyopathy had significant increase in the cord blood cardiac troponin-T levels ($P<0.0001$) and more significant systolic and diastolic dysfunction than infants of diabetic mothers without hypertrophic cardiomyopathy. There was no significant correlation between infant's birth weight and cord blood cardiac troponin-T levels while there was significant correlation between maternal glycosylated hemoglobin and cord blood levels of cardiac troponin-T. There were significant negative correlation between cord blood levels of cardiac troponin-T and E/A ratio at mitral valve, E'/A' ratio and S wave at mitral annulus, E/A ratio tricuspid valve, E'/A' ratio and S wave at tricuspid annulus. There were positive correlations between cord blood cardiac troponin-T levels with septal/posterior wall, and Tie indices.

Conclusion: cardiac troponin-T was a useful marker especially when combined with tissue Doppler echocardiography for evaluation of hypertrophic cardiomyopathy in infants of diabetic mothers.

Keywords: infants of diabetic mothers, hypertrophic cardiomyopathy, tissue Doppler, cardiac troponin-t, cord blood, echocardiography

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Introduction

Diabetes effects start in utero and affect neonates, infants, children and adolescent. Gestational diabetes may have overwhelming effects on the embryonic heart as well as the infants born to diabetic mothers. The neonates and infants suffering this metabolic disease may have considerable cardiovascular effects.¹ Hypertrophic cardiomyopathy is a well known condition observed in infants of diabetic mothers and described for the first time in a stillborn infant of a diabetic mother by Maron et al. 1978.² It occurred in about 30-40% of them. However, clinically manifest hypertrophic cardiomyopathy is present in 12% of cases with severity varies from an incidental finding on echocardiography to an infant with severe symptoms of congestive heart failure. Fatal cases of hypertrophic cardiomyopathy may occur in any infant of a diabetic mother.³ It characterized by stiff, hypertrophied ventricular muscle, predominant thickening of the ventricular septum, impaired relaxation, and powerful but uncoordinated contraction. Functional subaortic obstruction may occur in severe cases (idiopathic hypertrophic subaortic stenosis).⁴ The exact mechanism of hypertrophic cardiomyopathy in infants of

diabetic mothers is clear but it is suggested that fetal hyperinsulinism may trigger hyperplasia and hypertrophy of myocardial cells by increasing fat and protein synthesis.⁵ Natural history of infant of diabetic mother related-hypertrophic cardiomyopathy appeared to be benign, with a resolution of symptoms within 2-4 weeks and a resolution of septal hypertrophy within 2-12 months.⁶

Color flow Doppler echocardiography is effective diagnostic tool for the diagnosis of hypertrophic cardiomyopathy as it allows easy detection, and follow-up of its progression.^{7,8} Tissue Doppler is sensitive in detecting diastolic dysfunction allowing early diagnosis of hypertrophic cardiomyopathy.^{9,10}

Cardiac troponins are intracellular 3-unit complex contractile-regulating proteins of the cardiac muscle (troponin I, T and C) which are essential for the calcium-mediated regulation of the cardiac muscle contraction. Cardiac troponins in blood are the most preferred marker of myocardial damage as it is released into circulation following ischemic cardiac injury giving it a high level of clinical sensitivity and specificity even when cardiac lesions are small.^{11,12} Previous studies showed that elevated cardiac troponin-T levels of umbilical cord

blood may be associated with intrauterine hypoxia.¹³ It has been used as a useful diagnostic tool in the assessment of several diseases in children, term and preterm neonates, including myocarditis, Kawasaki disease, asphyxia, and congenital heart disease; and could work as a useful biomarker for cardiac insult.^{14,15} However; its significance as a cardiac biomarker in neonates is still unclear. Therefore, the purpose of this study was to compare cardiac troponin-T levels of postnatal umbilical cord blood in infants of diabetic mothers with and without hypertrophic cardiomyopathy and to relate cardiac troponin-T levels with echocardiographic variables.

Subjects and methods

The study was conducted as a prospective case-control analysis of 60 consecutive full-term infants of diabetic mothers, who were followed in the obstetrics and Gynecology Department, International Hospital of Bahrain; from June, 2009 to November, 2013. An age- and sex-matched cohort of 60 healthy full-term newborn was studied as a control group. Matching was done as a group matching and not as a case to case matching. Inclusion criteria included: full term infant of confirmed diabetic mothers. Exclusion criteria included: preterm neonates (less than 37 weeks), neonates with intra-uterine growth retardation (IUGR), presence of any cardiac malformation other than HCM, and neonates with major systemic disorder that could affect troponin-T level including: neonatal asphyxia, congenital heart disease, central nervous system anomalies, pulmonary anomalies, or neonatal sepsis. Maternal use of medications other than tonics and insulin therapy during the last 3 months of pregnancy was also an exclusion criterion. All the pregnant mothers had glycosylated hemoglobin % during the last month of pregnancy. Glycosylated hemoglobin% was used as an indicator of the long term integrated blood glucose control among diabetic pregnant mothers. Babies of mothers with glycosylated hemoglobin not done in the last month prior to delivery were excluded from the study. A well trained neonatologist attended all deliveries where neonatal resuscitation was done when needed and APGAR scoring at 1 and 5 minutes was calculated. Approximately 5 ml of umbilical cord blood was obtained for cardiac troponin-T measurement.

Full history taking including gestational age, maternal name and age, type of maternal diabetes, type of delivery, and maternal blood glucose level were taken. All infants underwent a thorough clinical examination by pediatric neonatologist and pediatric cardiologist with special attention to cardiovascular system. Serial blood glucose levels were done in the first day of life and until the infants' blood sugar becomes stable with normal feedings. After physical examination, both conventional and tissue Doppler echocardiography were performed for all cases. To avoid intra-observer variability, two examinations were performed by the same operator for each patient within 2 days and we considered the average results. Serial follow up conventional and tissue Doppler echocardiography were done at 1, 3, 6 months for evaluation of hypertrophic cardiomyopathy. The study was approved by the Institutional Ethical and Research Review Board of International Hospital of Bahrain. All the parents of the included newborns signed a written informed consent before enrolment into the study.

Troponin-T measurement

Cord blood was collected and samples were spun, separated, and frozen at -20°C until batch analysis was performed. We performed biochemical analysis with highly sensitive, fifth-generation troponin-T assay, using the Elecsys 2010 analyzer (Roche Diagnostics

GmbH, Mannheim, Germany). The high-sensitivity assay has a limit of detection of 0.003 µg/L, and 99th percentile upper reference limit of 0.016 µg/L as recently described.

Conventional echocardiography

Echocardiographic examination was done using (Vingmed Vivid-7, General Electric Vingmed, and Milwaukee, Wisconsin, USA). Data acquisition was performed with a S7 probe at a depth of 16 cm in all the standard echocardiographic views according to the recommendation of the American Society of Echocardiography.¹⁶ All neonates were examined while they were lying quietly in the right anterior oblique position breathing room air. Cardiovascular malformations including patent ductus arteriosus were carefully searched by all standard views. M-mode and two-dimensional images obtained and stored in cine loop format from 3 consecutive beats. M-mode and two-dimensional echocardiography-to assess left ventricle internal dimensions including left ventricle end-diastolic dimension, left ventricle endsystolic dimension, ventricular septal thickness, posterior wall thickness, and fractional shortening- were done from the parasternal and apical views. The ejection fraction was measured by Teichholz formula based on short axis measurements of left ventricle inner diameter by M-mode.¹⁷ The left ventricle end-diastolic and end-systolic volumes were measured from the M Mode. The left ventricle volume was derived from "cubed equation" (i.e. volume=D³ where D is the ventricular dimension measured by M-Mode). Pulmonary arterial flow was recorded with pulsed-wave Doppler, placing the sample volume centrally between the leaflets of the pulmonary valve in a short-axis view at the base of the heart. Systolic pulmonary artery pressure was measured when tricuspid regurgitation was present. The left ventricle and right ventricle diastolic functions were evaluated by the mitral and tricuspid inflow pattern obtained by pulsed-wave Doppler echocardiography. The mitral and tricuspid Doppler signals were recorded in the apical four-chamber view, with the Doppler sample volume placed at the tip of the mitral or tricuspid valve. Tricuspid regurgitation flow was determined by a continuous wave Doppler method from the apical four-chamber view.¹⁸ Tei index, which is a Doppler-derived time interval index that combines both systolic and diastolic cardiac performance, was also calculated as previously described by Tei and colleagues.¹⁹ Hypertrophic cardiomyopathy was diagnosed when the absolute values of inter ventricular septum and left ventricular posterior wall diameters were above normal ranges, and in addition, the ratio of left ventricular septum in diastole to the left ventricular posterior wall in diastole exceeded 1.3.²⁰

Tissue doppler imaging

Tissue Doppler imaging was performed using the same machine and probe at a depth of 16 cm in the parasternal and apical views (standard long-axis and two-and four-chamber images). Using pulsed-wave angle-corrected color-coded tissue Doppler filters, the baseline was adjusted to a low velocity range (-20 to 20 centimeters/second) and Doppler frame rates were varied between 80 and 115 frames/second depending on the sector width of the range of interest with minimal gain setting to minimize background noise and to obtain the highest quality images. A two mm sample volume was placed within the myocardium equidistant from the endocardial and epicardial borders. From the apical four-chamber planes, using pulsed-wave tissue Doppler, the myocardial velocity curves of septal mitral valve annulus, lateral mitral valve annulus, and lateral tricuspid valve annulus were recorded. The electrocardiogram and respiration curve monitoring were connected and traced simultaneously to define the

timing of cardiac cycle events and its relation to respiratory events. The beginning of QRS complex was used as a reference point.²¹ At least 10 cardiac cycles were recorded at a speed of 100 millimeters/second and the images were stored electronically.²² The mean values for three heart beats during expiration were used for the analysis. The systolic wave (S) reflects the systolic function of either right or left ventricle. The early/atrial (E'/A') ratio of tricuspid and mitral valve annulus reflects the diastolic function of the right and left ventricle, respectively. Isometric contraction time was defined as the time duration between the beginnings of QRS complex in the electrocardiogram to the beginning of tissue Doppler S wave. The isometric relaxation time was defined as the interval between the end of S wave and the beginning of the early wave. Both isometric contraction time and isometric relaxation time were corrected for heart rate.²³

Statistics

The statistical power of the study was more than 90% (using a computerized program: Power and Precision V3; www.PowerAnalysis.com). Data are presented as mean (\pm standard deviation) values. The two-way analysis of variance with repeated measures and chi-square test by SPSS V.16 were used to identify statistically significant differences in the different parameters among the groups. For all analyses, a statistical significance of P-value less than 0.05 was used. Wilcoxon's signed-rank test was used to assess the normality of distributions of the data. The Bonferroni correction/adjustment procedure was performed to avoid "significance" due to chance only, in multiple comparisons with echocardiographic parameters. Correlation between cardiac troponin-T and echocardiographic variables was evaluated using Pearson's correlation coefficient.

Results

(Figure 1) showed the flow chart of the study that included 60 infants of diabetic mothers and 60 healthy neonates as a control group. Among the infants of diabetic mothers, there were 19

infants with confirmed hypertrophic cardiomyopathy but without left ventricular outlet obstruction (31.7%) and 41 infants without hypertrophic cardiomyopathy (68.3%). Hypertrophic cardiomyopathy was resolved in 12 (63%), 15 (79%) out of 19 cases on repeated echocardiography at 1 and 3 months respectively and no cases of hypertrophic cardiomyopathy was detected at 6 months. (Table 1) showed the demographic data and clinical features of both patients and control group. It showed no significant difference as regard to maternal age (P=0.2) and male/female ratio (P=0.2) in both infants of diabetic mothers and control groups. However; the maternal glycosylated hemoglobin % (P<0.0001), the rate of caesarean section (P= 0.037), neonatal birth weight (P<0.0001), and cord cardiac troponin T (P<0.0001) were significantly higher while gestational age (P<0.0001), APGAR score at 1 and 5 minutes (P<0.0001 and P=0.002 respectively), and cord pH (<0.0001) were significantly lower in in infants of diabetic mothers than non-diabetic mothers. The table also showed the frequency of complication in both groups.

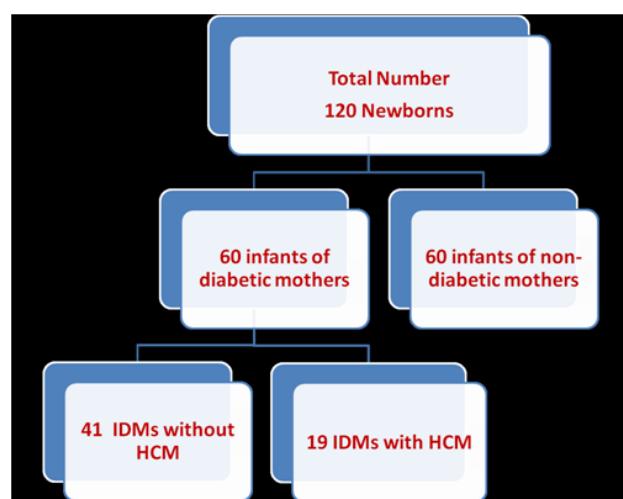


Table I Demographic Data and Clinical Features of both patients and control group

		IDM (n=60)	Control Group (n=60)	t/X2	P-Value	
Maternal Age	Mean \pm SD	31.23 \pm 3.9	30.3 \pm 4.1	1.2	0.2	
Maternal Hb A1C%	Mean \pm SD	7.3 \pm 2.4	4.8 \pm 0.5	7.9	<0.0001	
Caesarean section	Ratio	28 (46.6%)	16 (26.6%)	4.3	0.037*	
Birth weight (g)	Mean \pm SD	4.3 \pm 0.5	3.4 \pm 0.7	8.1	<0.0001*	
Gestational age (wks)	Mean \pm SD	36.3 \pm 1.2	37.3 \pm 1.5	4	<0.0001*	
Male/female	ratio	31 (51.6%) 29 (48.4%)	28 (46.6%) 32 (53.4%)	5	0.7	
APGAR score		6.7 \pm 0.4	7.2 \pm 0.6	-5.4	< 0.0001*	
1 min	Mean \pm SD	9.1 \pm 0.3	9.3 \pm 0.4	-31	0.002*	
5 min		Respiratory distress	13 (21.6%)	0	12.3	0.0004*
		Neonatal jaundice	36 (60%)	- 18 (30%)	9.7	0.002*
Post natal Complications		Hypocalcaemia	16 (26.6%)	- 1 (1.6%)	13.5	0.0002*
		Hypoglycemia	9 (15%)	0	7.7	0.005*
		Hypothyroidism	8 (13.3%)	- 1 (1.6%)	4.4	0.03*
Cord pH	Mean \pm SD	7.35 \pm 0.035	7.32 \pm 0.04	-4.37	< 0.0001*	
Cord Cardiac troponin T (ng/ml)	Mean \pm SD	0.031 \pm 0.04	0.010 \pm 0.002	-4.06	0.0001*	

A1C%: Percent of glycosylated Hemoglobin; t: t test; X2: Chi-squared;* Significant

(Table 2) showed the demographic data and clinical features of two patients' subgroups (with and without hypertrophic cardiomyopathy). It showed no significant difference as regard to maternal age ($P=0.16$), type of treatment ($P=0.09$), rate of caesarean section ($P=0.7$), birth weight ($P=0.23$), gestational age ($P=0.27$), male/female ($P=0.85$), APGAR score ($P>0.05$), or cord pH ($P=0.7$). Type 1 DM was more common in the group of IDMs with HCM than those without while gestational DM was more common in those without HCM. However, the glycosylated hemoglobin ($P=0.02$) and cardiac troponin-T ($P<0.0001$) were significantly higher in infants of diabetic mothers with hypertrophic cardiomyopathy than those without hypertrophic cardiomyopathy. As regard to complications; there was no significant difference in most of the associated complications except for respiratory distress which was significantly more common in infants of diabetic mothers with hypertrophic cardiomyopathy than those without hypertrophic cardiomyopathy ($P=0.004$).

(Table 3) showed the echocardiographic data in infants of diabetic mothers with and without hypertrophic cardiomyopathy as well as the control groups. The intra-observer agreement K values of the echocardiographic measurements were between 77 and 88 which indicated good agreement between the 2 readings. The table showed presence of significant difference between various echocardiographic data in the control group when compared with the two patients' subgroups. It also showed significant difference between the

infants of diabetic mothers with hypertrophic cardiomyopathy and those without. It also showed that the tissue Doppler (as indicated by E'/A' ratio and S wave at mitral annulus, and E'/A' ratio and S wave at tricuspid annulus) was more sensitive than the conventional echocardiography in detecting cardiac dysfunction in both patients subgroups. In addition, it showed that the septal/posterior wall ratio was significantly higher in infants of diabetic mothers with hypertrophic cardiomyopathy subgroup than in control group and the subgroup of infants of diabetic mothers without hypertrophic cardiomyopathy ($P<0.0001$ for both subgroups). Moreover, it showed that Tei index was more sensitive in detecting impairment of myocardial performance than left ventricle fractional shortening.

(Table 4) showed no significant correlation between infant's birth weight and plasma levels of cardiac troponin-T while there was significant correlation between maternal glycosylated hemoglobin and plasma levels of cardiac troponin-T. It showed presence of significant negative correlation between plasma levels of cardiac troponin-T and E/A ratio MV, E'/A' ratio and S wave at mitral annulus, E/A ratio TV, E'/A' ratio and S wave at tricuspid annulus. There were positive correlations between plasma levels of cardiac troponin-T with septal/posterior wall, and left and right ventricles Tie indices. However, there was no correlation between cardiac troponin-T plasma levels and left ventricle fractional shortening or pulmonary systolic pressure.

Table 2 Demographic Data and Clinical Features of IDM with HCM and those without HCM

		IDM with HCM (n=19)	IDM without HCM (n=41)	t/X2	P-Value
Maternal Age	Mean \pm SD	30.4 \pm 3.9	32.3 \pm 5.2	1.4	0.16
	- Type 1	9 (47.4%)	6 (14.6%)	2.7	0.006*
Type of DM (ratio)	- Gestational	3 (15.8%)	26 (63.4%)	3.4	0.0006*
	- Type 2	7 (37%)	9 (22%)	1.2	0.2
Maternal Hb A1C%	Mean \pm SD	8.3 \pm 1.4	6.9 \pm 2.4	2.35	0.02*
Type of treatment	Insulin Ratio	15 (80%)	22 (53.6%)	2.8	0.09
	Diet	4 (20%)	19 (46.4%)		
Caesarean section	Ratio	10 (52.6%)	18 (43.9%)	0.12	0.7
Birth weight (g)	Mean \pm SD	4.4 \pm 0.3	4.2 \pm 0.7	1.2	0.23
Gestational age (wks)	Mean \pm SD	36.1 \pm 1.1	36.5 \pm 1.4	1.1	0.27
Male/female	Male Ratio	10 (52.6%)	21 (51.2%)	0.3	0.85
	Female	9 (46.4%)	20 (48.8%)		
APGAR score					
1 min	Mean \pm SD	6.5 \pm 0.3	6.7 \pm 0.4	1.9	0.57
5 min		9.0 \pm 0.3	9.2 \pm 0.4	1.9	0.057
	- Respiratory distress	- 8 (42.1%)	- 5 (12.2%)	8.3	0.009*
Post natal Complications	- Neonatal jaundice	- 13 (68.4%)	- 23 (56%)	0.4	0.5
	- Hypocalcaemia	- 8 (42.1%)	- 8 (19.5%)	0.004	0.06
	- Hypoglycemia	- 6 (28.5%)	- 3 (7.3%)	3.2	0.7
	- Hypothyroidism	- 6 (13.3%)	- 2 (4.8%)	0.4	0.5
Cord pH	Mean \pm SD	7.34 \pm 0.034	7.36 \pm 0.033	0.3	0.7
Cord Cardiac troponin T (ng/ml)	Mean \pm SD	0.051 \pm 0.03	0.015 \pm 0.006	7.4	<0.0001*

Hb A1C%: percent of glycosylated Hemoglobin; t: t test; X2: Chi-squared; * Significant

Table 3 Comparison of Echocardiographic Data in IDMs with and without hypertrophic cardiomyopathy (HCM) and control groups

	IDM with HCM (Group I) (n= 19)	IDM without HCM (Group I) (n= 41)	Control Group		
			(n=60)	t	P-Value
LV FS	37.3 Mean \pm SD \pm 4.4	39.04 \pm 4.12	41.56 \pm 5.14	t1 t2 t3 3.25 3.6 1.5	< 0.002* 0.01* 0.14

Table Continued...

	IDM with HCM (Group 1) (n= 19)	IDM without HCM (Group 1) (n= 41)	Control Group			P-Value	
			(n=60)	t	t1		
E/A ratio MV	Mean ±SD	0.7	0.8	t1	4.4	< 0.0002*	
		±0.27	±0.22	±0.2	t2	4.6	< 0.0001*
					t3	1.4	0.1
Septal/posterior wall (sw/pw)	Mean ±SD	1.9	1.1	1.05	t1	15.4	< 0.0001*
		±0.42	±0.28	±0.06	t2	1.3	0.2
					t3	8.7	< 0.0001*
E'/A' wave mitral annulus	Mean ±SD	0.7	0.9	1.1	t1	11	< 0.0001*
		±0.13	±0.14	±0.14	t2	7	< 0.0001*
					t3	5.4	< 0.0001*
S wave mitral annulus (Cm/s))	Mean ±SD	3.2	5.4	6.1	t1	21	< 0.0001*
		±0.6	±0.8	±0.5	t2	5.02	< 0.0001*
					t3	10.6	< 0.0001*
LV TEI index	Mean ±SD	0.47	0.42	0.38	t1	5.9	< 0.0001*
		±0.051	±0.04	±0.06	t2	3.7	< 0.001*
					t3	4.1	0.0001*
Pul Systolic Pressure (mmHg)	Mean ±SD	38.5	33.5	30.5	t1	7.1	< 0.0001*
		±5	±6	±4	t2	3	< 0.01*
					t3	3.2	< 0.01*
E'/A' wave tricuspid annulus	Mean ±SD	0.84	0.93	1.21	t1	33	< 0.0001*
		±0.05	±0.06	±0.04	t2	28.2	< 0.0001*
					t3	5.7	< 0.0001*
S wave tricuspid annulus cm/sec)	Mean ±SD	4.3	5.9	7.6	t1	27.5	< 0.0001*
		±0.6	±0.5	± 0.4	t2	18.9	< 0.0001*
					t3	10.8	< 0.0001*
RV TEI index	Mean ±SD	0.44	0.41	0.36	t1	3.5	< 0.001*
		±0.05	±0.03	±0.06	t2	4.9	< 0.0001*
					t3	2.9	< 0.01*

Tei index: Cardiac performance index;

t1 is the comparison between control group and group 1; t2 is the comparison between control group and group 2; t3 is the comparison between Group 1 and group 2

* = P value < 0.05 and is significant

Table 4 Correlation between Cardiac troponin T (cTnT) and maternal glycosylated Hemoglobin, infant's birth weight and echocardiographic findings in Infants of Diabetic mother (IDMs) with and without hypertrophic cardiomyopathy (HCM)

	Cardiac Troponin T			
	IDMs with HCM (n= 19)		IDMs without HCM (n=41)	
	R.	P. value	R.	P. value
Birth weight	0.265	0.072	0.284	0.1
Maternal Hb A1C	-0.582	0.020*	0.438	0.03*
LV FS	0.225	0.052	0.215	0.06
E/A ratio MV	-0.396	0.020*	0.428	0.023*
E'/A' wave mitral annulus	-0.386	0.034*	-0.362	0.043*
Septal/posterior wall	0.625	0.001*	0.488	0.016*
S wave mitral annulus (Cm/s))	-0.425	0.01*	0.488	0.016*
LV TEI	-0.388	0.01*	0.327	0.02*
Pul Systolic Pressure	0.255	0.062	0.215	0.07
E/A ratio TV	-0.575	0.01*	0.457	0.02*
E'/A' wave tricuspid annulus	-0.456	0.02*	-0.374	0.031*
S wave tricuspid annulus	-0.625	0.001*	0.588	0.004*
RV TEI	0.599	0.001*	0.527	0.01*

*= P-value< 0.05 is significant

Discussion

In a cohort of 60 infants of diabetic mothers we detected hypertrophic cardiomyopathy in 19 cases (31.6%) which is matching with what was previously published with a range between 13% and 59% concerning the potential teratogenic effect of diabetes.^{24,25} There was no significant difference in the type of diabetes between the group of infants of diabetic mothers with hypertrophic cardiomyopathy and those without. This agreed with the work of Plides who found that hypertrophic cardiomyopathy was more common in offspring of type 1 diabetic mothers than offspring of mother with either type 2 or gestational diabetes.²⁶ It also agreed with the work of Ullmo, et al.²⁴ who found increased incidence of hypertrophic cardiomyopathy in infants of mother with either type 1 or type 2 than infants of mothers with gestational diabetes.²⁴

The course of infant of diabetic mother related-hypertrophic cardiomyopathy appears to be benign, with a resolution of symptoms with time, starting from two to four weeks and complete resolution of septal hypertrophy within two to 12 months. In our study; complete resolution of septal hypertrophy occurred within the first 6 postnatal months. This agreed with the observation of Zielinsky, et al.²⁷ who reported spontaneous regression of ventricular septum thickness in infants of diabetic mothers during the first 6 months of life.²⁷ However, Way et al.⁶ reported delayed complete resolution of hypertrophic cardiomyopathy associated septal hypertrophy in infants of diabetic mothers until 1 year of age. Nevertheless, they reported starting of septal hypertrophy resolution as early as 6 weeks of age.⁶ Zielinsky et al.²⁷ described the association between regression of ventricular septum thickness and the decrease of insulin levels occurred up to the age of 1 month. It might be possible that intra uterine environmental factors including the glucose metabolism contributed to myocardial septal hypertrophy.²⁷ Kozák-Bárány, et al.²⁸ related the cardiac changes that occurred in infants of diabetic mothers; to the effects of maternal hyperglycemia during the third trimester and subsequent fetal hyperinsulinaemia leading to neonatal cardiac hypertrophy.²⁸ This agreed with our study findings of presence of significantly increased maternal glycosylated hemoglobin in the Infants of diabetic mothers with hypertrophic cardiomyopathy compared to the control group and the mothers of infants of diabetic mothers without hypertrophic cardiomyopathy.

Various echocardiographic modalities are available to evaluate the cardiac function in infants of diabetic mothers. In our study, there was significant diastolic dysfunction in both patients' subgroups when compared to the control group. The infants with hypertrophic cardiomyopathy had also more diastolic dysfunction than the infants of diabetic mothers without hypertrophic cardiomyopathy. Tissue Doppler was able to detect both systolic and diastolic dysfunction than conventional Doppler in infants of diabetic mothers with hypertrophic cardiomyopathy when compared to the control group. This higher sensitivity of tissue Doppler over the conventional Doppler was previously reported in various studies.^{20,29,30} We also found that Tei index was more sensitive than left or right ventricle fractional shortening in detecting impaired cardiac performance. The Tei index is a simple, noninvasive, simple to estimate and reproducible index which has close correlation with the widely accepted systolic and diastolic hemodynamic parameters as well as the potential for clinical application in the assessment of overall cardiac performance including isovolumetric contraction time, ejection time, and isovolumetric relaxation time. Bokiniec, et al.³¹ found that Tei index is able to detect with reliability milder types of diastolic dysfunction but is not reliable indicator for more severe form of left ventricle diastolic dysfunction in acute myocardial infarction patients.³¹

Cardiac troponins are highly specific cardiac markers, extremely sensitive, and valuable in diagnosis of myocardial necrosis. Many studies proved cardiac troponin-T was valuable in diagnosing cardiovascular dysfunction. Adamcov'a et al.³² studied the increase of cord blood cardiac troponin-T with fetal distress and myocardial compromise³² while Trevisanuto et al.³³ described high cardiac troponin-T concentrations in preterm infants due to the myocardial damage associated with respiratory distress and observed a significant relationship of troponin-T levels with the use of vasopressors, and mechanical ventilation.³³ In our study we found significant increase in cord blood cardiac troponin-T in infants of diabetic mothers than infants of non-diabetic mother ($P=0.0001$). We also found significant increase in cord blood cardiac troponin-T in the Infants of diabetic mothers with hypertrophic cardiomyopathy than in Infants of diabetic mothers without ($P<0.0001$). This together with the presence of positive correlation with the indicators of the cardiac diastolic and systolic dysfunction imply the value of cord blood cardiac troponin-T as an indicator of the cardiac injury associated with diabetes during pregnancy. Russell, et al.³⁴ found higher concentration of cardiac troponin-T in the diabetic cohort than in the normal cohort and found higher concentration of cardiac troponin-T in infants of diabetic mothers, especially those with cardiomyopathy and those with poor perinatal outcome.³⁴ Tarkowska & Furmaga-Jabłońska³⁵ found significantly higher cardiac troponin-T levels in newborns with heart pathology than in healthy ones.³⁵ However, they did not find significant correlation between clinical symptoms of heart failure, or with echocardiographic markers of left ventricle dysfunction in contrast to our finding of the positive correlation of the cardiac dysfunction with the cord blood cardiac troponin-T levels. This difference may be related to the different pathologies between the studied groups. The accurate mechanisms responsible for the elevation of troponin serum concentration in diseases other than acute coronary syndromes needs more research.³⁶ However, false positive elevation may occur in absence of cardiac reason or in presence of non-cardiac pathologies as in some cases of emergency situations.³⁷ Because of the possible false positive result, we advise combining measurement of serum cardiac troponin-T with echocardiography to facilitate and making accurate clinical decisions.

Limitations of the study

We excluded neonates with IUGR patients. However, we do not know whether this may alter the results or not, since many fetuses of DM or GDM mothers may have growth restriction due to placental insufficiency and concomitant comorbidities such as hypertension. Certainly, placental dysfunction could lead to alterations in both systolic and diastolic function of both ventricles. If these infants did not have LV hypertrophy; it may have altered their Doppler ventricular functional data in this group. Another limitation in our study was that we did not measure serum glucose and insulin level in the babies and relate their levels with the rate of resolution of the septal defect. We also did not follow Troponin levels during the neonatal course that we can use as a marker to monitor the resolution of HCM and to expect the prognosis.

Conclusion

Hypertrophic cardiomyopathy is present in a significant portion of infants of diabetic mothers. Cardiac troponin-T is a useful biochemical marker especially when combined with tissue Doppler echocardiography for monitoring cardiac dysfunction and hypertrophic cardiomyopathy in infants of diabetic mothers.

Ethical standards

The authors assert that all procedures contributing to this work

comply with the ethical standards of the National Health Regulatory Authority of Bahrain national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Institutional Ethical and Research Review Board of International Hospital of Bahrain.

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