Original Article

Predicting Myocardial Injury Among Native Congenital Heart Disease Patients Through Cardiac Enzymes And Tissue Doppler

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Abstract

Our aim was To determine if there is baseline elevation of troponin T and creatine kinase-MB in native congenital heart disease and to evaluate the accuracy of these biomarkers for prediction of myocardial injury in congenital heart disease. Methods: This study included 70 age and sex-matched children. All of them underwent Echocardiographic and tissue Doppler examinations and estimation of serum creatine kinase-MB and cardiac troponinT. Results: Creatine kinase-MB and cardiac troponinT were higher in cases compared with controls [2.48 (0.43 - 27.82) and 17.5 (4.12 - 186.2) vs 1.97 (0.9 - 4.1) and 7.5 (3 - 13.8) ng/ml, p values 0.003]. Mitral
E`/A` velocity ratio was less in patients than controls (1.75± 0.48 vs 2.18± 0.57 cm/sec, p=0.002). Accuracy of creatine kinase-MB and cardiac troponinT in prediction of myocardial injury in native congenital heart disease were67.1% and 87.1% respectively. Conclusion:Subtle myocardial injury and subclinical LV diastolic dysfunction are present in our patients. Serum cardiac troponinT is a more sensitive and specific marker of myocardial injury compared with creatine kinase-MB.

Keywords: Ultrasound; Congenital Heart Disease, Creatine Kinase-MB, Myocardial injury, Troponin T.

INTRODUCTION

One of the most critical health problems, congenital heart disease (CHD) is characterized by volume and pressure overloads, two types of hemodynamics. Additional hemodynamic abnormalities that may be seen in CHD include arterial desaturation and pulmonary artery hypertension. **(1)**. When myocardial cells are exposed to such overloads, damage begins to occur in terms of necrosis, apoptosis and mechanical stressors that in turn cause direct pressure and stretching of myocardium leading to cellular damage **(2)**. Consequently, cardiac myocytes are stimulated to release cardiac enzymes into the circulation **(3)**.
In patients with CHD, it is vital to know to what extent the heart is damaged and to determine the severity of heart failure. Grading of severity might become easier when depending on these biomarkers in management **(4)**. In adults, creatine kinase-MB (CK-MB), myoglobin and cardiac troponins I and T are widely used. In children, there are no current guidelines to use them as routine investigations but the interest in their utilization is increasing **(5)**. Measuring cardiac enzymes may help indicating the nature and extent of myocardial stress and/or damage and declaring the response of neurohumoral factors and the overall ventricular remodeling **(6)**.
Objectives: To determine if there is baseline elevation of troponin T and CK-MB in native CHD and to evaluate the accuracy of these two biomarkers in prediction of myocardial injury in CHD.

Subjects Methods

This cross-sectional study was carried out at Pediatric Cardiology Unit of Zagazig University Hospitals in Egypt from January 2019 to February 2021.Written consents from care-takers of the studied group were taken. This study was approved by the Institutional Review Board of Faculty of Medicine at Zagazig University. This study was performed on 70 age and sex-matched children classified into two groups:
Patients: Included 35 patients with native CHD. They were 16 females and 19 males with an age range from 2 months to 7 years

and a median age of 9 months. Members of this group were selected from children with CHD examined at Echocardiography laboratory of Pediatric Cardiology Unit or hospitalized at Zagazig University Children's Hospital.
Inclusion criteria: Patients more than one month old with native CHD.
Exclusion criteria: Patients less than one month old, myocarditis or myocardial ischemia, acute or chronic heart failure, hypotension or hypovolemia, chronic renal failure, sepsis, or tachyarrhythmias.
Initially, we had 43 patients enrolled in this study. Five patients were excluded being less than one month old. Three patients were not included due to acute myocarditis.
*Control subjects**:*** Included 35 healthy children, matching with patients in age and sex; they were 11 females and 24 males with an age range from 4 months to 7 years and a median age of 9 months. Members of this group were chosen from children examined at Echocardiography laboratory of Pediatric Cardiology Unit who turned out to have normal cardiac anatomy.

Methodology

All children participating in this study were subjected to complete history taking, physical examination as well as echocardiography.
Echocardiography: Echocardiographic and tissue Doppler examinations were performed using a My Lab Six (Esáote) machine by a 3-11 MHz transducer. Simultaneous ECG recording was performed. All patients were examined in the supine and occasionally left lateral position.

Echocardiographic measurements were carried out according to the recommendations of the American Society of Echocardiography **(7)**.
Conventional Echocardiography: The ejection fraction (EF%) was calculated through Simpson's biplane method.
*Tissue Doppler Echocardiography**:*** Tissue Doppler examination was performed in apical four- chamber view with the pulsed-wave Doppler sample volume of 3 mm placed at the medial and lateral mitral annulus. The average of the two recordings for each parameter was used in statistical analysis. Tissue Doppler examination of mitral valve was used to assess S wave velocity (peak systolic wave velocity), E` wave velocity (peak early diastolic wave velocity) and A` wave velocity (peak late diastolic wave velocity).
Laboratory investigations: were performed for all study participants. We measured serum levels of CK-MB and cardiac troponin T.
Specimen collection: Two mls of venous blood were collected from every participant aseptically by venipuncture. Each blood sample was delivered into a sterile plain vacutainer tubes with a stopper and left to clot at 37°C for 10 minutes in a water bath. Serum was separated by centrifugation at 3000 rpm for 15 minutes. The separated serum was kept in a sterile plastic tube then auto-analyzed by Cobas 8000 series-602 module (Ro-diagnostic, Germany).
Principle of the assay: Electro-chemilumenscence technique.

Statistical Analysis

The collected data were coded, entered and analysed using Statistical Package for Social Science (SPSS) version 20. Qualitative data were represented as frequencies and percent. Chi square (X2) test was used to detect the relation between different qualitative variables. For quantitative variables mean ± standard deviation (SD) for normally distributed data and median with range for not normally distributed data were computed. Independent student's t-test was used for detection of difference between different quantitative variables in case of parametric data, while nonparametric quantitative data was evaluated with Mann-Whitney U test. The results were considered statistically significant and highly statistically significant when the significant probability (P value) was < 0.05 and <0.001 respectively. Accuracy was measured by the area under the Receiver Operator Characteristic (ROC) curve. An area of 1 represents a perfect test and an area of 0.5 represents a worthless test. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated at 95% confidence interval to measure the validity **(8)**.

Results

We had 16 female patients and 19 male patients, 11 female and 24 male control subjects (p value of 0.220). The age of patients ranged from 2 months to 7 years with a median age of 9 months while that of control subjects ranged from 4 months to 7 years with a median age of 9 months (p value of 0.874). Four of our patients had tetralogy of Fallot. Five patients had atrial septal defect (ASD). Two patients had ASD, ventricular septal defect (VSD) and patent ductus arteriosus (PDA). Six patients had ASD and VSD. Only one patient had bilateral branch pulmonary stenosis (PS). Three patients had coarctation of Aorta and ASD. Only one patient had congenital mitral regurgitation ,mitral stenosis and pulmonary regurgitation. Three patients had PDA. Two patients had left ventricular outflow tract obstruction. Only one patient had valvular PS. Two patients with valvular PS and PDA. Two patients with valvular PS and VSD. Three patients with VSD and small PDA.

Table 1. Tissue Doppler parameters, EF and cardiac enzymes in studied participants

	Case group (n=35)	**Control group (n=35)**	**P value**
S wave velocity (cm/s): Median (Range)	8.3 (3.7-15)	7.8 (5-13.2)	0.295*
E` wave velocity (cm/s): Median (Range)	11.9 (6.4-19.5)	13.1 (10.3-21)	0.957*
A` wave velocity (cm/s): Median (Range)	6.3 (4.8-13.4)	6.4 (4-13.9)	0.282*
E`/A` velocity ratio: Mean±SD	1.755±0.485	2.185±0.576	0.002†
EF (%): Mean± SD	70.63±15.19	70.54±9.79	0.978†
CK-MB (ng/ml): Median (Range)	2.48 (0.43 - 27.82)	1.97 (0.9 - 4.1)	0.003*
Troponin T (ng/ml): Median (Range)	17.5 (4.12 - 186.2)	7.5 (3 - 13.8)	0.003*

*: Mann–Whitney U test, †: Independent sample student's t-test.
A`: peak late diastolic wave, cm/s:centimeter per second, CK-MB: Creatine Kinase-MB, E`: peak early diastolic wave, EF: ejection fraction, S: peak systolic wave, SD: standard deviation.

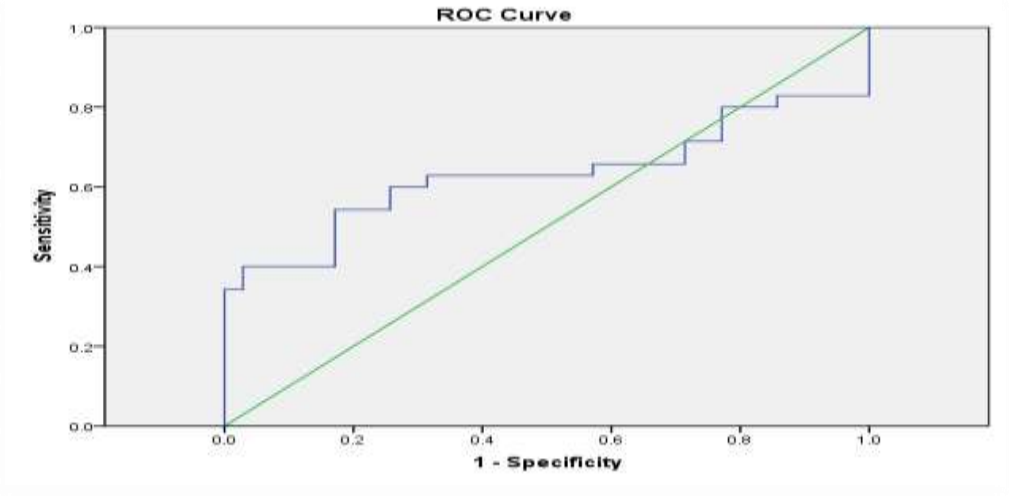

Figure 1. Validity of CK-MB enzyme

Table 2. Validity of CK-MB and cardiac troponin-T for prediction of myocardial injury in congenital heart disease

	Cases (n=35)	**Control (n=35)**
Cardiac injury (CK-MB>2.1 ng/ml) (n=30)	21	9
Non cardiac injury (CK-MB <2.1 ng/ml) (n=40)	14	26
Cardiac injury (TT>4.95 ng/ml) (n=38)	32	6

Non cardiac injury (TT<4.95 ng/ml) (n=32)			3			29		
CK-MB	**AUC**	**95%CI**	**Cutoff**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
	0.631	0.49-0.77	2.1 ng/ml	60%	74.3%	70%	65%	67.1%
TT	0.814	0.71-0.92	4.95 ng/ml	91.4%	82.9%	84.2%	90.6%	87.1%

AUC: Area under receiver operator characteristic curve, CI:Confidence Interval, CK-MB: Creatine Kinase-MB, NPV: Negative Predictive value, PPV: Positive Predictive value, TT: troponin T.

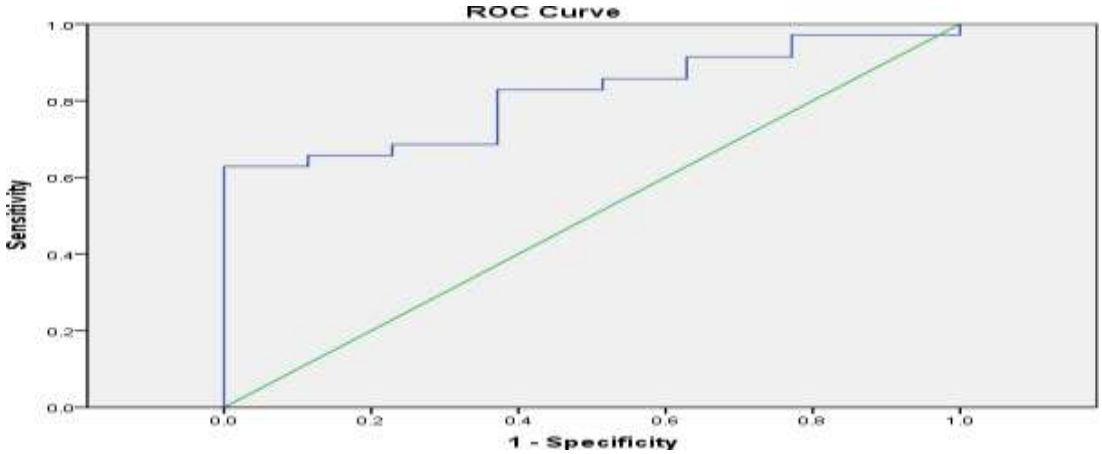

Figure 2. Receiver operator characteristic curve for cardiac troponin-T enzyme

Table 3. Tissue Doppler findings and cardiac enzymes in patients

*:Mann–Whitney U test,†:Independent sample student's t- test
A`: peak late diastolic wave, CKMB: creatine kinase-MB, cm/s: centimeter per second, E`: peak early diastolic wave, S wave:

	CKMB< 2.1 ng/ml (n=14)	**CKMB> 2.1 ng/ml (n=21)**	**P**	**TT<4.95 ng/ml (n=3)**	**TT>4.95 ng/ml (n=32)**	**P**
S wave velocity (cm/s): Mean±SD	8.007±2.252	9.485±3.475	0.17 †	9.366±2.554	8.850±3.173	0.787 †
E` wave velocity(cm/s): Median (Range)	8.9 (12.6 - 7.8)	12 (14.1 -11.1)	0.037 *	12 (13.5- 9.1)	8.3 (19.5 - 14)	0.760 *
A` wave velocity (cm/s): Median (Range)	6.3 (8.1 - 4.7)	6.3 (7.2 - 5.3)	0.727 *	6(10.2 - 5.6)	4.8 (13.4 - 8.3)	0.207 *
E`/A` velocity ratio: Mean±SD	1.603±0.390	1.857±0.622	0.184 †	1.649±0.338	1.765±0.567	0.732 †

peak systolic wave, SD: standard deviation, TT: troponin T

Discussion

Creatine kinase-MB and troponin-T seem to be useful for prediction of myocardial injury being elevated soon after myocardial damage **(9)**.
Different modalities for diagnosis of CHD are available. One of the most important investigating methods is tissue Doppler that

is considered a robust echocardiographic technique used for quantification of global and regional myocardial contractile function besides left ventricular relaxation. Its measurements are powerful prognostic markers in a variety of cardiovascular conditions **(10)**.

Our study showed no statistically significant difference between case and control groups regarding S wave velocity, early diastolic wave (E`) and late diastolic wave (A`) velocities (table1) indicating absence of LV systolic or diastolic dysfunction in our patients as measured by those parameters. However, Friedman et al. **(11)** used tissue Doppler in newborns and measured E` and A` waves to evaluate postnatal left ventricular diastolic function after fetal Aortic valvuloplasty and found their lower values in cases of aortic stenosis and post-aortic valvuloplasty than control which may be due to presence of pressure overload in all of their patients while only 3 of our patients had pressure overload and 13 patients had combined volume and pressure overload.

In our study there was a statistically significant decreased in E`/A` velocity ratio in patients with CHD compared to control (table 1) denoting LV diastolic dysfunction in our patients. Similarly, **Kim et al. (12)** evaluated E`/A` ratio as a marker of diastolic function and demonstrated a correlation between it and brain natriuretic peptide levels.

There was no statistically significant difference between case and control groups regarding ejection fraction (EF), (table 1), denoting absence of LV systolic dysfunction using conventional echocardiography.

Elevation of CK-MB in cases with CHD was highly related to myocardial cell injury as reported by **Kozar et al. (13)** who examined 45 children with CHD and found that CK-MB levels

in infants with structural heart disease are increased in the pre- and postoperative period. In addition, our results concerning CK-MB (table 1**)** coincide with the studies conducted by **Simovic et al. (14)** and **Nassef et al. (15)** as they found that CK-MB was significantly higher in patients with CHD than in control group.

Troponin has been reported to be elevated in association with sepsis, septic shock, and systemic inflammatory response syndrome, hypotension or hypovolemia, acute and chronic heart failure and tachyarrhythmias. In all of these clinical settings there is a mismatch between myocardial oxygen demand and supply in the absence of flow-limiting epicardial stenosis of coronary arteries which may induce troponin elevation in circulation. Simultaneously, myocardial oxygen delivery may be decreased by reduced coronary perfusion because of tachycardia and decreased oxygen delivery to the heart(**16)**.

Our study clarified more elevation of cardiac troponinT levels in CHD patients than normal children (table 1). A possible explanation for elevation cardiac troponinT and CK-MB levels is that in Egypt and other developing countries, surgical correction of CHD is delayed due to limited resources causing prolonged exposure of cardiac muscle to pressure and volume overloads giving rise to a high incidence of myocardial affection **(17).**

We studied the validity of CK-MB for prediction of congenital heart disease-induced myocardial injury (table 2). The cutoff point of CK-MB was 2.1 ng/ml. An area of 0.631 under ROC curve (figure 1) was accompanied with 60% sensitivity and 74.3% specificity for detecting cardiac injury in CHD. The NPV was 65% and PPV was 70% which makes the CK-MB accuracy 67.1%. **Neves et al. (18)** found that CK-MB cutoff of ≥ 4.6 ng/mL showed sensitivity of 87.5% and specificity of 63.6% but unlike us, they evaluated the value of CK-MB in newborns with congenital heart disease which are known to have higher levels of serum cardiac enzymes compared with older age groups.

We used ROC curveanalysis to define the diagnostic performance of cardiac troponinT as a marker of CHD (figure 2). The ROC curve analysis showed that the area under curve for cardiac troponin T was 0.814. We were interested in proposing a cut-off value of cardiac troponin-T that could be used as a predictor of the presence of cardiac cell injury in CHD. The cut off value of cardiac troponin-T was 4.95ng/ml with 91.4% sensitivity and 82.9% specificity for detection of myocardial damage in congenital heart diseases. Positive predictive value was 84.2% and negative predictive value was 90.6%. This makes the accuracy of cardiac troponinT in our study 87.1%. **Abdelrahman et al. (19)** found that, sensitivity of the test was 72%, specificity was 92%, positive predictive value was 90% and negative predictive value was 76.7%. **Jarolim (20)** found that the increased sensitivity of the new high-sensitivity assays of cardiac troponinT provides a potential for earlier diagnosis of myocardial injury.

Our study shows that cardiac troponinT is both more sensitive and specific than CK-MB (figures 1 and 2). This comes in accordance with **Montaldo et al. (21)** who found that troponin is considered the most specific cardiac biomarker and that it is superior to CK-MB for predicting CHD-induced myocardial injury. Our findings are also in agreement with **Shastri et al. (22)** who strongly suggested that among the four biomarkers they assessed, cardiac troponinT had the highest diagnostic value for detecting myocardial injury. **Jiang et al. (23)** found that ROC curve analysis shows a diagnostic value of troponin I which is higher than that of CK-MB, myoglobin, or brain natriuretic peptide. Consequently, serum troponin I levels may be a useful biomarker for early prediction of myocardial injury.

In our study, there was no statistically significant difference between patients with cardiac troponinT level > 4.95 ng/ml and those with cardiac T level < 4.95 ng/ml regarding S wave peak velocity, E` wave peak velocity, A` wave peak velocity, or E`/A` velocity ratio (table 3) although the absolute values of the former 3 parameters were less in patients with higher levels of cardiac troponinT probably suggesting the need of follow up studies of our patients to determine presence or absence of LV systolic or diastolic dysfunction on the long term.

Conclusion

Patients with coronary heart disease have evidence of subclinical LV diastolic dysfunction and myocardial damage. We propose serum cardiac troponinT at baseline evaluation of CHD patients because it is a more sensitive and specific marker of myocardial

damage than CK-MB. To confirm the function of cardiac enzymes in assessing heart injury due to hemodynamic anomalies in CHD, additional studies with a larger number of patients are required.

Follow up studies are helpful to investigate the benefits of CK-MB and cardiac troponinT in serial evaluation of myocardial cell injury in patients with CHD.

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