Cardiac Troponin T in Dilated Cardiomyopathy

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Abstract: Introduction: In the field of cardiovascular disease, troponins have emerged as the most reliable clinical measure of myocyte injury. Despite the widespread use of cardiac troponins as biomarkers for diagnosis and risk stratification, their condition in cardiomyopathy are not known. **Patients and methods:** The study was conducted on 20 children with dilated cardiomyopathy, attending the Cardiology Unit of Assiut University Children Hospital, for recurring episodes of heart failure. Determination of serum level of cardiac troponin T was done on admission and discharge after relief of presenting symptoms. **Results:** Serum cardiac troponin T concentrations were normal (below the lower detection limit which is 0.01 ng/ml) on admission and on discharge. **Conclusion:** Serum cardiac troponin T does not increase in dilated cardiomyopathy.
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1. Introduction:

Cardiac troponins are protein components of the tropnin-tropomyosin complex in myocardium. Since troponins do not occur in extracellular space, their appearance in serum is sensitive and specific marker of myocardium damage. Troponins appear in blood in 2 to 4 hours after insult, peak in about 12 hours and then remain elevated for 7–10 days. Sensitivity of both Cardiac troponin T(cTnT) and Cardiac troponin I (cTnI) in the diagnosis of myocardial damage is clinically almost equal. They differ in intracellular compartments, biological half-life, and molecular weight (Agata and Wanda, 2012).

Cardiac troponins (cTn) are biochemical markers of myocardial injury with unquestionable significance in diagnostic strategy in adults. In literature, the following applications of cTn in pediatrics are mentioned: acute myocarditis, heart arrhythmias, perinatal asphyxia in newborns, perioperative myocardial injury in patients operated for congenital heart disease, drug-induced cardiotoxity, and cardiac transplantation (Agata and Wanda, 2012).

In the field of cardiovascular disease, troponins have emerged as the most reliable clinical measure of myocyte injury. Myocarditis is a clinically heterogeneous myocardial inflammatory condition that is most definitively diagnosed by endomyocardial biopsy. It may be genetic, infectious, or autoimmune in etiology and may lead to dilated cardiomyopathy (DCM),(Ziya Kaya et al., 2010).

Troponin participates in the regulatory complex of the myofibrillar thin filament that plays a critical role in regulating excitation-contraction coupling in the heart (Morita et al., 2005). It is composed of three distinct gene products: troponin C, the 18-kD Ca2+-binding subunit; cardiac troponin I (cTnI), the 23-kD inhibitory subunit that prevents contraction in the absence of Ca2+ binding to troponin C; and cardiac troponin T (cTnT), the 35kD subunit that attaches troponin to tropomyosin and to the myofibrillar thin filament. The functional unit of the cardiac myocyte is the sarcomere. Sarcomere thin filament proteins are composed of actin and troponins C, T, and I. Sarcomere thick filament proteins include myosin heavy chain, myosin essential and regulatory light chains, myosin-binding protein-C and titin. Cardiac troponin I and T isoforms from the heart are structurally different from the corresponding forms found in skeletal muscle (Ziya Kaya et al., 2010). Because of this distribution, the measurement of cTnI and cTnT isoforms is superior to other serum biomarkers of cardiac lesions such as creatine kinase. Therefore, troponins in blood are now the preferred markers of myocardial damage (Horwich et al., 2003). Despite the widespread use of cardiac troponins as biomarkers for diagnosis and risk stratification, their condition in cardiomyopathy are not known.

Cardiomyopathies are myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease, sufficient to cause the observed myocardial abnormality. They are classified into a number of morphological and functional phenotypes that can be caused by genetic and non-genetic mechanisms. There were few advances in treatment reported and it remains clear that there is a need for properly conducted randomized trials in all forms of cardiomyopathy (Perry and Saidi**,** *2012*).

DCM, the most common form of cardiomyopathy, is characterized predominantly by left ventricular dilatation and decreased left ventricular systolic function. Hypertrophic cardiomyopathy demonstrates increased ventricular myocardial wall thickness, normal or increased systolic function, and often, diastolic (relaxation) abnormalities. Restrictive cardiomyopathy is characterized by nearly normal ventricular chamber size and wall thickness with preserved systolic function, but dramatically impaired diastolic function leading to elevated filling pressures and atrial enlargement. Arrhythmogenic right ventricular cardiomyopathy and left ventricular non-compaction are characterized by specific morphologic abnormalities and heterogeneous functional abnormalities (Robert Spicer and Stephanie Ware, 2011).

DCM, when defined as left ventricular (LV) dilatation and systolic impairment in the absence of previous myocardial infarction, is one of the most common heart muscle diseases in developed countries. Over the past year, research emphasizing the importance of genetics in the etiology of inherited and apparently acquired forms of DCM has been a prominent feature. Patient management continues to consist largely of standard symptomatic and prognostic heart failure treatments, but recent work has begun to identify the importance of etiology in determining management (Perry and Saidi**,** *2012*).

Aim of the work:

1- Determination of serum level of cardiac troponin T (cTnT) in dilated cardiomyopathy; hence a diagnostic measure of dilated cardiomyopathy is acquired.

2- Identify a possible pathogenic role of cTnT in dilated cardiomyopathy.

2. Patients and Methods:

The study was conducted on children having dilated cardiomyopathy, in the Cardiology Unit of Assiut University Children Hospital. 20 children, the ages of whome ranged from 0.5 – 14 years with a mean of 4.88± 4.56 years, were included in the study.

Detailed history was obtained from every child inculding age, sex, onset of the disease, presenting symptoms (palpitation; chest pain; cough; syncope; and others), and family history of cardiomyopathy.

Then children were subjected to full clinical examination including general examination (pulse, blood pressure, jugular venous pressure, and edema of lower limbs); systemic examination (congestive hepatomegaly, ascites, and signs of pulmonary edema {bubbling crepitations on lung bases}); and local examination of the heart (precordial bulge, abnormal pulsations, criteria of the apex, and abnormal auscultatory findings).

All children were subjected to the following investigations: chest x-ray, electrocardiography (ECG), and detailed echocardiography. Determination of serum level of cTnT was done on admission and discharge after relief of presenting symptoms.

Methodology:

A venous blood sample was withdrawn from each child to obtain serum for determination of serum cTnT. The blood samples were allowed to clot for 30 minutes at room temperature and were subsequently centrifuged for 10 minutes at 3500 r/m. Aliquots of serum samples, 1 ml each, were stored at -40º C until analysis.

Cardiac troponin T determination

Elecsys Troponin T employs two monoclonal antibodies specifically directed against human cardiac troponin T. The antibodies recognize two epitopes (amino acid position 125-131 and 136- 147) located in the central part of the cardiac troponin T protien, which consists of 288 amino acids. Elecsys Troponin T assay detects free troponin T as well as binary and ternary complexes of it.

Test principle

Sandwich principle. Total duration of assay was 18 minutes.

First incubation: 15 microlitres of the sample, a biotinylated monoclonal troponin T-specific antibody and a monoclonal troponin T-specific antibody labeled with a ruthenium complex react to form a sandwich complex.

Second incubation: after addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with procell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomuliplier.

Results are determined via a calibration curve which is instrument-specifically generated by two-point calibration and a master curve (five-point calibration) provided via the reagent barcode.

***Calculation** Elecsys 1010 automatically calculate the troponin T concentration of each sample in ng/ml.

***Analytical sensitivity (lower detection limit)**

0.01 ng/ml. The lower detection limit represents the lowest measurable troponin T concentration that can be distinguished from zero.

The normal range for cardiac troponin T is 0.01 to 0.1 ng/ml and the lower detection limit of the assay is 0.01 ng/ml(Adelhan et al., 2004).

Echocardiography

Simultaneous M-mode and two-dimensional echocardiography was performed with 3.5 and 5 MHz-transducers using Acuson XP 128 equipment.

Two-dimensionally guided M-mode tracings were obtained. Chamber dimensions and wall thickness were measured with a pair of electronic calipers in accordance with the recommendations of the American Society of Echocardiography. Chamber enlargement was identified by comparing observed measures (indexed for body surface area) with reference values for age-matched normal subjects. Fractional shortening of the left ventricle during systole (%FS) was calculated from the left ventricular internal dimensions and used as an index of left ventricular systolic function.

Doppler colour flow imaging was performed with the use of a standard velocity colour map. Each examination was performed with the use of the shallowest depth and narrowest sector angle capable of encompassing the jet area of regurgitant flow.

Valvular regurgitation was diagnosed when colour Doppler flow mapping demonstrated reversed flow away from the valve when the valve was closed. To differentiate abnormal from physiological regurgitation, the high velocity turbulent jet had to extend beyond the paravalvular region (more than one cm) and had to be confirmed by colour-guided pulsed Doppler spectral analysis.

Treatment of children was accomplished by different means including salt restriction, inotropic drugs, after load reducing agents, diuretics, and antiarrhythmics.

Data entry was done by using the excel program and statistical analysis was done with SPSS software (Version 16 SPSS Inc. , Chicago, Il, USA). The qualitative variables were summarized as percentages and the quantitative ones as means and standard deviations. Fisher exact test was used to compare the qualitative data. Mann-Whitney Test was used to compare means of quantitativevariables of males and females. Wilcoxon Signed Ranks Test was used to compare means of quantitative variables at admission and discharge. P value < 0.05 was considered statistically significant.

3. Results:

The study was conducted on 20 patients whose ages ranged from 0.5 – 14 years with a mean of 4.88± 4.56 years. The number of males was 12 (60%). The age at onset of cardiomyopathy in different children ranged from two months to six years (2.45 ± 1.9 years). No etiology of cardiomyopathy was known in any of our patients. Also there was no family history of cardiomyopathy in any of our patients.

The presenting symptoms included palpitation affecting eight patients (40%), chest pain affecting 12 patients (60%), cough affecting all patients (100%), and dyspnoea affecting 12 patients (60%). Syncope was not reported by any of our patients. Table 1 shows a comparison between males and females as regard the presenting symptoms. No significant statistical differences were found between males and females as regard presenting symptoms.

Table (1): presenting symptoms in males and females

	Male		Female		P-value
	No.	%	No.	%	
Palpitation	3	25.0	5	62.5	0.167
Chestpain	6	50.0	6	75.0	0.373
Cough	12	100.0	8	100.0	--
Dyspnea	6	50.0	6	75.0	0.373

Fisher Exact Test

Abnormal findings on general and systemic examination included tachycardia occurring in eight patients (40%), raised jugular venous pressure occurring in 20 patients (100%), congestive hepatomegaly occurring in eight patients (40%), and ascites occurring in four patients (20%). Edema of lower limbs and pulmonary edema did not occur in any of our patients. Other conditions discovered on general and systemic examination included upper respiratory infection (URI) occurring in three patients (15%) and pneumonia occurring in 17 patients (85%). Table 2 shows a comparison between males and females as regard the abnormal findings on general and systemic examination. Heart rate of children ranged from 100 to 140 (114 ± 11). All patients had normal blood pressure ranging from 80/50 to 120/90 (96 ± 13/66 ± 14). No significant statistical differences were found between males and females as regard the abnormal findings on general and systemic examination, but significant statistical differences were found between males and females as regard the associated conditions, where pneumonia affected males more than females, while URI affected females more than males.

On local examination of the heart abnormal findings included precordial bulge found in eight patients (40%); abnormal precordial pulsations in 12 patients (60%), including epigastric pulsation in four patients (20%) and left parasternal pulsation in eight patients (40%); outward and lateral displacement of the apex in 10 patients (50%); and abnormal auscultatory findings in eight patients (40%), including muffled first heart sound (s1) in four patients (20%) and pansystolic murmur on the apex radiating toward the axilla in eight patients (40%). Table 3 shows a comparison between males and females as regard the abnormal findings on local examination of the heart.

Table (2): Signs found in males and females on general and systemic examination

	Male		Female		P-value
	No.	%	No.	%	
Tachycardia	5	41.7	3	37.5	1.000
Increased JVP	12	100.0	8	100.0	--
Congestive hepatomegaly	5	41.7	3	37.5	1.000
Ascites	3	25.0	1	12.5	0.619
Associated conditions:					
a) URI	0	0.0	3	37.5	0.049*
b) Pneumonia	12	100.0	5	62.5	0.049*

Fisher Exact Test *Statistical significant difference (P < 0.05)

Table (3): Abnormal findings in males and females, found on local examination of the heart

	Male		Female		P-value
	No.	%	No.	%	
Precordial bulge	3	25.0	5	62.5	0.167
Abnormal precordial pulsations:	7	58.3	5	62.5	1.000
a) Epigastric	0	0.0	4	50.0	0.014*
b) Left Parasternal	7	58.3	1	12.5	0.070
Displaced apex	5	41.7	5	62.5	0.650
Abnormal auscultatory findings:	3	25.0	5	62.5	0.167
a) Pan systolic murmur	3	25.0	5	62.5	0.167
b) Muffled S1	0	0.0	4	50.0	0.014*

Fisher Exact Test * Statistical significant difference (P < 0.05)

No significant statistical differences were found between males and females as regard precordial bulge, left parasternal pulsation, outward and lateral displacement of the apex, and pansystolic murmur on the apex radiating toward the axilla; while significant statistical differences were found as regard epigastric pulsation and muffled first heart sound (S1); which occurred more in females.

Cardiomegaly on X-ray chest was found in 16 patients (80%). Abnormal findings on ECG (electrocardiography) were found in 11 patients (55%), including right axis deviation in eight patients (40%) and left ventricular hypertrophy in four patients (20%). On echocardiography, dilatation of the four chambers of the heart was found in 12 patients (60%); dilated LV and lefr atrium (LA) in three patients (15%); dilated LV only in five patients (25%); mitral regurgitation (MR) in 11 patients (55%); and pulmonary hypertension (PHT) in six patients (30%).

Table 4 shows a comparison between males and females as regard the abnormal investigatory findings, where no significant statistical differences were found between males and females as regard them.

Time passed from admission till remition ranged from 3 to 5 days (4.4 ± 0.68). Table 5 shows the echocardiographic measures of the patients at admission and discharge (after remission).

There are significant decrease in right ventricular diameter and left ventricular end systolic diameter and significant increase in interventricular septum thickness and fractional shortening on discharge (after remission). These findings indicate a decrease in cardiac dilatation and improvement in systolic function of the heart. Serum cTnT concentrations were below the lower detection limit (0.01 ng/ml) on admission and discharge i.e. normal.

Table (4): Abnormal investigatory findings in males and females

	Male		Female		P-value
	No.	%	No.	%	
Cardiomegally	10	83.3	6	75.0	1.000
Abnormal ECG findings:	6	50.0	5	62.5	0.670
a) Rt axis deviation	3	25.0	5	62.5	0.167
b) LV hypertrophy	4	33.3	0	0.0	0.117
Echocardiographic abnormalities:					
a) Dilated four chambers	7	58.3	5	62.5	1.000
b) Dilated LA and LV	2	16.7	1	12.5	1.000
c) Dilated LV only	3	25.0	2	25.0	1.000
d) MR	6	50.0	5	62.5	0.670
e) PHT	3	25.0	3	37.5	0.642

Fisher Exact Test

Table (5): Echocardiographic measures of the patients at admission and discharge

	At admission	At discharge	P-value
	Mean ± SE	Mean ± SE	
RVAW (mm)	4.75 ± 0.34	5.80 ± 0.62	0.178
RV (mm)	23.30 ± 3.29	16.30 ± 1.75	0.002*
IVS (mm)	5.55 ± 0.43	7.65 ± 0.80	0.001*
LVEDD (mm)	46.68 ± 2.88	44.85 ± 2.70	0.230
LVESD (mm)	38.60 ± 2.34	36.18 ± 2.41	0.046*
LVPW (mm)	4.40 ± 0.09	6.75 ± 0.96	0.133
FS(%)	17.20 ± 0.93	21.00 ± 1.03	0.001*

Wilcoxon Signed Ranks Test *Statistical significant difference ($P < 0.05$)

RVAW: right ventricular anterior wall thickness, RV: right ventricular diameter, IVS: interventricular septum thickness, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LVPW: left ventricular posterior wall thickness, FS: fractional shortening.

4. Discussion:

Serum cTnT was normal (below the lower detection limit) on admission and discharge, so cTnT is normal in DCM. cTnI and cTnT have recently emerged as very specific and sensitive markers of myocardial damage. They are released by the cardiac cells in a proportion to the degree of cardiac injury (Joel Kamblock, 2003). In DCM a weakening of systolic contraction is associated with dilatation of the four cardiac chambers. Histologic examination show varying degrees of myocyte hpertrophy and fibrosis. Inflammatory cells are usually absent, but a varying incidence of inflammatory myocarditis has been reported (myocarditis, 2008). So significant myocyte necrosis does not occur in DCM; hence cTnT does not increase.

In this study we tried to determine whether cTnT assay, that has been approved for detection of myocardial infarction, can help in diagnosis of DCM or not, but the results showed no increase in cTnT in DCM.

Males constituted 60% of our patients. This coinsides with Robert Spicer and Stephanie Ware, 2011, who stated that the incidence of dilated cardiomyopathy is higher in males.

No etiology of cardiomyopathy was known in any of our patients. Also there was no family history of cardiomyopathy in any of our patients. The difficulty in distinguishing between inherited and acquired cases of DCM remains a major challenge as the profile of clinical findings rarely helps to identify etiology. In cases of sporadic disease (i.e, in the absence of affected family members), circumstantial evidence may suggest the causative cardiac injury is inflammatory, toxic, load or heart rate-dependent, or due to metabolic abnormalities. However, recently published data suggest that genetic susceptibility is often underestimated in apparently sporadic disease. In the past, animal data have demonstrated the importance of host genetic factors in determining susceptibility to cardiomyotrophic viral pathogens (Wiltshire et al., 2011).

Clinical manifestations of dilated cardiomyopathy are most commonly those of congestive heart failure, but can also include palpitations, syncope, respiratory symptoms (tachypnea, wheezing, cough, or dyspnea on exertion). Patients can be tachycardic and have hepatic enlargement and rales. The heart may be enlarged. Auscultation may reveal murmurs of mitral or less commonly tricuspid insufficiency (Robert Spicer and Stephanie Ware, 2011).

This coincides with our findings, where the presenting symptoms included palpitation (40%), chest pain affecting (60%), cough (100%), and dyspnoea (60%), but fortunately, syncope was not reported by any of our patients. In several clinical studies, patients with non-ischemic dilated cardiomyopathy (NIDCM), who experienced syncope have been shown to beat high risk of sudden death (Sercan Okutucu and Ali Oto, 2010). Abnormal signs included tachycardia (40%), raised jugular venous pressure (100%), congestive hepatomegaly (40%), and ascites (20%), but edema of lower limbs and pulmonary edema did not occur in any of our patients. Other conditions discovered on general and systemic examination included upper respiratory infection (URI) (15%) and pneumonia (85%). These associated conditions may be the inciting agents of recurrent heart failure in our patients. Signs found on local examination of the heart included precordial bulge (40%); abnormal precordial pulsations (60%), including epigastric pulsation (20%) and left parasternal pulsation (40%); outward and lateral displacement of the apex (50%); and abnormal auscultatory findings (40%), including muffled first heart sound (S1) (20%) and pansystolic murmur on the apex radiating toward the axilla (40%), which indicate mitral regurgitation.

No significant statistical difference was found between males and females as regard almost all clinical manifestations. To our knowledge clinical manifestations of dilated cardiomyopathy have no sex predilection.

In DCM electrocardiographic screening reveals atrial or ventricular hypertrophy, non specific T-wave abnormalities, and occasionally atrial or ventricular arrhythmias. The chest x-ray demonstrates cardiomegaly. The echocardiogram is often diagnostic demonstrating left ventricular enlargement and decreased ventricular contractility. Echo Doppler studies can reveal pulmonary hypertension, mitral regurgitation, or other structural cardiac abnormalities (Robert Spicer and Stephanie Ware, 2011).

This coincides with our findings, where cardiomegaly on X ray chest was found in (80%) of our patients. Abnormal findings on ECG (electrocardiography) were found in (55%) of our patients, including right axis deviation in (40%) and left ventricular hypertrophy in (20%). On echocardiography, dilatation of the four chambers of the heart was found in (60%); dilated left ventricle (LV) and left atrium (LA) in (15%); dilated left ventricle only in (25%); mitral regurgitation (MR) in (55%); and pulmonary hypertension (PHT) in (30%) of our patients.

Echocardiography is the most important investigation in establishing the diagnosis of DCM, by defining the presence and severity of LV dilatation and dysfunction. Diagnostic criteria have relied on the identification of a fractional shortening (FS) <25%, in association with a LV end-diastolic dimension >112% of predicted value corrected for age and body surface area. This is of particular relevance in the long-term follow-up of DCM patients, in order to comment on disease progression or response to treatments (Dewiet al., 2009).

In our patients FS ranged from 12-24% (17.20 ± 0.93) on admission, increasing to 13-26 (21.00 ± 1.03) on discharge with significant statistical difference. Also there was significant statistical decrease in the diameters of both ventricles on remission.

Conclusion:

Serum cTnT, that has been approved for detection of myocardial infarction, does not increase in dilated cardiomyopathy.

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