Cardiac Troponin I in Dilated Cardiomyopathy

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Abstract: Introduction: Dilated cardiomyopathy is one of the most common heart muscle diseases in developed countries. 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 is not known. **Patients and methods:** The study was conducted on 20 children with dilated cardiomyopathy, attending the Cardiology Unit of Children Hospital in Assiut University, for recurring episodes of heart failure. Determination of serum level of cardiac troponin I (cTnI) was done on admition and discharge after relief of presenting symptoms. **Results**: Serum cTnI concentrations ranged from 0.11 to 0.15 ng/ml (0.12 ± 0.003) on admition and from 0.1 to 0.14 ng/ml (0.11 ± 0.004) on discharge, all are within the normal range, but there is a significant decrease in serum cTnI concentrations on remetion. **Conclusion:** Serum cardiac troponin I (cTnI) does not increase in dilated cardiomyopathy, however in patients having DCM who presented wtith hear failure (HF), assay of cTnI can be used for follow up of these patients. Further studies are needed to support this proposal.
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Introduction

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 randomised trials in all forms of cardiomyopathy **(Perry and Saidi, *2012*).**

Dilated cardiomyopathy, 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. Aarhythmogenic right ventricular cardiomyopathy and left ventricular non-compaction are characterized by specific morphologic abnormalities and heterogeneous functional abnormalities (**Robert Spicer and Stephanie Ware, 2011).**

Dilated cardiomyopathy (DCM):

DCM, when defined as 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*).

Cardiac Troponins

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 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, 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. After myocardial injury the troponins enter the circulation where they can be used for diagnosis of acute coronary syndromes (ACS) and for prognosis (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. In addition, the fact that the cTnI and cTnT are normally not found in the circulation means that the cardiac troponins provide a high level of clinical sensitivity and specificity even when cardiac lesions are small. Therefore, troponins in blood are now the preferred markers of myocardial damage (Horwich, 2003). Cardiac injury often results in the exposure of intracellular cardiac-specific proteins and, if recognized by the immune system, production of autoantibodies directed against these antigens (Ziya Kaya et al., 2010). Despite the widespread use of cardiac troponins as biomarkers for diagnosis and risk stratification, their condition in cardiomyopathy are not known.

Aim of the work:

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

2- Identify a possible pathogenic role of cardiac troponin I (cTnI) in dilated cardiomyopathy.

Patients and Methods:

The study was conducted on 20 children with dilated cardiomyopathy, attending the Cardiology Unit of Children Hospital in Assiut University, for recurring episodes of heart failure. The ages of children ranged from 0.5 – 14 years with a mean of 4.88± 4.56 years.

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 pulmonar 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 cardiac troponin I (cTnI) was done on admition and discharge after relief of presenting symptoms.

Principle of the procedure and methodology:

Immulite/Immulite 1000 Turbo Troponin 1 is a solid-phase, enzyme-labeled chemiluminescent immunometric assay. The solid phase (bead) is coated with monoclonal murine anti-troponin I antibody. The liquid phase consists of alkaline phosphatase conjugated to polyclonal goat anti-troponin I in buffer. The patient sample and the reagent are incubated together with the coated bead for 8 minutes. During this time, troponin I in the sample forms the antibody sandwich complex with monoclonal murine anti-troponin I antibody on the bead and enzyme conjugated polyclonal goat anti-troponin I in the reagent. Unbound patient sample and enzyme conjugate are then removed by centrifugal washes. Finally, chemiluminescent substrate is added to the test unit containing the bead and the signal is generated in proportion to the bound enzyme. Volume required: 100 µl serum or plasma.

The normal level of cardiac troponin I in children is 2 ng/ml or less and is frequently below the level of detection for the assay **(myocarditis, 2008).**

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 categorical variables were summarized as percentages and the continuous 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 quantitative variables 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.

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 2 months to 6 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 8 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 was 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
Chest pain	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 8patients (40%), raised jugular venous pressure occurring in 20 patients (100%), congestive hepatomegaly occurring in 8 patients (40%), and ascites occurring in 4 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 3 patients (15%) and pneumonia occurring in 17 patients (85%). Table 2 shows a comparison between males and females as regard the abormal 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 was found between males and females as regard the abnormal findings on general and systemic examination, but significant statistical differences was 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 8 patients (40%); abnormal precordial pulsations in 12 patients (60%), including epigastric pulsation in 4 patients (20%) and left parasternal pulsation in 8 patients (40%); outward and lateral displacement of the apex in 10 patients (50%); and abnormal auscultatory findings in 8 patients (40%), including muffled first heart sound (s1) in 8 patients (40%) and pansystolic murmur on the apex radiating toward the axilla in 8 patients (40%). Table 3 shows shows a comparison between males and females as regard the abormal findings on local examination of the heart. No significant statistical differences was found between males and females as regard precordial bulge, abnormal precordial pulsations, outward and lateral displacement of the apex, and pansystolic murmur on the apex radiating towarde the axilla; while significant statistical differences was found as regard muffled first heart sound (s1); which occurred more in females.

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)

Cardiomegaly on X ray chest was found in 16 patients (80%). Abnormal findings on ECG (electrocardiography) was found in 11 patients (55%), including right axis deviation in 8 patients (40%) and left ventricular hypertrophy in 4 patients (4%). On echocardiography, dilatation of the four chambers of the heart was found in 12 patients (60%); dilated left ventricle (LV) and lefr atrium (LA) in 3 patients (15%); dilated left ventricle only in 5 patients (25%); mitral regurge (MR) in 11 patients (55%); and pulmonary hypertension (PHT) in 6 patients (30%).

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)

Table 4 shows a comparison between males and females as regard the abormal investigatory findings,

where no significant statistical differences was found between males and females as regard them.

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 hypotrophy	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

Time passed from admition till remition ranged from 3 to 5 days (4.4 ± 0.68). Table 5 shows the echocardiographic measures and serum cardiac troponin I (cTnI) of the patients at admition and discharge (after remition).

Table (5): Echocardiographic measures and serum cTnI of the patients at admition 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*
cTnI (ng/ml)	0.12 ± 0.003	0.11 ± 0.004	0.000*

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

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 remetion). These findings indicate a decrease in cardiac dilatation and improvement in systolic function of the heart.

Serum cTnI concentrations ranged from 0.11 to 0.15 ng/ml (0.12 ± 0.003) on admition and from 0.1 to 0.14 ng/ml (0.11 ± 0.004) on discharge, all are within the normal range, but there is a significant decrease in serum cTnI concentrations on remetion.

Discussion:

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 (ie, 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).

The incidence of DCM is increasing in part due to advances in diagnostics and increased awareness among physicians. In the early stages of the disease, minimal symptoms may be present and diagnosis delayed (Subha et al., 2010). 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 duspnea 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 nonischemic dilated cardiomyopathy (NIDCM), who experienced syncope have been shown to be at 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) (40%) and pansystolic murmur on the apex radiating toward the axilla (40%), which indicate mitral regurge.

No significant statistical differences 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 dignostic demonstrating left ventricular enlargement and decreased ventricular contractility. Echo Doppler studies can reveal pulmonary hypertension, mitral regurge, 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) was found in (55%) of our patients, including right axis deviation in (40%) and left ventricular hypertrophy in (4%). On echocardiography, dilatation of the four chambers of the heart was found in (60%); dilated left ventricle (LV) and lefr atrium (LA) in (15%); dilated left ventricle only in (25%); mitral regurge (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% 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. (Dewi et al., 2009).

In our patients FS ranged from 12-24% (17.20 ± 0.93) on admition, 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 remetion.

Serum cardiac troponin I (cTnI) ranged from 0.11 to 0.15 ng/ml (0.12 ± 0.003) on admition. All values were in the normal range, so cTnI is normal in DCM. However, there was significant statistical decrease in the level of cTnI on remetion. Cardiac troponin I (cTnI) and cardiac troponin T have recently emerged as very specific and sensitive markers of myocardial damage. They are released by the cardiac cells in the proportion to the degree of cardiac injury (**Joel, 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 cTnI does not increase.

In this study we tried to determine whether cTnI 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 cTnI in DCM, however in patients having DCM who presented wtith heart failure (HF), cTnI decreased significantly after remetion. thus assay of cTnI in patients with DCM can be used for follow up of these patients. Further studies are needed to support this proposal.

Conclusion:

Serum cardiac troponin I (cTnI), that has been approved for detection of myocardial infarction, does not increase in dilated cardiomyopathy, however in patients having DCM who presented wtith heart failure (HF), cTnI decreased significantly after remetion. thus assay of cTnI in patients with DCM can be used for follow up of these patients. Further studies are needed to support this proposal.

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