
Cardiac Troponin-T as a Diagnostic Marker in Children with Rheumatic Carditis

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Abstract:

Rheumatic carditis is the most serious major manifestation of acute rheumatic fever in children. Cardiac Troponin-T (cTnT) is established as a new specific marker of myocardial damage or injury.

The present work was carried out to study the value of cTnT as a diagnostic marker of myocardial injury in children with rheumatic carditis, and to compare it to established parameters of myocardial injury such as creatine kinase (CK) and its MB isoenzyme.

Forty-five children with acute rheumatic fever were enrolled in the study; classified into 3 groups: group (A): 15 children with rheumatic carditis without cardiomegaly, group (B): 15 children with rheumatic carditis and cardiomegaly and group (C): 15 children with other rheumatic presentations. Fifteen normal healthy children were enrolled as a control group. All children included in the study were subjected to diagnostic laboratory and radiological investigations, including serum total CK, CK-MB isoenzyme % (using electrophoresis) and cTnT (by immunoassay test).

Our results showed significant elevation of cTnT, total CK and CK-MB isoenzyme in children with rheumatic carditis (groups A and B), as compared to the control group ($P < 0.05$). These values were significantly higher in group (B) children (with cardiomegaly), as compared to group (A) children ($P < 0.05$). Also, the ideal cut-off point for cTnT was found to be 0.1 $\mu\text{g/L}$ with a sensitivity 100%, while the sensitivity for CK-MB was 86.7% and that for total CK was 53.3%.

We conclude that cardiac troponin-T (cTnT) can be used as a diagnostic marker of myocardial injury in children with rheumatic carditis, with a higher sensitivity than CK and its MB isoenzyme.

Introduction:

Rheumatic fever continues to exert a fearsome toll in cardiovascular morbidity and mortality in the economically developing areas of our planet,⁽¹⁾ particularly when it affects the heart (rheumatic heart disease).⁽²⁾ In many developing countries, including Egypt, rheumatic heart disease accounts for over 30% of cardiac patients and it is the main cause of death from cardiovascular diseases, where it is responsible for more than 75% of cardiac death in the young.⁽³⁾

The hallmark of acute rheumatic fever is carditis, which is the rheumatic inflammatory process involving the endocardium, myocardium and pericardium, i.e. pancarditis. Residual rheumatic heart disease depends on the severity of the initial episode of carditis.⁽⁴⁾

Myocardial injury leads to increase in serum levels of the enzymes glutamic oxalacetic transaminase (SGOT), lactate dehydrogenase (LD), and creatine kinase (CK). But, these enzymes may be released into blood from other organs besides the heart. However, delineation of isoenzyme profiles improves the diagnostic specificity.⁽⁵⁾ So, diagnosis of injury to the myocardium is facilitated by information on the activities of CK-MB isoenzyme and LD-1 isoenzyme in serum.⁽⁶⁾ However, more

precise tests are needed, and new immunoassays to measure proteins of the heart are currently being investigated.^(7,8) The troponins, present as a group of three subunits in the troponin complex on the thin filament of muscle myofibrils, are involved in the regulation of muscle contraction. Troponin-T is the tropomyosin-binding subunit, troponin-I is the actomyosin ATPase-inhibiting subunit, and troponin-C is the calcium-binding subunit. Only troponins T and I have cardiospecific isoforms.^(9,10) Cardiac troponin-T (cTnT) is established in adult cardiology as a specific marker of myocardial damage or injury.^(11,12) It is found in myocardial cells mainly as a part of the myofibrillar troponin complex of the cellular structure, and to a lesser degree in the cytoplasm.⁽¹³⁾

The present work aims to study the value of cardiac troponin-T (cTnT) as a diagnostic marker of myocardial injury in children with rheumatic carditis.

Subjects and Methods:

The present study was conducted in the Pediatric Cardiology Unit, Pediatric Department, Tanta University Hospital, in the period from October 1997 to December 1998. Forty-five (45) children with acute rheumatic fever were enrolled in the study (18 boys and 27 girls, mean age 10 years, range 6 to 14 years). They were classified into 3

groups, according to the clinical diagnosis and investigations:

- Group A: 15 children with rheumatic carditis without cardiomegaly.
- Group B: 15 children with rheumatic carditis and cardiomegaly (Cardiomegaly was diagnosed by measuring cardiothoracic ratio in X-ray chest & heart, and by echocardiography). Four children of this group showed signs of congestive heart failure; including congested neck veins, enlarged tender liver and edema of lower limbs.
- Group C: 15 children with other rheumatic presentations than carditis (6 children with rheumatic arthritis and 9 children with rheumatic chorea).

Fifteen (15) normal healthy children were enrolled as a control group (6 boys and 9 girls, mean age 10 years, range 6 to 14 years). None of the patients or controls received any treatment with intramuscular injections, salicylates, or corticosteroids prior to inclusion in the study. Children with the possibility of any muscle disease or renal disease (according to the clinical diagnosis and investigations) were excluded from the study.

All children included in this study were subjected to thorough history taking, full clinical examination and routine investigations for diagnosis:

- Erythrocyte sedimentation rate (ESR).
- C-reactive protein (CRP).
- Anti-streptolysin O titre (ASOT).
- Renal function tests (blood urea and creatinine).
- X-ray chest & heart (plain posteroanterior view, with measuring cardiothoracic ratio).
- ECG
- Echocardiography, using Aloka SSD 630 (Japan), with a 5 MHz transducer. A combined M-mode and two-dimensional echocardiography with Doppler study, was done for every patient.
- Blood samples from the diseased children were collected within 24 hours of hospital admission, and other laboratory investigations included:

[1] Serum total creatine kinase (CK): Using Stanbio kinetic procedure (NAC activated) for the quantitative determination of serum CK [Stanbio, 1989].⁽¹⁴⁾

[2] CK-MB isoenzyme %: Using Titan Gel Iso-Dot CK for the qualitative and quantitative analysis of CK isoenzymes by electrophoresis on agarose (Helena Laboratories).⁽¹⁵⁾

[3] Cardiac Troponin-T (cTnT): Immunoassay test (ELISA) was used for the quantitative

determination of cTnT (Boehringer Mannheim, Mannheim, Germany) in accordance with the manufacturer's instructions.⁽¹⁶⁾ The level of sensitivity of this test is 0.1 µg/L. Values of cTnT > 0.1 µg/L were considered positive.

Statistical Analysis:

Data were expressed as means ± SD. Student's "t" test was used to compare between the patient groups and the control group. Data were considered statistically significant at P value < 0.05 (*).

The ideal cut-off point level of laboratory parameters that differentiate rheumatic carditis from other rheumatic presentations, is the point at which nearly all true +ve are detected with a low amount of false +ve results. The sensitivity was determined by subdividing true +ve results by true total patients with disease.⁽¹⁷⁾

Results:

Table I shows the characteristics of children in different groups as regards age, sex, pulse (disproportionate tachycardia is important for diagnosis of active carditis), and percentage of symptoms and signs of rheumatic fever in every group. Table II illustrates the diagnostic laboratory and radiological investigations of children with rheumatic carditis and other rheumatic presentations, as compared to the control group. The ESR, CRP and ASOT significantly increased in all groups as compared to the control group (P < 0.05). The cardiothoracic ratio (in X-ray chest & heart) significantly increased in group B children (rheumatic carditis with cardiomegaly) as compared to the control group (P < 0.05). Table III shows the values of cardiac troponin-T (cTnT), total CK and CK-MB isoenzyme in children with rheumatic carditis and other rheumatic presentations. cTnT was significantly higher in group A children (rheumatic carditis without cardiomegaly) (0.29 ± 0.21 µg/L) and group B children (rheumatic carditis with cardiomegaly) (0.82±0.63 µg/L), as compared to the control group (0.02 ± 0.02 µg/L) (P < 0.05). Also, total CK was significantly higher in group A children (83.1 ± 44.7 U/L) and group B children (134.1 ± 52.5 U/L), as compared to the control group (40.3 ± 32.8 U/L) (P < 0.05). Moreover, CK-MB isoenzyme was significantly higher in group A children (10.9 ± 3.9%) and group B children (21.4 ± 6.1%), as compared to the control group (1.7 ± 1.1%) (P < 0.05).

The values of cTnT, total CK and CK-MB isoenzyme were significantly higher in group B children (with cardiomegaly), as compared to group A children (without cardiomegaly) (P < 0.05). As

regards group C children (other rheumatic presentations), there was no significant difference between their values and the values of the control group ($P > 0.05$).

Table IV shows the cut-off points and sensitivity of cTnT, CK-MB isoenzyme and total CK in children with rheumatic carditis. The ideal cut-off point for cTnT was found to be 0.1 $\mu\text{g/L}$. All rheumatic carditis cases (30) had cTnT levels $> 0.1 \mu\text{g/L}$

(sensitivity 100%). Four cases with other rheumatic presentations (4 /15) had cTnT levels $> 0.1 \mu\text{g/L}$. The cut-off point for CK-MB isoenzyme was 6% (26/30 cases had levels $> 6\%$: sensitivity 86.7%). Two cases with other rheumatic presentations (2/15) had CK-MB isoenzyme levels $> 6\%$. The cut-off point for total CK was 114 U/L (16/30 cases had levels $> 114 \text{ U/L}$: sensitivity 53.3%).

Table I. Characteristics of children in different groups

Characteristic	Control group (n = 15)	Group A (n = 15)	Group B (n = 15)	Group C (n = 15)
Age(year): Mean \pm SD	10 \pm 1.8	10 \pm 2.2	10 \pm 1.9	10 \pm 2
Range	6 - 14	6 - 14	6 - 14	6 - 14
Sex (M/F ratio)	6 / 9 (0.67)	7 / 8 (0.88)	6 / 9 (0.67)	5 / 10 (0.50)
Pulse (Beats/min.): Mean \pm SD	82 \pm 5.3	130 \pm 9.8	130 \pm 9.8	90 \pm 10.3
Range	75 - 90	115 - 145	115 - 145	80 - 110
Symptoms & Signs (%):				
- Fever		12 (80%)	12 (80%)	7 (47%)
- Dyspnea		13 (87%)	15 (100%)	1 (7%)
- Palpitation		14 (93%)	15 (100%)	0
- Pallor		12 (80%)	14 (93%)	2 (13%)
-Arthralgia		4 (27%)	5 (33%)	6 (40%)
- Arthritis		0	0	6 (40%)
-Chorea		0	0	9 (60%)
- Signs of CHF		0	4 (27%)	0

Table II. Diagnostic laboratory and radiological investigations of children in different groups

	Control group (n = 15)	Group A (n = 15)	Group B (n = 15)	GroupC (n = 15)	P ₁	P ₂	P ₃
ESR (mm): 1st h.	8.8 \pm 1.5 (6-10)	74 \pm 25.7 (35-100)	56.7 \pm 34.2 (10-100)	29.3 \pm 26.1 (10-80)	<0.05*	<0.05*	<0.05*
2nd h.	16.2 \pm 2.9 (12-20)	107 \pm 22.4 (75-135)	79 \pm 40.1 (20-135)	49 \pm 37.3 (20-105)	<0.05*	<0.05*	<0.05*
CRP (mg/L)	Less than 6	74.4 \pm 69.1 (12-192)	80 \pm 71.4 (12-384)	28.8 \pm 39.7 (0-96)	<0.05*	<0.05*	<0.05*
ASOT (IU/mL)	Less than 200	620 \pm 257.3 (400-1200)	600 \pm 280.8 (400-1200)	240 \pm 200.5 (0-600)	<0.05*	<0.05*	<0.05*
Cardiothoracic ratio (X-ray)	0.47 \pm 0.03 (0.43-0.50)	0.48 \pm 0.02 (0.45-0.50)	0.65 \pm 0.05 (0.59-0.76)	0.50 \pm 0.03 (0.45-0.55)	>0.05	<0.05*	>0.05

All parameters are expressed as mean \pm SD (range), * = Significant.

P₁: Control group versus group A, P₂: Control group versus group B, P₃: Control group versus group C.

Table III. Cardiac Troponin-T (cTnT), total CK and CK-MB isoenzyme in children with rheumatic carditis and other rheumatic presentations

	Control (n = 15)	Group A (n = 15)	Group B (n = 15)	GroupC (n = 15)	P ₁	P ₂	P ₃	P ₄
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cTnT (µg/L)	0.02±0.02 (0-0.06)	0.29±0.21 (0.12-0.80)	0.82±0.63 (0.12-1.80)	0.04±0.06 (0-0.20)	<0.05*	<0.05*	>0.05	<0.05*
Total CK(U/L)	40.3±32.8 (8-114)	83.1±44.7 (13-140)	134.1±52.5 (57-254)	44.2±30.7 (8-114)	<0.05*	<0.05*	>0.05	<0.05*
CK-MB isoenzyme (%)	1.7±1.1 (0-6)	10.9±3.9 (4.9-18.6)	21.4±6.1 (5.3-30.3)	1.8±1.4 (0-8)	<0.05*	<0.05*	>0.05	<0.05*

All parameters are expressed as mean ± SD (range), * = Significant.

P₁: Control group versus group A, P₂: Control group versus group B, P₃: Control group versus group C, P₄: Group A versus group B

Table IV. Cut-off points and sensitivity of cTnT, CK-MB isoenzyme total CK in children with rheumatic carditis

	Children with rheumatic carditis (n = 30)	Other rheumatic presentations (n = 15)	Cut-off point	Sensitivity (%)
cTnT	30	4	0.1 µg/L	100%
CK-MB isoenzyme	26	2	6%	86.7%
Total CK	16	0	114 U/L	53.3%

Discussion:

Rheumatic carditis is the most serious major manifestation of acute rheumatic fever because it is the only one that can cause death during the acute attack, or cause late sequelae of valvular rheumatic heart disease with chronic disability and eventually death.⁽¹⁸⁾

Biochemical markers are presently the "gold standard" for the diagnosis of minor myocardial injury, particularly the cardiac troponins.⁽¹⁹⁾ The important diagnostic impact of cardiac troponin-T (cTnT) in the assessment of myocardial damage or injury in adults has been extensively demonstrated, mainly in patients with myocardial infarction^(7,8,11-13) or undergoing cardiac surgery.^(20,21)

The present study investigated the usefulness of cTnT as a diagnostic tool in children with rheumatic carditis, and compared its diagnostic value to established parameters of myocardial injury such as CK activity and its MB isoenzyme.

Our results showed that the values of cTnT, total CK and CK-MB isoenzyme were significantly higher in children with rheumatic carditis (groups A and B), as compared to the control group (P < 0.05). cTnT is found in myocardial cells mainly as a part of the myofibrillar troponin complex of the cellular structure, and to a lesser degree (6%-8%) free in the cytoplasm^(10,13) This cytosolic pool of cTnT is released early from the cardiac myocyte with even minor myocardial injury, and can be measured with the cTnT assay within 4-6 hours of presentation⁽²²⁾ It remains elevated for many days to weeks.⁽¹²⁾

Previous studies showed higher sensitivity and specificity of cTnT for the detection of myocardial injury, as it is normally absent from the blood.^(12,22) Luscher et al.⁽²³⁾ reported that cTnT provided

sensitive detection of small amounts of early myocardial damage in patients with unstable angina, and it had potent prognostic value. Also, Koh et al.,⁽²⁴⁾ in their study, showed that the increased release of cTnT occurred in the presence of reversible myocardial damage. Moreover, Franz et al.⁽²⁵⁾ showed the importance of cTnT as a diagnostic marker for acute myocarditis due to any cause.

Few studies investigated the diagnostic importance of cTnT in children, including newborn infants. Immer et al.⁽²⁶⁾ and Kaku et al.⁽²⁷⁾ studied cTnT levels in children after cardiac surgery, and showed that it might improve the diagnostic assessment of myocardial damage in childhood. Fink et al.⁽²⁸⁾ showed increased cTnT levels due to myocardial injury in children receiving aggressive oncological drug therapy. Moreover, Agnoletti et al.⁽²⁹⁾ reported the importance of cTnT as a diagnostic tool in ischemic myocardial dysfunction of newborn infants. However, cTnT may be increased in chronic muscle disease as polymyositis and Duchenne's muscular dystrophy,⁽³⁰⁾ or in chronic renal disease;⁽³¹⁾ but this does not pose a problem in routine clinical practice.^(32,33) We excluded children with the possibility of any muscle disease or renal disease from our study.

As regards the significant increase of total CK and CK-MB isoenzyme in children with rheumatic carditis, our results were in agreement with those of Hess et al.⁽³⁴⁾ and Lott and Stang.⁽⁶⁾ Also, Marmor et al.⁽³⁵⁾ reported that the inflammatory process in rheumatic carditis may lead to alterations in membrane permeability without cell death, and these are responsible for leakage of CK and CK-MB isoenzyme from the intact myocardial cells.

Our results showed a significant increase of cTnT, total CK and CK-MB isoenzyme in children with rheumatic carditis with cardiomegaly, as compared to those without cardiomegaly ($P < 0.05$). This was in agreement with Ingwall,⁽³⁶⁾ who reported that the hypertrophied myocardium with cardiomegaly leads to more hypoxia and ischemia of myocardial cells, with more release of the accumulated enzymes and proteins into the circulation.

Our results showed also that the ideal cut-off point for cTnT was 0.1 $\mu\text{g/L}$, and this was in agreement with the previous studies in adults,^(7,8,11-13) and children.⁽²⁶⁻²⁹⁾ This value has been demonstrated to represent the optimal balance between clinical sensitivity and detection of minor myocardial damage.⁽⁸⁾ All rheumatic carditis cases (30) had cTnT levels $> 0.1 \mu\text{g/L}$ (sensitivity 100%). On the other hand, the cut-off point for CK-MB isoenzyme was 6% (26/30 cases had levels $> 6\%$: sensitivity 86.7%), and the cut-off point for total CK was 114 U/L (16/30 cases had levels $> 114 \text{ U/L}$: sensitivity 53.3%).

We did not determine specificity because four cases with other rheumatic presentations (4/15) had cTnT levels $> 0.1 \mu\text{g/L}$, and two cases (2/15) had CK-MB isoenzyme levels $> 6\%$. These cases (3 children with rheumatic chorea and 1 child with rheumatic arthritis) represented the so-called "sub-clinical carditis". Echocardiography identified the presence of carditis in those patients.

Thus, our results, that showed a higher sensitivity of cTnT than CK and its MB isoenzyme in the assessment of myocardial injury in children with

rheumatic carditis, were in agreement with all the previous studies in adults^(7,8,11-13,20,21) and in children.⁽²⁶⁻²⁹⁾ Katus et al.⁽²²⁾ showed that cTnT was very sensitive (100%) in the detection of myocardial damage, as compared to CK-MB (sensitivity 96%). Also, Immer et al.⁽²⁶⁾ in their study in children, showed that sensitivity of cTnT was 100%, while that of CK-MB isoenzyme was 92%. Furthermore, necrosis in certain conditions such as acute myocarditis may be limited or occur over an extended period that diagnostic elevations of CK-MB are not achieved.⁽³⁷⁾ Also, the sensitivity of CK-MB isoenzyme as a diagnostic marker in children is lower than in adults, because developmental expression of the B subunit results in increased concentration of CK-MB in skeletal muscle.⁽³⁸⁾

CONCLUSIONS:

1. Cardiac Troponin-T (cTnT) can be used as a diagnostic marker of myocardial injury in children with rheumatic carditis.
2. The addition of cTnT as a "new gold standard" to the classic diagnostic tests such as electrocardiography, chest radiography and echocardiography, may be useful for early detection of cardiac injury in children.
3. cTnT shows a higher sensitivity than CK and its MB isoenzyme in the assessment of myocardial injury in children with rheumatic carditis

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