FULL LENGTH ARTICLE

Prognostic value of homocysteine and highly sensitive cardiac troponin T in children with acute heart failure

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Objective: **Heart failure (HF) is a progressive disorder in children. Many HF biomarkers have been identified to assess its severity and predict its course. The aim of this study was to evaluate the prognostic value of plasma levels of homocysteine (HCY) and highly sensitive cardiac troponin T (hs-cTnT) in children with HF.**

Materials and Methods: **Eighty children with acute HF were enrolled in this study as the patient group and 80 healthy children of matched age and sex served as the control group. HCY and hs-cTnT serum levels were measured before and after HF treatment; additionally, echocardiographic examinations were performed before and after therapy. All patients were followed up for 3 months.**

Results: **Plasma levels of HCY and hs-cTnT were significantly higher in children with HF before treatment, compared with their levels in children with HF after treatment and with the control group. This increase in serum levels of both biomarkers was associated with increased severity of HF according to the Ross classification of HF. HCY had higher specificity, positive predictive value, and accuracy than hs-cTnT. Serum levels of both biomarkers had a significant positive correlation with cardiomegaly and a significant negative correlation with left ventricular ejection fraction and fraction shortening. Marked elevation of both serum biomarkers was significantly associated with poor outcome with mortality rate of 10%.**

Conclusion: **Plasma HCY and serum hs-cTnT levels have a good prognostic value in children with congestive heart failure (CHF) and their levels significantly correlated with clinical and echocardiographic data, severity of HF, and adverse outcome in children with CHF.**

Keywords: Acute heart failure, Children, Highly sensitive cardiac troponin T, Homocysteine, Prognostic

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Disclosure: Authors have nothing to disclose with regard to commercial support.

Received 14 August 2017; revised 21 November 2017; accepted 26 November 2017.
Available online 2 December 2017

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Peer review under responsibility of King Saud University.
URL: www.ksu.edu.sa
https://doi.org/10.1016/j.jsha.2017.11.007

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Introduction

Heart failure (HF) is defined as the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues. HF in children may arise from structural or nonstructural heart diseases, which may be congenital or acquired [1]. It has a high morbidity and mortality in children [2].

It is very crucial that intensivists can use simple biomarkers to aid in the early diagnosis and predicting of adverse outcomes to optimize the treatment strategy. Recently, many HF biomarkers have been identified that aid in assessing the severity of HF and in predicting the course of the disease. The mechanism for the release of these markers seems to be from ventricular remodeling, myocyte injury, and reduced coronary reserve [3,4].

Cardiac troponin T is considered to be a highly sensitive and specific biomarker for myocardial injury as in ischemic heart disease. It is also reported to be increased in HF and this increase is correlated with severity and bad prognosis of HF. Highly sensitive assays for cardiac troponin T detect it in blood even at concentrations much lower than could be detected by standard methods of assay [5].

Homocysteine (HCY) is an amino acid that is derived from the conversion of methionine to cysteine. Several recent studies have reported that elevated plasma HCY level in patients with congestive heart failure (CHF) was associated with increased incidence and severity of the disease [6,7].

Hyperhomocysteinemia causes adverse cardiac remodeling, through direct effect on the myocardium or independent vascular effect leading to myocardial fibrosis, stiffness, and systolic dysfunction [8]. The prognostic value of serum HCY and highly sensitive cardiac troponin T (hs-cTnT) levels in children with acute HF is still under evaluation.

In this study, we aimed to assess the prognostic value of HCY and hs-cTnT plasma levels in children with acute HF and to correlate their levels with the severity of HF. To the best of our knowledge, this is the first study investigating the prognostic value of these two markers in children with HF.

Abbreviations

CHF	congestive heart failure
CTR	cardiothoracic ratio
EF	ejection fraction
FS	fraction shortening
HCY	homocysteine
Hs-cTnT	highly sensitive cardiac troponin T
HF	heart failure
LV	left ventricle
ROC	receiver operating characteristic

Materials and methods

This study was conducted in the Pediatric Cardiology Unit, Pediatric Department, Tanta University Hospital (Tanta, Egypt) from April 2016 to August 2017. Eighty children with acute CHF were enrolled in this study (age range, 2 months to 6 years; 44 males and 36 females). Patients were classified according to the Ross classification of HF in infants and children as Class I, II, III, and IV [9]. Eighty healthy children matched for age and sex served as the control group (age range, 2 months to 6 years; 40 males and 40 females). The study has been approved by the local ethics committee of the Faculty of Medicine, Tanta University. Consent was signed by parents of all patients.

We included infants and children with manifestations of acute HF either due to acquired or congenital heart disease. We excluded those with hypertension, active myocarditis, ischemia, pericarditis, renal diseases, acute or chronic infection, metabolic diseases, any chronic illness, neoplastic disease, or those receiving drugs (e.g., methotrexate) that would increase the serum level of HCY.

All children included in the study were subjected to the following:

- Complete history taking.
- Thorough clinical examination including body weight, heart rate, respiratory rate, and complete cardiac examination.
- Electrocardiography: Performed using a three-channel α 1000 apparatus (Chandigarh, India) to diagnose any associated arrhythmias.
- Plain X-ray (chest): Chest X-ray was obtained and cardiothoracic ratio (CTR) was measured for assessment of cardiomegaly.
- Conventional echocardiography: Performed using Vivid 7 ultrasound machine (GE Medical System, Horten, Norway, with 4S and 3.5-MHz multifrequency transducers) to evaluate cardiac function. We also evaluated fraction shortening (FS), ejection fraction (EF), and Tei index of the left ventricle (LV). Tei index is defined as the sum of isometric relaxation time and isovolumic contraction time divided by the LV ejection time obtained from LV inflow and outflow. This index is used for assessing global systolic and diastolic functions of the LV. The echocardiographic examinations were performed by two different pediatric cardiologists for all included children to assess interobserver reliability.
- Plasma HCY level: Venous blood samples (2 mL) were obtained by venipuncture from patients and controls after

Table 1. Demographic, clinical, and echocardiographic data of the patients and controls.

Variables	Patient group	Control group	*p*
Age (mo)	15.5 ± 19.9	15.55 ± 16.63	0.993
Sex (male:female)	1.2:1	1:1	0.752
Weight (kg)	7.02 ± 3.72	9.25 ± 3.19	0.073
Etiology of HF, *n* (%)			
Cardiomyopathy	20 (25)		
TGA	4 (5)		
VSD	20 (25)		
Common AVC	8 (10)		
CoA	4 (5)		
VSD + atrial septal defect	16 (20)		
VSD + posterior descending artery	8 (10)		
Heart rate (beat/minute)	140 ± 15	117 ± 12	<0.001**
Respiratory rate (cycle/minute)	52 ± 7	30 ± 4	<0.001**
CTR (%)	64.6 ± 5.21	50 ± 0.00	<0.001**
Echocardiographic data			
EF%	55.55 ± 9.66	65.25 ± 7.29	0.01*
FS%	28.85 ± 8.3	34.7 ± 3.58	0.04*
LV MPI (Tie index)	0.77 ± 0.14	0.32 ± 0.11	0.001**
E/A ratio	0.95 ± 0.19	1.24 ± 0.23	0.01*

AVC = atrioventricular canal; CoA = coarctation of aorta; CTR = cardio-thoracic ratio; E/A = peak early filling velocity (E), peak late filling velocity (A); EF = ejection fraction; FS = fraction shortening; HF = heart failure; LV MPI = left ventricular myocardial performance index; TGA = transposition of great arteries; VSD = ventricular septal defect.
* Significant.
** Highly significant.

night fasting for at least 8 hours. Blood samples were put in heparinized vacutainer tubes that were centrifuged immediately, and plasma samples were separated and stored at −20 °C until further analysis. In patients with CHF, venous blood samples were obtained again after 3 months following treatment. Samples were measured by the particle-enhanced immunonephelometry method using kits provided by Siemens Healthcare Diagnostics (Tarrytown, NY, USA) [10].

- Serum hs-cTnT level: Venous blood samples (2 mL) were obtained by venipuncture from patients and controls. Blood samples were put in glass tubes that were centrifuged immediately at room temperature. The serum was aspirated and put in Eppendorf Tubes and frozen at −80 °C until further analysis. In patients with CHF, venous blood samples were obtained again 3 months after the treatment. Serum hs-cTnT level was measured using a commercially available electrochemiluminescence immunoassay (Elecsys 1010/2010 Troponin T Stat, 3rd generation; Roche Diagnostics, Mannheim, Germany) [11].

Statistical analysis

A sample size of 71 CHF patients was required to achieve power of 80% with alpha = 0.05. Statistical analysis of this study was conducted using SPSS version 17 (SPSS Inc., Chicago, IL, USA). Continuous data were represented as mean and standard deviation. Categorical data were presented as number and percentage. The mean between the two groups was compared through an independent *t* test. A paired *t* test was used to compare the means within the same group. The Chi-square test was used to compare categorical data (e.g., sex). One-way analysis of variance was used to compare the means of more than two groups. Linear correlation was done using the Pearson correlation coefficient to assess the strength of association between the variables. The receiver operating characteristic curve was constructed to test the predictive value of HCY and Hs-cTnT and to obtain a cutoff value. Interobserver reliability in this study was assessed using a two-way mixed-effects model. The interclass correlation coefficients and the 95% confidence interval were calculated to assess the degree of reliability. All *p* values of less than 0.05 were considered significant.

Results

This study was conducted on 80 patients (44 males and 36 females) with CHF. Their age range varied from 2 months to 72 months (mean, 15.5 ± 19.9 months). Eighty healthy children with matching age and sex served as the control group. The mean weight of the patient group was 7.02 ± 3.72 kg, whereas that of the control group was 9.25 ± 3.91 kg. There was no significant difference between the two groups in age, sex, or body weight ($p > 0.05$). Heart rate and respiratory rate were significantly higher in the patient group than in the control group ($p < 0.001$) (Table 1).

There was a significant increase in CTR in the patient group compared to the control group ($p < 0.001$). Echocardiographic examination revealed that there was a statistically significant difference between the patient group and the control group in EF%, FS%, Tei index, and E/A ratio (E: peak early filling velocity. A: peak late filling velocity) ($p < 0.05$) (Table 1).

The etiology of HF among the studied patients with CHF revealed that 25% of patients ($n = 20$) had dilated cardiomyopathy and 75% ($n = 60$) had congenital heart disease [20 patients had ventricular septal defect (VSD), 4 patients had transposition of great arteries, 8 patients had common atrioventricular canal, 4 patients had coarctation of aorta, 16 patients atrial septal defect + VSD, and 8 patients had VSD + posterior descending artery; Table 1].

Patients with CHF were classified based on the Ross classification of CHF into Class I (0%), Class II (60%), Class III (20%), and Class IV (20%) (Table 2).

Table 2. Classification of the patient group before and after treatment of CHF by the pediatric Ross classification system of HF.

Ross classification	Before treatment		After treatment	
	No.	%	No.	%
Class I	0	0	12	15
Class II	48	60	44	55
Class III	16	20	12	15
Class IV	16	20	12	15

CHF = congestive heart failure; HF = heart failure.

In patients with CHF, the HCY plasma level before treatment (11.150 ± 1.960 μmol/L) was significantly higher, compared with that after treatment (9.030 ± 1.616 μmol/L) as well as with the control group (6.69 ± 0.97 μmol/L) (Table 3). Furthermore, in patients with CHF, the serum level of hs-cTnT was also higher before treatment (75.63 ± 14.2 pg/mL), compared with that after treatment (66.4 ± 10.5 pg/mL) as well as with the control group (5.16 ± 2.63 pg/mL) (Table 3).

The mean levels of hs-cTnT and HCY were elevated in Ross Class IV patients more than in Ross Class III and Ross Class II patients ($p = 0.001$) (Table 4).

Receiver operating characteristic curve analysis of HCY and hs-cTnT plasma levels in patients with CHF before treatment revealed that HCY at a cutoff point over 8.1 μmol/L had a sensitivity of 100%, specificity of 95%, positive predictive value (PPV) of 95.2%, negative predictive value (NPV) of 100%, and accuracy of 99.5%. By contrast, hs-cTnT at a cutoff point over 10 pg/mL showed a sensitivity of 100%, specificity of 85%, PPV of 87%, NPV of 100%, and accuracy of 92.5% (Table 5).

There was a significant positive correlation between HCY levels and age, weight, CTR, and Tei index. There was also a significant negative correlation between HCY levels and both EF% and FS% ($p < 0.05$) (Table 6).

By contrast, there was a significant positive correlation between plasma levels of hs-cTnT and both Tei index and CTR. However, there was a significant negative correlation between hs-cTnT

Table 3. Comparison of plasma levels of homocysteine and highly sensitive troponin T of the studied groups.

Biomarkers	Patients before treatment	Patients after treatment	Control group	P1	P2	P3
Troponin T	75.63 ± 14.2	66.4 ± 10.5	5.16 ± 2.63	0.001**	0.001**	0.033*
Homocysteine	11.15 ± 1.96	9.03 ± 1.61	6.69 ± 0.97	0.001**	0.001**	0.01*

P1 = patients before treatment versus control; P2 = patients after treatment versus control; P3 = patients before treatment versus patients after treatment.
* Significant.
** Highly significant.

Table 4. Plasma levels of homocysteine and serum highly sensitive troponin T in relation to pediatric Ross classification system of heart failure among the studied HF patients.

Ross classification	Homocysteine level (μmol/L)		Hs-cTnT (pg/mL)	
	Range	Mean ± SD	Range	Mean ± SD
Class II	8.30–13.00	9.99 ± 1.32	13.49–83.55	55.35 ± 10.25
Class III	11.00–13.20	12.05 ± 0.90	26.52–141	72.36 ± 14.77
Class IV	12.50–15.20	13.72 ± 1.33	36.45–179	92.35 ± 14.52
Analysis of variance	*F*	14.371	6.325	
	p	0.001**	0.001**	

HF = heart failure; Hs-cTnT = highly sensitive cardiac troponin T; SD = standard deviation.
** Highly significant.

Table 5. Receiver operating characteristic curve analysis for the plasma level of homocysteine and troponin T as a diagnostic predictor in patients with CHF before treatment.

Biomarker	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
Homocysteine	>8.1 μmol/L	100%	95%	95.2%	100%	99.5%
Hs-cTnT	>10 pg/mL	100%	85%	87%	100%	92.5%

CHF = congestive heart failure; hs-cTnT = highly sensitive cardiac troponin T; NPV = negative predictive value, PPV = positive predictive value.

Table 6. Correlation between plasma (HCY) and serum hs-cTnT levels and variables of the studied patients with CHF before treatment.

Variables	Homocysteine level (μmol/L)		Hs-cTnT (pg/mL)	
	r	*p*	*r*	*p*
CTR	0.62	0.004**	0.42	0.008**
EF%	−0.70	0.001**	−0.49	0.041*
FS%	−0.74	0.001**	−0.52	0.004**
E/A ratio	−0.03	0.910	−0.53	0.002**
LV MPI (Tie index)	0.20	0.001**	0.17	0.001**

CHF = congestive heart failure; CTR = cardiothoracic ratio; EF = ejection fraction; E/A: E: peak early filling velocity, A: peak late filling velocity; FS = fraction shortening; HCY = homocysteine; Hs-cTnT = highly sensitive cardiac troponin T; LV MPI = left ventricular myocardial performance index.
* Significant.
** Highly significant.

Table 7. Prognostic value of (HCY) and hs-cTnT levels according to the outcome of patients with heart failure.

Patients ($n = 40$)	*N*	%	HCY (μmol/L)	Hs-cTnT (pg/mL)
Adverse outcome	16	20		
Death	8	10	13.23 ± 1.03	110.50 ± 10.98
Readmission	8	10		
Favorable outcome	64	80	10.96 ± 0.87	69.78 ± 16.35
p			<0.001**	<0.001**

HCY = homocysteine; hs-cTnT = highly sensitive cardiac troponin T.
** Highly significant.

levels and EF%, FS%, and E/A ratio ($p < 0.05$) (Table 6).

The mortality rate in our study was 10% (8 patients); readmission within 3 months occurred in another eight patients (10%). These adverse outcomes were associated with significant increase in both HCY and hs-cTnT plasma levels (Table 7).

Interobserver reliability in this study was assessed, and echocardiographic examination suggested an interclass correlation coefficient of 0.84 (95% confidence interval, 0.80–0.87), which indicated that there was a good agreement between the two echocardiographic examinations for each patient.

Discussion

CHF is one of the leading causes of death in children. Early detection of CHF and high-risk patients using biomarkers is thus crucial for choosing the appropriate strategy of management by intensivist and determining the prognosis in children with HF to improve mortality and morbidity rates [4]. In our study, we investigated the prognostic value of HCY and hs-cTnT in children with acute HF.

Our study showed a significant increase in the serum level of hs-cTnT in patients with CHF before treatment, compared with that after treatment as well as with the control group. This is in agreement with other previous studies [12,13]. Because hs-cTnT increases in the serum following even minimal cardiac stress or injury, it is considered a very accurate biomarker for diagnosis of early HF.

There are several mechanisms responsible for cardiac troponin release in circulation other than myocardial necrosis, such as inadequate oxygenation of myocardial cells, hibernating myocardium, production of plebs on myocardial cell membranes that contain troponin, cardiac damage from oxidative stress or inflammatory cytokines, release of cellular proteolytic products, or increased permeability of myocardial cell wall due to stretch or stress as in HF [14].

Our study showed that increased serum level of hs-cTnT was associated with increased severity of

HF (based on Ross classification of HF). This was in agreement with other studies [15,16], which reported that hs-cTnT was elevated in chronic and symptomatic HF and in proportion to the severity of the disease, indicating ongoing myocardial damage in children with HF.

Interestingly, our study also showed that there was a highly significant increase in the plasma level of HCY in patients with CHF before treatment, compared with that after treatment as well as with the control group. This is also in agreement with other investigators [6,17].

In this study, there was a significant increase of plasma HCY level, which was associated with severity of HF (in relation to Ross class of CHF). This is in agreement with other studies [18,19]. Our study also showed a significant positive correlation between plasma HCY level and CTR in the patient group. This is in agreement with Blacher et al. [20] who reported the presence of a significant positive correlation between plasma HCY and cardiomegaly. Furthermore, there was a significant negative correlation between plasma HCY level and LV systolic function (EF% and FS %). These results are in agreement with the results of previous studies [18,21,22], which reported that left ventricular ejection fraction decreased with elevated HCY levels.

Both HCY and hs-cTnT had a high sensitivity and NPV of 100%. However, HCY specificity, PPV, and accuracy were superior to those of hs-cTnT. Elevated levels of both biomarkers were associated with poor outcome. This can be explained by the adverse effect of HCY on endothelium, cardiac muscle remodeling, and coagulation system, and therefore, its high plasma level would be expected to be associated with poor outcomes [19].

Conclusion

Plasma HCY and serum hs-cTnT have a good prognostic value in children with CHF and their levels were significantly correlated with clinical and echocardiographic data, severity of HF, and adverse outcome in children with CHF.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Financial disclosure

All authors have no financial relationships relevant to this article to disclose.

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