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Serum High Sensitive Cardiac Troponin-T (hs-cTnT) as a Biomarker in Pediatric Pulmonary Hypertension due to Congenital Left to Right Cardiac Shunt

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Authors' contributions

This work was carried out in collaboration among all authors. Author HTAES designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors AHS and DEAA managed the analyses of the study. Author AMZ managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) is a frequent complication of congenital heart disease (CHD) with left-to-right shunt. Increased pulmonary pressure leads to vascular remodeling and RV dysfunction.
Objectives: To analyze the role of high-sensitive cardiac troponin T (hs -cTnT) in the determination of myocardial injury caused by volume and pressure load due to pulmonary hypertension (PH) in children with left to right cardiac shunt.
Patients and Methods: Twenty patients with congenital heart disease (CHD) with left to right shunt and PAH-CHD, 20 patients with CHD with left to right shunt but without PH, and 20 healthy children, in total 60 individuals, were included in the study. All cases aged between 3 and 36 months. Plain x-ray chest and heart, electrocardiography, Doppler and Two –dimensional, M-mode echocardiographic evaluation of CHD and pulmonary pressure were performed in all patients. Blood samples were obtained from all cases for measurement of serum high-sensitive cardiac troponin T (hs-cTnT) levels by highly sensitive third-generation quantitative test.

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Results: The mean hs-cTnT levels were significantly higher in patients with PH than in patients without PH ($p < 0.05$) with a sensitivity 70% and specificity 95%. A statistically significant positive correlation was determined between pulmonary artery pressure and hs-cTnT levels, and significant negative correlation with EF% and FS %(by echocardiography).
Conclusions: Serum levels of high-sensitive cardiac troponin T (hs-cTnT) were significantly elevated in PAH-CHD children denoting myocardial injury caused by volume and pressure load due to PH in children with left to right cardiac shunts, so it could be used as a cardiac biomarker in PAH-CHD children with good diagnostic and prognostic value and high sensitivity and specificity, which may be useful in the management of PH in childhood.

Keywords: Pulmonary arterial hypertension; congenital heart disease; high-sensitive cardiac.

1. INTRODUCTION

Nearly 1 in 100 children are born with congenital heart disease (CHD), making it one of the most common inborn birth defects worldwide [1].

Improvements in surgical correction or palliation concomitant with advancements in the ability to detect CHD lesions have allowed improved survival into adulthood [2,3].

Pulmonary hypertension in congenital heart diseases (PAH-CHD) triggers myocardial damage independently of increased volume or pressure load and resistance, occurring by disrupting the perfusion via increasing ventricular wall tension and the myocardial oxygen requirement [4].

The right ventricle especially, being thinner and more flexible, is forced to resist the afterload mismatch caused by increased pulmonary flow and consequently increased pulmonary resistance. In order to increase the right heart flow, right ventricle dilatation occurs. According to Laplace's law, all these alterations result in hypertrophy of the right ventricular wall at the same time [5].

In recent years, many biomarkers have been identified that may be helpful, especially in the follow-up of PH patients. Among these biomarkers, natriuretic peptides; in different studies, BNP and pro-BNP levels were found to raise with an increase in the left to right shunt lesions [6].

With the development of new-generation sensitive cardiac troponins, the determination of cardiac troponin levels at much lower serum concentrations is possible. This condition enables the early diagnosis of myocardial injury, as well as the usage of cardiac troponins in conditions other than acute coronary syndromes, such as CHD with left to right shunts having myocyte injury [7].

2. SUBJECTS AND METHODS

Forty (40) children with congenital heart disease (left to right shunt), were enrolled in this study. They were selected from those admitted at the Pediatric Cardiology Unit, Pediatric Department, and Tanta University Hospital.

They were classified into: Group 1: 20 children with CHD with pulmonary hypertension (PH) and Group 2: 20 children with CHD without pulmonary hypertension.
Twenty healthy children, matched for age and sex, were enrolled as a control group.
The inclusion criteria were: Children with CHD with left to right shunt lesions (VSD, ASD, and PDA).
The exclusion criteria were: Patients with acute and chronic inflammatory disease, sepsis, renal failure, or patients with history of cardiac operations, were not included in the study, since cardiac troponin levels may be affected in these circumstances.

3. METHODOLOGY

Between September 2018 and June 2020, the study was conducted on a total of 60 children: 20 patients with CHD with mean pulmonary arterial pressure≥25 mmHg by echocardiography; 20 patients with CHD without pulmonary hypertension (PH) and 20 healthy controls. For the standardization of the study, only patients with left to right shunt lesions as ventricular septal defect (VSD), atrial septal defect (ASD) and patent ductus arteriosus (PDA) were included. Since serum cardiac troponin levels may be high in the first three months of life, only infants or children aged between 3 and 36 months were included in the study.

All children in this study were subjected to the following:

1. **Complete history taking** (Name, Age, Gender, Weight, complain, present history, past history).
2. **Thorough clinical examination** with particular emphasis on: Heart rate (beat /min), respiratory rate (cycle/min), temperature ˚C, blood pressure (mm Hg) and O2 saturation (%), Complete local cardiac examination, Signs of congenital heart disease and Signs of pulmonary hypertension.
3. **Investigations:** Plain x-ray chest and heart (postero-anterior view), with measurement of C/T ratio. Electrocardiography (ECG) using (3 channel 1000 apparatus). Echocardiographic assessment: Doppler and Two –dimensional, M- mode Echocardiographic evaluations of CHD and pulmonary pressure.
4. **Serum High - Sensitive Cardiac Troponin-T (hs - cTnT)**; Using commercially available kits [8].

3.1 Limits and Ranges

The upper reference limit (99th percentile) for troponin T was determined at 14 ng/L (pg/mL), 95 % confidence interval 12.7‑24.9 ng/L (pg/mL). The lowest concentration less than or equal to 10 % (Limit of Quantitation) with the Elecsys Troponin T hs assay was 13 ng/L (pg/mL). Based on the WHO criteria for the definition of AMI, the cutoff (clinical discriminator) value for troponin T is 0.1 µg/L (ng/mL) or100 ng/L (pg/mL) as determined from ROC analysis in results with an earlier test generation of the Elecsys Troponin T assay.

The Limit of Quantitation (functional sensitivity) is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 10 % (10 independent runs; 1 run per day). It has been determined using low concentration troponin T samples.

3.2 Statistical Analysis

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, student t- test, Chi-square, Linear Correlation Coefficient and Analysis of variance [ANOVA] tests by SPSS V20.

4. RESULTS

*The mean age of Group I was [14.850±9.098 months] (range 3-36 months), the mean age of Group II was [21.650±10.199 months] (range 8-36 months), whereas the mean age of Control group was [16.400±9.670 months] (range 3-36 months), with no statistically significant difference in age between the studied groups (P>0.05). *As regards gender; Group I comprised [9] males (45%) and [10] females (55%), Group II comprised [7] males (35%) and [11] females (65%), whereas control group comprised [12] males (50%) and [12] females (50%), with no statistically significant difference in sex between the studied groups (P>0.05) (Table 1).

Of the 40 studied patients; [12.5% had PDA, 35% had VSD, 15% had ASD, 2.5% had PFO, 5% had VSD+PDA, 2.5% had ASD+PDA, 20% had ASD +VSD , 5% had PFO +VSD, and 2.5% had ASD + VSD + PDA] (Fig. 1).

*The mean serum level of hs-cTnT of Group I was [114.325±69.055 pg/ml] (range 38.7-372 pg/ml), the mean serum level of hs-c TnT of Group II was [54.584±21.517pg/ml] (range 18.8-98.5pg/ml) whereas the mean serum level of hs-cTnT of control group was [34.925±17.023pg/ml] (range 15-78 pg/ml), with significant increase in serum level of hs-cTnT in Group I as compared to Group II and control (P<0.05) (Table 2).

*There was significant positive correlation between serum hs-cTnT and heart rate, respiratory rate and PAP (P<0.05). *There was significant negative correlation between hs-cTnT and age, weight, temperature, SBP, O2 saturation (%), EF (%) and FS (%) (P<0.05) (Table 3).

*At hs-cTnT cut off value of [>85.2 pg/ml]; the sensitivity of hs-cTnT was (70%), specificity was (95%), Positive Predictive Value (PPV) was (93.3%), Negative Predictive Value (NPV) was (76%), and accuracy was (88.4%) (Table 4).

5. DISCUSSION

In the view of results of our study; participants' ages ranged between 3 and 36 months. There was no statistically significant difference between CHD group with PH (PH group) or without PH (non-PH group) in terms of age or gender (p <0.05).

Table 1. Demographic data of the studied groups

		Groups			ANOVA		Tukey's test		
		Group I (n=20)	Group II (n=20)	Control (n=20)	F	P-value	I&II	I&control	II&control
Age (Months)	**Range**	3-36	8-36	3-36	2.719	0.075			
	Mean ±SD	14.850±9.098	21.650±10.199	16.4±9.670					
Weight (kg)	**Range**	4-12	8-15	6-16	4.192	0.020*	0.026*	0.064	0.924
	Mean ±SD	9.535±3.243	11.825±2.111	11.5±2.646					
					Chi-Square				
		N	**%**	**N**	**%**	**N**	**%**	**X^2**	**P-value**
Gender	**Male**	9	45.00	7	35.00	10	50.00	0.950	0.622
	Female	11	55.00	13	65.00	10	50.00		

Table 2. Serum level of hs- cTnT of the studied groups

hs -cTnT (pg/ml)	Groups			ANOVA		Tukey's test		
	Group I (n=20)	Group II (n=20)	Control (n=20)	F	P-value	I&II	I&contrl	II&control
Range	38.7-372	18.8-98.5	15-78	18.582	<0.001*	<0.001*	<0.001*	0.323
Mean ±SD	114.325±69.055	54.584±21.517	34.925±17.023					

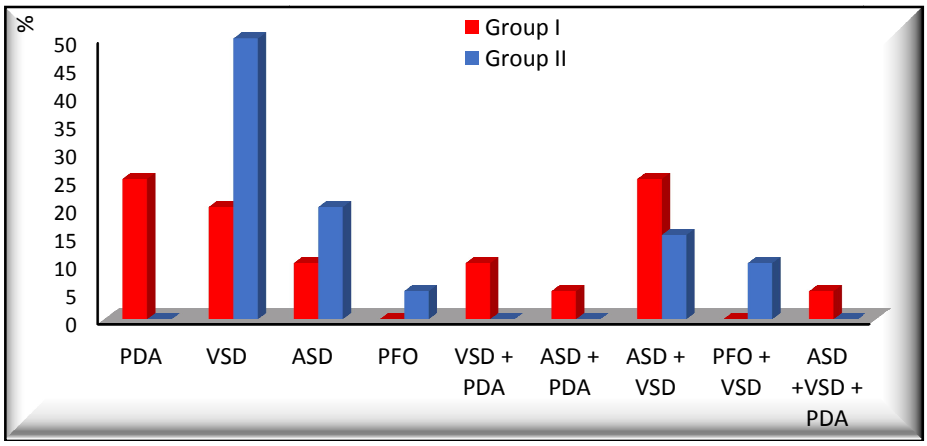

Fig. 1. Distribution of the patient groups according to the CHD present

Table 3. Correlation between serum hs-cTnT, and variable parameters of the patient groups

Correlations	hs-cTnT (pg/ml)			
	Group I(n=20)		Group II(n=20)	
	r	P-value	r	P-value
Age (Months)	-0.470	0.037*	0.042	0.860
Weight (kg)	-0.496	0.026*	0.075	0.752
PAP (mmHg)	0.767	<0.001*	0.010	0.965
HR (beats/min)	0.718	<0.001*	-0.162	0.495
RR (cycle/min)	0.625	0.003*	-0.076	0.750
Temperature©	-0.445	0.049*	-0.140	0.555
SBP (mmHg)	-0.826	<0.001*	-0.271	0.247
DBP (mmHg)	-0.410	0.073	0.205	0.386
O2 saturation %	-0.849	<0.001*	0.089	0.708
EF (%)	-0.632	0.003*	-0.162	0.495
FS (%)	-0.713	<0.001*	-0.485	0.060

PAP=pulmonary artery pressure HR= heart rate
RR= respiratory rate SBP = systolic blood pressure
DBP= diastolic blood pressure EF%= ejection fraction
FS%= fractional shortening

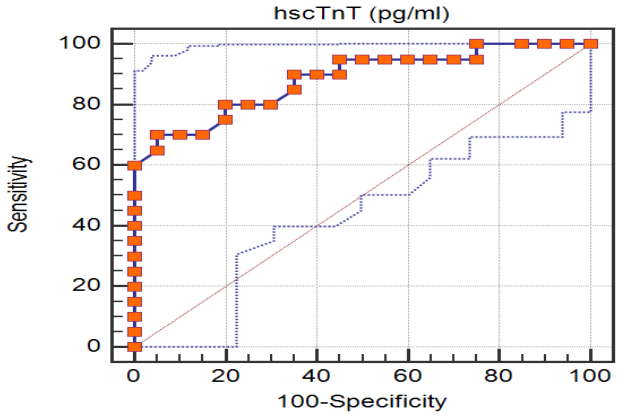

Fig. 2. ROC curve of serum hs-cTnT as novel biomarker in pediatric pulmonary hypertension due to left to right shunt lesions

Table 4. Cutoff, Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Accuracy of Highly Sensitive Cardiac Troponin T (hs- cTnT) as a novel biomarker in Pediatric Pulmonary Hypertension due to congenital left to right shunt lesions

ROC curve between Group I and Group II						
	Cutoff	**Sens.**	**Spec.**	**PPV**	**NPV**	**Accuracy**
hs-cTnT (pg/ml)	>85.2	70.0	95.0	93.3	76.0	88.4%

In the present study, there was significant decrease in weight in PH group compared with the healthy control cases and CHD cases with normal pulmonary artery pressure (the non-PH group). This may be attributed to that most of patients showing challenge in feeding while in respiratory distress. Often, they have diaphoresis during feedings that triggers decreased body weight and may be cachexia.

According to Nugent et al. [9], Azevedo et al. [12] and Madriago and Silberbach [10] reported that infants and children with heart failure have feeding difficulties (and therefore growth failure) which are commonly recognized as a presenting symptoms of heart failure in infant and young toddlers (age 0-2 years) due to dyspnea, increased fatigability and secretion of anorexic hormones that limit the volume of feedings .When heart failure is established for more than one month , weight loss becomes evident.

In the present study, hs-cTnT levels were statistically significantly higher in the PH group compared with the healthy control cases and the non-PH group.

This is in agreement with Kayali et al. [13], who reported that both hs-cTnI and hs-cTnT levels were statistically significantly higher in the PH group compared with the healthy control cases and CHD cases with normal pulmonary artery pressure (the non-PH group).

According to El-Khuffash and Molloy [11] also reported that cTnT levels in newborns with heart pathology were significantly higher than in healthy ones.

According to Muñiz [14] presented a case report of patient at the age of 9 weeks with combined congenital heart defect and chronic heart failure, in whom significantly elevated troponin levels were observed.

According to Selvin et al. [15] reported that the affinity of hs-cTnT levels secondary to structural heart disease was observed to be higher than epicardial coronary diseases , and high hs-cTnT levels are linked to myocardial damage.

According to Kriechbaum et al. [16] also reported that hs-cTnT increased in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and suggested that persistent subclinical myocardial damage was potentially triggered due to increased RV pressure. hs-cTnT levels significantly decreased with balloon pulmonary angioplasty treatment and were correlated with reduced RV wall stress.

According to Moreover, Sato et al. [17] reported that myocardial scarring and RV dysfunction may develop as a result of increased myocardial ischemia due to pressure load leading to increased hs-cTnT release.

In the current study, there was significant positive correlation between serum hs-cTnT and heart rate, respiratory rate and PAP ($P<0.05$), whereas, significant negative correlation was found between hs-cTnT and age, weight, temperature, SBP, O2 saturation (%), EF (%) and FS (%) ($P<0.05$).

In the current study, no correlation between shortening fraction (FS %) evaluated by echocardiography and hs-cTnT concentration in patients with CHD was observed. This is difficult to be referred with data from the literature, as yet only one study led by EL-Khuffash et al. [18] showed correlation between FS% and cardiac troponins concentration in newborns. They showed that cTnT concentrations in newborns with persistent ductus arteriosus (PDA) significantly correlated with the arterial duct diameter, the shunt velocity, and end diastolic volume in descending aorta.

The correlation between hs-cTnT concentration and hemodynamic significance of CHD creates potential possibility for above biomarker to be used for early detection of children with significant heart defects, who need urgent cardiology consultation.

The present study showed that at hs-cTnT cut off value of [>85.2 pg/ml]; the sensitivity of hs-cTnT was (70%), specificity was (95%), Positive Predictive Value (PPV) was (93.3%), Negative

Predictive Value (NPV) was (76%), and accuracy was (88.4%).

This in agreement with Kayali [13], who reported that the sensitivity and specificity of serum hs-cTnT levels in the prediction of pulmonary hypertension were determined as 78% and 80%, respectively. Besides; in patients with CHD having higher serum hs-cTnI and hs-cTnT levels, there was an increased probability of the presence of pulmonary hypertension. They also reported that in PH patients, hs-cTnT levels, compared with hs-cTnI, were determined to be statistically more significantly associated with PH. In logistic regression analysis, although both parameters were defined to be valuable for the prediction of PH, hs-cTnT was observed to be statistically more sensitive.

Torbicki et al. [19] reported the potential prognostic role of hs-cTnT in PAH. Although the prevalence of detectable hs-cTnT was only 14%, elevated levels were found to be associated with poor prognosis.

According to Masson et al. [20] reported that serial measurement of hs-cTnT levels had robust prognostic value beyond that of a single measurement. Also,Velez Martinez et al. [21] reported that cardiac troponin T indicated disease severity and predicted worse outcome in mixed cohorts of patients with pulmonary hypertension.

6. CONCLUSION

High-sensitive cardiac troponin T (hs-cTnT) could be used as a cardiac biomarker in PAH-CHD children with good diagnostic and prognostic value and high sensitivity and specificity, which may be useful in the management of PH in childhood.

CONSENT AND ETHICAL APPROVAL

Written informed consent was obtained from all subjects of the study or their parents or guardians. The study was approved by the Ethics Committee of Faculty of Medicine, Tanta University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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