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Original Research Article

Role of Highly Sensitive Cardiac Troponin I in the Prediction of Pediatric Pulmonary Hypertension due to Congenital Heart Disease

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Abstract: ***Background:*** CHD is a major health problem in pediatric population. It is associated with abnormal hemodynamic load and neurohormonal activation. Which leads to pulmonary hypertension causing myocardial injury. So, it needs timely intervention. Cardiac troponins are specific for myocardial injury. HscT I enhances accuracy for diagnosis of myocardial injury even in early stage of Pulmonary Hypertension. In recent years role of HscT I suggested to be useful in evaluation of PAH due to CHD in children. ***Objectives:*** To analyze the role of HscT I as a diagnostic tool for PAH due to CHD in Children. ***Methods***: This prospective cross-sectional study was conducted in Pediatric cardiology department, BSMMU over a period of 1 year. The study included total 54 patients with moderate to large VSD/PDA. Patients were selected according to inclusion and exclusion criteria. ***Results:*** Total 54 cases was divided into two group PAH group (n=27) and non-PAH (n=27) group. Among PAH group 20 patient (74.1%) had VSD and 7 patient (25.9%) had PDA. In non PAH group 15 had VSD (55.6%) and 12 had PDA (44.4%). The mean troponin I level was significantly higher in PAH group than non-PAH group (0.03052±0.0511 vs. 0.0087±0.0075, p=0.03). ***Conclusion:*** In this study, there was significant difference between HscT I level of PAH group and non-PAH group and significant positive correlation between HscT I level and mean PAP. As a marker of myocardial injury, HscT I can be a predictor of raised pulmonary arterial pressure in children with post tricuspid left to right shunt.

Keywords: Cardiac Troponin, Pediatric Pulmonary Hypertension, Congenital Heart Disease.

INTRODUCTION

Among most frequently diagnosed congenital disorders, congenital heart disease afflicts approximately 0.8% to 1.2% of live births worldwide [1]. Generally, CHD is defined as a structural abnormality of the heart and (or) great vessels that is present at birth. The incidence of CHD is relatively high in developing countries located in Africa and Asia, while low in most developed countries. Over the last 3 decades, the age-standardized mortality rate of CHD declined substantially, regardless of sex, age, and region. The decline is more prominent in developed countries [2]. CHD can occur as single lesions or in combination with other heart defects. Among diagnosed

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CHD lesions, isolated lesions include ventricular septal defects (VSD), atrial septal defects (ASD), and patent ductus arteriosus (PDA). Complex or combination lesions include atrioventricular septal defects (AVSD), Tetralogy of Fallot (TOF), and transposition of the great arteries (TGA). It is broadly classified as acyanotic and cyanotic congenital heart disease. TOF and TGA are the two most common cyanotic CHD that result in oxygen saturation below 90%. Majority of acyanotic defects are VSD, PDA, ASD and AVSD and those patients- have oxygen saturation above 95% [3]. Most CHD specially left to right shunt lesions including VSD and PDA have specific hemodynamics, including volume and pressure overload as well as pulmonary hypertension (PHN), which cause myocardial injury by activation of neurohormones & inflammatory cytokines [4]. Pulmonary hypertension is a condition characterized by increased pressure and resistance in the arterial vasculature of the lung as the result of numerous pathological mechanisms, eventually resulting in right ventricular failure [5]. Pulmonary arterial hypertension (PAH) is a common complication of congenital heart disease (CHD), particularly in patients with left-to-right (systemic-to-pulmonary) shunts. Persistent exposure of the pulmonary vasculature to increased blood flow and pressure results in vascular remodeling and dysfunction. Luminal obliteration and remodeling of the pulmonary vasculature leads to progressive increments in pulmonary vascular resistance. This leads to overload of the right ventricle, eventually right ventricular failure (RVF) develops and patient suffers premature death [6].

The defects associated with left to right shunt, if untreated, result in irreversible alterations in the pulmonary vascular bed, which is called pulmonary vascular obstructive disease. At this stage, surgical correction is impossible. Hence, the most essential point in the treatment of pulmonary arterial hypertension that has developed as a result of CHD is the timing of intervention. [7] The timing of treatment for congenital heart defect is based on the hemodynamic and anatomic situations, with consideration of myocardial cell adaptation and chamber remodeling. So it is important to have multiple methods available to detect the time of intervention [8]. Risk stratification is paramount in order to identify individuals at highest risk of death or progression of disease requiring more intense pharmacological treatment. So far, there are only few established parameters for follow-up and prognosis of patients with PAH [9].

Elevated cardiac troponins have also been noted in situations of right ventricular overload, both acute, as in acute pulmonary embolism [10] and chronic, as in pulmonary hypertension [11, 12]. HscTnI is a very specific and sensitive marker of myocardial injury [13]. High sensitive Troponin I (HscTn I) assay allows detection of 10-fold lower concentration of cardiac troponin [14]. This group of troponin assays might further enhance the accuracy of the diagnosis of myocardial ischemia, and could therefore offer improved diagnostic sensitivity and specificity, even in patients with early presentation [15, 16]. However, there is a substantioal gap on level of hscT I in healthy children. HscT I in pediatric age, for male child 0.0029ng/ml and for female child 0.0021ng.ml [17]. Although right heart catheterization is the gold standard test determining PH, it is not convenient for screening, as it is an invasive procedure [15]. Transthoracic echocardiography is a noninvasive and more practical way of diagnosing PH, but it is less sensitive and specific than catheterization [16]. To detect cardiac muscle injury Cardiac troponins can be the most sensitive and specific biochemical markers.

So the aim of study is to detect the level of HscTn I in children with CHD as a predictor of myocardial injury caused by hemodynamic load due to PH and to investigate whether this marker can be used in management of pediatric PH.

METHODS

This prospective cross-sectional study was conducted in Pediatric cardiology department, BSMMU over a period of 1 year. The study included total 54 patients with moderate to large VSD/PDA. Patients were selected according to inclusion and exclusion criteria. For the standardization of the study, only patients aged 4 month and above with moderate and/or large post-tricuspid shunts such as a Ventricular Septal Defect (VSD) and Patent Ductus Arteriosus (PDA) will be included. Exclusion criteria were Complex congenital heart disease like TGA,TA, T/PAPVC, VSD/PDA with PS, Patient less than 4 mo of age (Trop I may be high in first 3 mo age) and Patients with acute infections, diabetes mellitus, sepsis, or renal failure, or patients with a history of cardiac operations, is not included in the study, since cardiac troponin levels may be affected in these circumstances. Approval from the Institutional Ethical Committee of BSMMU, Dhaka was obtained before the commencement of this study. The aim and objective of the study along with its procedure, risk and benefits were explained to the respondents in easily understandable local language and informed written consent was taken from each parent. It was assured that all information and record would be kept confidential and the result of the study would be helpful both for the physicians and patients in making proper decisions.

RESULTS

This prospective cross-sectional study was conducted in the department of pediatric cardiology and biochemistry, BSMMU, Shahabag, Dhaka. A total of 54 children of aged 4 month and above with post tricuspid shunt with or without PAH were included in this study. The main objective of the study was to analyze the role of highly sensitive cardiac troponin I as a diagnostic tool for prediction of Pulmonary Arterial

Hypertension (PAH) in CHD. The study patients were divided into two groups according to PAH such as PAH group and non-PAH group. Quantitative variables were presented as mean±SD and comparison between two groups were performed by means of unpaired t test. Qualitative variables were presented as percentages and compared into groups by the chi square test. To find out the correlation between troponin I and various echocardiographic parameters of PAH, Pearson's correlation was used. Logistic regression analysis was performed to find out the predictors of interested variable. Differences with p values <0.05 were considered statistically significant. All analysis was performed using SPSS V 20.0 for Windows. Required statistical analyses with graphical presentations were documented below:

Table-1: Demographic characteristics of the patients between two groups (N= 54).

	PAH group (n = 27)		**Non-PAH group (n = 27)**		**Total (N=54)**		**p value**
Age							
Mean ± SD	50.7±57.8		33.1±34.1		41.9±47.8		0.27^{ns}
Range (min – max)	(5–204 months)		(4-120 months)		(4-204 months)		
	n	**%**	**n**	**%**	**n**	**%**	
Sex							
Male	13	48.1	11	40.7	24	44.4	0.58^{ns}
Female	14	51.9	16	59.3	30	55.6	
Residence							
Urban	8	29.6	8	29.6	16	29.6	1.00^{ns}
Rural	19	70.4	19	70.4	38	70.4	

ns = Not significant (p>0.05), p value reached from Mann Whitney U test and chi-square test.

Table-II: Comparison of echocardiographic parameters between two groups (N=54).

Variable	PAH group (n = 27)	Non-PAH group (n = 27)	P value
	Mean ± SD	Mean ± SD	
Shunt size (cm)	9.3±4.0	5.9±2.2	<0.001s
Tricuspid velocity (m/s)	3.5±0.7	1.9±0.5	<0.001s
PASP mmHg	54.8±23.1	21.3±7.6	<0.001s
PADP mmHg	37.4±15.3	14.6±5.1	<0.001s
Mean PAP mmHg	43.5±13.1	16.4±3.0	<0.001s

The above table shows the comparison of echocardiographic characteristics between two groups. The table indicates that shunt size, TI, PASP, PADP and mean PAP were found to be significantly higher in PAH group than non-PAH group patients (p<0.05).

Table-III: Comparison of serum troponin I level in two groups (N=54).

Varriable	**PAH group (n = 27) Mean ± SD**	**Non-PAH group (n = 27) Mean ± SD**	**P value**
Troponin I (ng/ml)	0.03052±0.0511	0.0087±0.0075	0.03^{s}

The above table demonstrates that the mean troponin I level was significantly higher in PAH group than non-PAH group (0.03052±0.0511 vs. 0.0087±0.0075, p=0.03) with statistically significant difference.

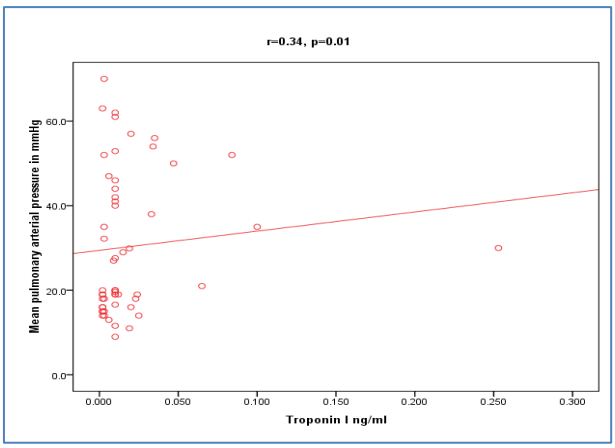

Fig-1: Scatter plot diagram showing correlation between serum troponin I and mean PAP among study patients.

The diagram shows that there is a positive moderate correlation between mean PAP and troponin I (r=0.34). It was observed that the Pearson's correlation was statistically significant (p=0.01) by correlation t-test. The above diagram also shows that mean PAP is increasing as well as troponin I level is also increasing. Hence there was an significant association between mean PAP and troponin I level.

DISCUSSION

In PH group VSD was more predominant as 20 cases out of 27 were VSD (74.1%) and only 7 (25.9%) cases were PDA. This is probably because transcatheter device closure of PDA has become more successful than previous years and most of the PDA cases are closed within 1-2 year. So there is less chance of developing PHTN in PDA cases. Meanwhile transcatheter VSD closure is not as popular as apart from peri membranous and muscular the other VSD types are not suitable for device closure. So, there is chance of developing PHTN in VSD cases. On the other hand, in non-PH group the distribution of VSD (15 cases, 55.6%) and PDA (12 cases, 44.1%) cases were almost equal.

Comparison of echocardiographic parameter between PH and non-PH group including shunt size, tricuspid velocity, PASP, PADP and mean PAP was significant between two groups. Mean shunt size in PH group was much larger than non-PH group. The mean shunt size in PH group was 9.3±4.0mm and in non-PH group was 5.9±2.2 mm. The larger shunt size causes more volume and pressure overload than smaller shunts leading to abnormal shear stress, circumferential wall stretch and endothelial dysfunction. Altered expression of vasoactive mediators, such as endothelin-1, prostacyclin and nitric oxide, results in vasoconstriction, while aberrant expression of vascular endothelial and fibroblast growth factors promotes vascular remodeling (including smooth muscle hypertrophy and proliferation) and increased intracellular matrix deposition causing pulmonary arterial hypertension [18]. Mean tricuspid velocity in PH and non-PH group was 3.5±0.7 m/s and 1.9±0.5 m/s respectively. As expected PASP, PADP and mean PAP was significantly higher in PH group than the non-PH group. Mean PASP, PADP and mean PAP in PH group was 54.8±23.1 mm hg, 37.4±15.3 mm hg and 43.5±13.1mm hg. Where as in non-PH group the respective values are 21.3±7.6 mm hg, 14.6±5.1 mm hg and 16.4±3.0 mm hg. In a similar study conducted by Kayali *et al*.2018 the mean PASP in PH group was 65.3 ± 13.3 mm hg and in non-PH group was 30.3 ± 6.2 mm hg. PASP in PH and non-PH group was slightly more than our study.

The mean troponin I level was significantly higher in PAH group than non-PAH group. The mean Troponin I level in PH group was 0.03052±0.0511 ng/ml and in non-PH group was 0.0087±0.0075 ng/ml. similar statistically significant difference was described in several studies. Kayali *et al*., 2018 found the mean Troponin I level in PH group 0.036 ± 0.035 ng/ml and in non-PH group was 0.008 ± 0.007 mm hg which was significantly different like our study. Several previous studies have explained the cause of elevated Troponin I level in PAH. A study reported that both ventricular hypertrophy and tension on the ventricular wall due to left to right shunts disrupt the myocardial perfusion [19]. Moreover, increased intra-wall pressure due to the tension also disrupts the coronary perfusion. As a result of all these alterations, the left to right shunt due to CHD and increased pulmonary flow results in myocardial ischemia [20]. Similar explanation was stated by Hafiz MO *et al*. 2015 as they described CHDs with large left to right shunts may result in an augmentation of right or left ventricular volume load, as well as a rise in right ventricular pressure by increasing pulmonary arterial pressure. Increased pressure and/or volume load results in myocardial injury. All these events leading to Myocardial injury and ischemia causes increased level of Troponin I [21]. In this study we found weak positive correlation between Troponin I and Tricuspid velocity, PASP PADP and significant positive correlation with mean PAP. Another study found similar positive relation between Troponin I and Tricuspid velocity in CHD [22]. The positive relationship between the level of troponin I and Tricuspid velocity indicate that troponin and the right ventricular myocardial function criteria in some patients are likely to be affected by pulmonary arterial hypertension (PAH). As pulmonary arterial hypertension affects right ventricular myocardial function. Myocardial dysfunction can be exaggerated by PAH evidenced by increased Tricuspid velocity and Troponin I [23].

Kayali S *et al*. 2018 found similar positive correlation between PASP and Troponin I level in CHD patients. This positive correlation is probably due to right ventricular volume and pressure overload seen in shunt lesions indicating pulmonary arterial hypertension measured by raised PASP and mean PAP. This phenomenon subsequently results in myocardial ischemia and injury which thereby causes increased level of troponin I [10, 12].

CONCLUSION

In this study, there was significant difference between HscT I level of PAH group and non-PAH group who had evidence of volume and pressure overload of right ventricle in echocardiography.

mPAP significantly correlated with increased level of HscT I. As this is a marker of myocardial injury, it can be concluded that elevated level of HscT I can be a predictor of raised pulmonary arterial pressure in children with post tricuspid left to right shunt.

Limitation of the study

As it is a single and tertiary care center study, it could have limited the power of statistical analysis to conclude that HscT I can be used as a biomarker to predict pulmonary arterial hypertension in patients with post tricuspid left to right shunt.

RECOMMENDATION

It is recommended that, further study and research should be done, to establish HscT I as a biomarker for prediction of pediatric pulmonary hypertension in CHD which will help in timely intervention and follow up of the patients, to reduce mortality from pulmonary hypertension with shunt lesions in children.

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