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ORIGINAL ARTICLE

Relation Between High Sensitive C-Reactive Protein and Left Ventricular Speckle Strain in Critically Il Children

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Abstract:

Background: *left ventricular dysfunction is one of the major determinates of the clinical outcomes in critically ill children. Early detection of myocardial dysfunction may be of help in modifying treatment in those critically ill children. The aim of this study was to investigate the relationship between High sensitive CRP(Hs CRP) and echocardiographic values in patients with critical illness and also the role of speckle tracking of the left ventricle as a predictor of subclinical myocardial dysfunction and/or as a prognostic factor of survival in the studied patients.*

Methods: *Hs –CRP was measured and echocardiographic images using tissue Doppler and speckle tracking two dimensional echo (STE) were prospectively acquired in 30 critically ill children and also 30 healthy children as a control.*

Results: *There is significant decrease in the EF by M mode (29.4+4.98) compared to the control (38.1+2.84). Systolic velocity of the mitral valve(S) by tissue Doppler was significantly decreased (4.4 versus 6.8 for the control), É/Á ratio significantly decreased (1.10 for the patient versus 1.52 for the control). STE showed significant decreased Left ventricular longitudinal strain(LVGLSS) 11.9 versus 24 .5 for the control. Hs CRP was significantly correlated with the left ventricle ejection fraction(LVEF), (S) velocity by and longitudinal systolic strain by speckle tracking .ROC curve showed that Hs-CRP [The AUR is 0.760, Sensitivity 85.36, specificity 84.6, Accuracy 84.7, PPV 84.6, NPV 89.6] was significant with cutoff value 42.63. . É/Á ratio and TTP (time to peak) were the only echo parameters that showed significant relation with the fate of patients.*

Conclusion: *Abnormal left ventricular function by tissue Doppler and STE were detected in critically ill children and were significantly correlated with Hs CRP.*

Keywords: real time echocardiography, speckle r-tracking, children, critical care

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Introduction

Myocardial dysfunction is common in critically ill patients. It may be due to ischemia, trauma, surgery, sepsis, drugs and toxins. Assessment of cardiac function is useful when first dealing with an unstable patient. Transthoracic echocardiography is the powerful diagnostic tool in this setting [1,2]. However, conventional echocardiography has its limitation in detection of the left ventricular dysfunction. Tissue Doppler imaging (TDI) has gained increasing acceptance as a mean of non-invasively assessing myocardial properties and has been demonstrated as a prognostic tool in cardiac diseases [3]. However, there is a paucity of published data on TDI in critical illness . Speckle Tracking Echocardiography (STE) has evolved as a noninvasive ultrasound imaging technique that allows for an objective and quantitative evaluation of global and regional myocardial function independently from the angle of insinuation and from cardiac translational movements. Its advantage over conventional echo warrants its use in the assessment of the global and regional myocardial performance in critically ill children [4].

C-reactive protein (CRP) is a reliable marker for systemic inflammation and tissue damage. Due to its wide reference range, high-sensitive measurement methods were developed for screening properties. High-sensitivity C-reactive protein levels were suggested to provide a strong and independent indication of risk of cardiac insult in critically ill children [5].

This study investigated the relationship between Hs-CRP and echocardiographic values in patients with critical illness and. Also the role of speckle tracking of the left ventricle as a predictor of subclinical myocardial dysfunction and/or as a prognostic factor of survival in the studied patients.

Subject and Methods

This is a prospective randomized controlled study included 60 children divided into two groups :

Group I: included thirty critically ill children with their age 26.3 ± 3.4 months admitted to PICU of Pediatric Department, Tanta University Hospital, Tanta, Egypt.

Group II: included 30 healthy children with their age 31.3 ± 9.20 months. The study was conducted between December 2011 and March 2013. Any critical ill child admitted to PICU was included in the study. Written informed consent was obtained from the parents.

Exclusion criteria: Patients were excluded if they had non-sinus rhythm, any congenital heart disease, mitral or aortic valves disease, any prosthetic mitral and/or aortic valve.

All subjects were subjected to the following: complete history taking, through clinical examination, routine laboratory tests including complete blood count (CBC), and arterial blood gases (ABG), xcoring parameters; Sequential Organ Failure Assessment (SOFA) score within 24 hours of admission [6].

High sensitivity C-reactive protein (Hs-CRP): Blood sample was obtained from our patients using the standard venipuncture technique into standard collection tubes and were centrifuged at 15000g for 10 minutes. Serum was stored in warehouse with temperatures below -20°C. serum Hs-CRP was assessed by a nephelometric method with a Behring Nephelometer 100 Analyzer, Dade Behring [7]

Echocardiographic Examination: Each child underwent a detailed echocardiographic study ,including M-mode, two-dimensional, color Doppler, TDI and speckle tracking using a GE Vivid 7 ultrasound machine equipped with an X4 matrix-array transducer. All echo studies were performed within 24 hour of admission

Inter-and intra-observer variability analysis: Two echocardiographic, blinded to clinical data, independently measured LV global peak systolic stain (PSS) of 10 randomized subjects (five patients and five controls) for inter-observer variability analysis. One observer measured LV global PSS twice for the 10 randomized subjects on two consecutive days for intra- observer variability analysis

M-Mode: Echocardiographic evaluation included left ventricle (LV) end-diastolic and end-systolic diameters, septum and LV posterior wall thicknesses in diastole and systole, LV end-diastolic and end-systolic volumes, and LV ejection fraction by Simpson’s method. Transmitral flow patterns were obtained by pulsed-wave Doppler echocardiography from apical four chamber views. Mitral peak early (E) and late (A) diastolic velocities, E/A ratio were measured. These echo parameters were measured from M-mode echo derived from the parasternal long axis view at the mitral chordal level for LV parameters. Left ventricular fractional shortening (LVFS) was calculated. Left ventricular ejection fraction (LVEF) was also calculated from M-mode echo.

Tissue Doppler imaging (TDI) was evaluated at the level of basal segments of anterior, septal, lateral and inferior LV wall and peak myocardial systolic, and early and late diastolic velocities were measured from apical two and four chamber views. Mean peak systolic (S), early diastolic (É) and late diastolic (Á) annular velocities were obtained by averaging respective values measured at the septal and lateral sides of the mitral annulus. Mean É and the derived mean É/Á ratio were used as load-independent markers of ventricular diastolic relaxation.

Speckle Tracking Echocardiography: Apical four-and two-chamber views images were obtained using conventional two dimensional grey scale echocardiography with a stable ECG recording. Care was taken to obtain true apical images using standard anatomic landmarks in each view allowing a more reliable delineation of the left ventricular endocardial border. Three consecutive heart cycles were recorded and averaged. The frame rate was set between 60 and 80 frames per second. Analysis of files recorded was performed off-line by a single experienced and independent echo cardiographer who was not directly involved in the image acquisition and had no knowledge of hemodynamic measurements, using commercially available semi-automated two-dimensional strain software (EchoPac, GE, USA), L V endocardial border is manually traced in both four- and two-chamber views, thus delineating a region of interest (ROI), composed by 6 segments. Then, after the segmental tracking quality analysis and the eventual manual adjustment of the ROI, the longitudinal strain curves are generated by the software for each segment. Peak Ventricular longitudinal strain (LV GLSS), measured at the end of the reservoir phase, and is calculated by averaging values observed in all LV segments. The time to peak longitudinal strain (TTP) is also measured as the average of all segments .

Statistical analysis: IBM SPSS statistics (V. 21.0, IBM Corp., USA, 2012) was used for data analysis. Data were expressed as mean ± standard deviation for quantitative parametric measures. The differences in the variables were compared between the patients and controls using the t-test. Pearson correlation test was used to study the possible association between each two variables among each group for parametric data. Statistical significance was defined as a p value <0.05.A receiver operating characteristic (ROC) curve was used to illustrate the diagnostic properties of a test on a numerical scale. The discriminative power for the prediction probability of the subclinical alteration in myocardial function was tested by the area under the receiver operating characteristic (ROC) curve.

Results

The demographic and laboratory data of the studied groups are represented in Table 1) .The mean age of our group is 26.3 month while it is 31.3 month for the control group. Half of our patients were boys. Sofa score for our patients ranged from 3-13 with mean of 6.26 ± 2.2. Respiratory and neurological causes were the major causes of admission to the PICU, representing 43% and 20 % respectively (Table 2).

Left ventricular systolic and diastolic function by different echo modes in our patients are presented in (Table 3). There is significant decrease in the EF by M mode (29.4 ± 4.98) compared to the control (38.1 ± 2.84). while there was no significant difference in the E/A ratio and E/É. Systolic velocity of the mitral valve by tissue Doppler was significantly decreased (4.4 versus 6.8 for the control) É/Á ratio significantly decreased (1.10 for the patients and 1.52 for the control). STE showed significant decreased Left ventricular longitudinal strain (11.9 versus 24 .5 for the control.)

Among 30 patients enrolled in the study, only 4 (13%) patients died during their stay in the ICU. For those children who died, É/Á ratio and TTP are the only echo parameters that showed significant relation with the fate. Also High sensitive CRP was significantly related to the fate (Table 4). High sensitive CRP was significantly correlated with , the left ventricle ejection fraction(LVEF), systolic velocity of mitral valve annulus (S) by tissue Doppler and longitudinal systolic strain by speckle tracking (Table 5). ROC curve in Figure 1 showed that Hs-CRP [The AUR is 0.760, Sensitivity 85.36, specificity 84.6, Accuracy 84.7, PPV 84.6, NPV 89.6] was significant with cutoff value 42.63.Sofa score was significantly correlated with É/Á ratio implying that the diastolic function of the left ventricle has prognostic value in critically ill children (Table 6).

Table 1. Demographic, anthropometric and laboratory data of the studied groups

	Patients		Controls		p
	Range	Mean± SD	Range	Mean ± SD	
Age (months)	6-144	26.28±3.36	9-108	31.3±9.2	0.126
Sex (male%)		50		53.3	0.88
Weight (kg)	5-32	11.36±3.33	9-26	16.33±5.17	**0.023***
Length (cm)	65-135	81.7±20.9	71.5-119	98.5±14.2	**0.008***
SOFA	3-13	6.26±2.2			
Hs-CRP	0.2-202	77.09±14.2	0.2-2.5	1.28±0.77	**0.001***

*significant SOFA: Sequential Organ Failure Assessment score

Discussion

Myocardial dysfunction is the one of the leading causes of mortality in critically ill patients. It may be due to different causes as ischemia, trauma, surgery, sepsis, drugs and toxins. Early identification of myocardial dysfunction, before the appearance of symptoms, can alter the prognosis by optimizing therapy [8].

Given its non-invasiveness and widespread availability, transthoracic echocardiography is a powerful diagnostic tool in this setting [1]. Left ventricular (LV) systolic function has been reported to be a powerful predictor of long-term survival in patients affected by a wide spectrum of cardiac diseases [9]. The most widely used echocardiographic parameter to quantify LV systolic function has been LV ejection fraction (LVEF). While LVEF is a strong predictor of mortality [10]. In our study, there was significant decrease of LVEF by conventional echo and S velocity by tissue Doppler. However LVEF by M mode is extremely load-dependent, it depends critically on operator expertise, and it is affected by significant intraobserver and interobserver variability [1] Diagnostic evidence of LV diastolic dysfunction can be obtained noninvasively by tissue Doppler imaging (TDI) through E/ E' ratio if > 15. If the ratio is between 8-15 it's suggestive and needs addition of other parameters such as Doppler flow through mitral valve [11].

In our study the E'/ A' ratio assessed by tissue Doppler imaging (TDI) was significantly decreased in our patients when compared with control group. This denoted that our critically ill children had also LV diastolic dysfunction (LVDD). Superiority of TDI in detecting LVDD is due to tissue velocity imaging appears to be less limited by the compensatory changes in loading conditions that confound measurement of diastolic function by conventional echocardiographic methods. Therefore, TDI can detect early or mild diastolic dysfunction [12].

E/E' ratio has been proposed as a useful index to evaluate LV diastolic dysfunction. However, E/E' ratio in our study show non-significant increase in patients in comparison to control group.

Arques et al documented that the peak early diastolic mitral E velocity is primarily influenced by left atrial pressure, LV relaxation and LV systolic pressure. The tissue Doppler-derived peak early diastolic E' velocity at mitral annulus is regarded as a noninvasive indicator for LV relaxation. The combination of E' with peak E velocity (i.e., E/E 'ratio) is assumed to be a useful index for LV diastolic function overcome the influence of ventricular relaxation [12]. However, E/E' ratio in our study show non-significant increase in patients in comparison to control group.

Table 2: Diagnosis of enrolled patients.

Cause of admission	No.	%
Respiratory diseases:	**13**	**43%**
Bronchopneumonia with respiratory failure	1	
Status asthmaticus	2	
Aspiration pneumonia with respiratory distress	3	
Respiratory distress with ARDS	1	
Bronchopneumonia complicated by right side empyema	1	
Right side pneumonia with pleural effusion	2	
Stridor with respiratory failure	1	
Bronchopneumonia complicated by right side pyopneumothorax	2	
Neurologic diseases	**6**	**20%**
Meningoencephalitis	1	
Status Epilepticus	2	
Coma with signs of lateralization	2	
Hydrocephalus, brain atrophy, increased intracranial pressure	1	
Metabolic disorders	**5**	**16%**
Diabetic ketoacidosis	2	
Acute renal failure	2	
Acute hepatic failure	1	
Hematologic disorders	**2**	**6%**
acute hemolytic Anemia	1	
Disseminated Intravascular Coagulopathy	1	
Gastro Intestinal disorders	**4**	**13%**
Gastrointestinal bleeding, esophageal varices grade IV, portal hypertension	2	
Severe gastroenteritis ,septic shock	2	

Table 3. Comparison of echocardiographic findings between the studied groups

Echocardiographic findings	Control	Cases	Z	P
LV EF	38.1±2.84	29.4±4.98	4.417	**0.001***
E/A	1.59±0.26	1.52±0.52	0.635	0.441
E/É	7.04±0.91	7.46±0.98	0.452	0.336
E'/A'	1.52±0.28	1.10±0.33	3.196	**0.001***
Mitral S	6.8±0.79	4.4±1.16	4.326	**0.001***
TTP	424±18.97	348±67.99	3.564	**0.001***
LV GLSS	24.5±1.72	11.9±3.83	4.704	**0.001***

*Significant LVEF : left ventricular ejection fraction;A: Late diastolic mitral flow velocity Á:mitral annulua velocity , E: early mitral filling velocity É: Early mitral annulus diastolic velocity by tissue Doppler imaging; Á: late mitral filling velocity by tissue Doppler imaging,S: Mitral annulus systolic velocity estimated by tissue Doppler, TTP: time to peak LVGLSS **:** left ventricle global longitudinal systolic strain

Table 4. Comparison of echocardiographic findings and HsCRP in relation to fate of cases

Echocardiographic findings	Alive	Died	Z	P
EF LV	29.08+5.18	31.5+3.11	0.949	0.343
E'/A'	1.15+0.32	0.77+0.22	2.193	**0.028***
Mitral S	4.42+1.21	4.25+0.96	0.221	0.825
TTP	358+65.49	282+47.91	2.261	**0.024***
LV GLSS	12.12+3.91	10.50+3.32	0.677	0.536
Hs-CRP	29.3±6.39	84.4±15.7	9.635	**0.004***

*Significan LVEF : left ventricular ejection fraction; É: Early mitral annulus diastolic velocity by tissue Doppler imaging; Á: late mitral filling velocity by tissue doppler S: Mitral annulus systolic velocity estimated by tissue Doppler, TTP: time to peak LVGLSS **:** left ventricle Global longitudinal systolic strain

Table 5: Correlation between High sensitivity C-reactive protein and Echocardiographic findings

Echocardiographic findings	High sensitivity C-reactive protein	
	r	p
EF LV	-0.552	**0.001***
E'/A'	0.003	0.987
Mitral S	-0.339	**0.032***
TTP	-0.140	0.390
LV GLSS	-0.330	**0.038***

*Significant LVEF : left ventricular ejection fraction; É: Early mitral annulus diastolic velocity by tissue Doppler imaging; Á: late mitral filling velocity by tissue Doppler, S: Mitral annulus systolic velocity estimated by tissue Doppler, TTP: time to peak,LVGLSS **:** left ventricle global longitudinal systolic strain

Figure 1. ROC Curve of the sensitivity and specificity of Hs-CRP in detecting subclinical cardiac insult.

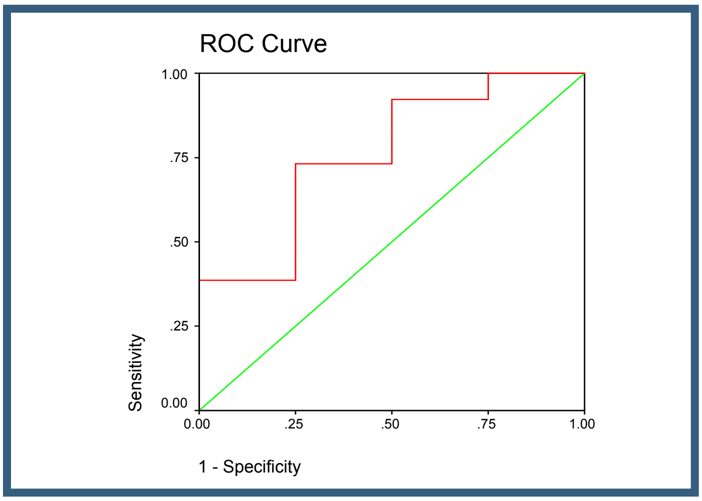

Table 6: Correlation between SOFA and echo variables

Variables	SOFA	
	r	p
LV EF	-0.190	0.314
Mitral annulus S	-0.069	0.718
Mitral annulus É/Á	-0.326	0.049*
TTP	-0.239	0.210
LV GLSS	0.226	0.230

Global LV function is result of the contraction and relaxation of a complex myocardial fiber architecture [13]. Myocardial fiber contraction determines changes of LV size and shape that are the result of concomitant longitudinal shortening, circumferential rotation, and radial thickening of the myocardium. The LVEF provides a global index of LV chamber function, ignoring the relative role of the different components of myocardial function (deformation in various directions and rotation), which may be affected to a different extent in different cardiac diseases even when LVEF is still in the normal range [14]. Two-dimensional speckle-tracking echocardiography has recently emerged as a novel technique for objective and quantitative evaluation of global and regional myocardial function, independent of the angle of myocardial insonation [15]. Two-dimensional speckle-tracking echocardiography done in our study showed significant decrease in the left ventricular longitudinal strain (11.9 ± 3.83) in critically ill children compared with the control group (24.5 ± 1.72). The survivors had no significant difference in the LV GLSS compared with the survivor indicating that LV GLSS alone had no prognostic value .

High-sensitivity C-reactive protein levels were suggested to provide a strong and independent indication of risk of cardiac insult in critically ill children [5].

In the current study, there was a significant increase in Hs CRP in patients group compared with the controls. This was in agreement with Rey et al., who found that serum level of Hs-CRP in all patients was significantly higher than that in the healthy control group [16]. Also, the study done by Pepys suggested that during any acute phase response, Hs-CRP has a remarkable and rapidly responsive dynamic range of up to a 10.000-fold increase, ranging from 0.05-500 mg/L [17]. Our current study showed significant difference in Hs CRP in survivors when compared with the non survivors. Same results were obtained by Anand et al. where mean serum HsCRP in survivor group was lower than in mortality group. That study included 200 cases with mortality rate 20% but our study included 30 cases with mortality rate 13% [18]. However , the study done by Das et al., found that the change in the levels of Hs-CRP in both surviving and non-surviving patients was not significant [19]. A CRP level of 3.76 mg/dL showed a sensitivity of 75% and a specificity of 65% in the study done by Rey et al [16]. Our ROC curve showed that Hs-CRP was significant with cutoff value 42.63.

The current study investigated the relationship between Hs-CRP and echocardiographic values in patients with critical illness . Interestingly that LVEF, S velocity and LV GLSS are significantly correlated with the Hs CRP.

Regarding SOFA score, there was significant increase in SOFA score in our patients in comparison with the control group . SOFA score was significantly lower in survivors than non-survivors. This is in agreement with precious studies that reported that SOFA score is a good indicator of prognosis and significantly negatively correlated with survival [6,20].

The ability of different variables measured in this study to expect survival was found being with higher with É/Á, TTP and Hs CRP only .However, there was statistically non-significant difference regarding LVLSS.

The early detection of subclinical myocardial dysfunction is an important target for management of sick children in PICU. The combination between laboratory and echocardiographic measurements can give us an opportunity for early diagnosis hence treatment for this life-threatening sequelae.

The ability to directly evaluate myocardial function may allow early sensitive detection of subclinical myocardial dysfunction, better risk stratification, and timely institution of interventions. However, large scale longitudinal studies are nonetheless required to substantiate the clinical values of these functional parameters in the management, risk stratification, and prognosis.

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