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Detection of Subclinical Left Ventricular Dysfunction by Speckle Tracking Echo in Patients with Sepsis

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Abstract

Background: Assessment of LV functions with M-mode or 2-dimensional echocardiography can be performed in the parasternal long- and short-axis views by placing the calipers perpendicular to the ventricular long axis. Current speckle-tracking echocardiography (STE) techniques require the acquisition of standard parasternal and apical images. The aim of this work was to detect the efficacy of STE to evaluate subclinical LV dysfunction in patients with sepsis. Methods: This case control study was carried out on 80 subjects. Subjects were divided into two equal group: group (I): diagnosed with sepsis or septic shock and group (II): normal individuals. Then group I was subdivided into two subgroups: subgroup I: 25 patients with septic shock and subgroup II:15 patients with sepsis. All patients were subjected to laboratory investigations (CRP, white blood cells, d-dimer, serum ferritin, platelets, bilirubin and creatinine), ECG, Echocardiography and STE. Results: PASP, LVEDV and LVESV were insignificantly different between septic shock and sepsis groups. A4C, A3C, A2C and GLS were significantly higher in septic shock group compared to sepsis and normal groups (P value < 0.05).Conclusions: Speckle-tracking echocardiography can detect early subclinical LV systolic dysfunction via the LV GLS, compared with conventional echocardiographic parameters in patients with septic shock.

Keywords: Subclinical Left Ventricular Dysfunction, Speckle Tracking Echo, Patients, Sepsis

1. Introduction:

Sepsis is defined as life-threatening organ dysfunction due to dysregulated host response to infection, and organ dysfunction is defined as an acute change in total Sequential Organ Failure Assessment (SOFA) score of 2 points or greater secondary to the infection cause. Septic shock occurs in a subset of patients with sepsis and comprises of an underlying circulatory and cellular/metabolic abnormality that is associated with increased mortality [1].

Assessment of left ventricular (LV) systolic function has a central role in the evaluation of cardiac disease. Accurate assessment is essential to guide management and prognosis. Numerous echocardiographic techniques are used in the assessment, each with its own advantages and disadvantages [2].

Conventional assessment of LV function: Linear dimensions

Assessment of LV function with M-mode or 2-dimensional echocardiography can be performed in the parasternal long- and short-axis views by placing the calipers perpendicular to the ventricular long axis. Change in LV cavity dimensions during systole can be used to calculate LV fractional shortening and ejection fraction (EF) [2-6].

Modified simpson biplane method:

The modified Simpson biplane method is the currently recommended method of quantifying LV volume and systolic function. This method calculates LV volume by manually tracking the LV endocardial border in 2 planes, the apical 4-chamber and the apical 2-chamber views. The LV is then approximated to a series of elliptical discs that are summated to determine LV volume. Assessment of the change in ventricular volumes between systole and diastole allows estimation of left ventricular ejection fraction (LVEF) [7, 8].

Strain echocardiography:

The more recent developments of tissue doppler imaging (TDI) and speckle-tracking imaging during the past decade have facilitated significant advances in noninvasive assessment of myocardial mechanics and cardiac function. These techniques used Doppler to assess myocardial motion and analysed motion at 1 point relative to another in the myocardium [9, 10].

Currentspeckle-tracking echocardiography (STE) techniques require the acquisition of standard parasternal and apical images. Global longitudinal strain (GLS) can be assessed from the apical window by using standard apical 4-chamber, 2-chamber, and long-axis images. Global circumferential strain (GCS) and global radial strain (GRS) can be assessed by using parasternal short-axis imaging performed at the basal, mid, and apical levels. Each technique requires the operator to mark the endocardial and epicardial borders [11].

The aim of this work was to detect the efficacy of STE to evaluate subclinical LV dysfunction in patients with sepsis.

2. Patients and methods:

This case control study was carried out on 80 subjects at cardiology and ICU Department of Benha and Kafr-Elsheikh University Hospitals. Adult patients (20 – 60 years old) with sepsis or septic shock.

An informed written consent was obtained from the relatives of the patients. The study was approved by the Ethics Committee of Faculties of Medicine, Benha and Kafr Elshiekh Universities.

Exclusion criteria were patients with moderate to severe valvular disease, with prior cardiac surgery, with

infective endocarditis, with ischemic heart disease, with post cardiopulmonary resuscitation state, with poor image echocardiography quality and with COVID 19.

2.1. Subjects were divided into two equal group:

Group (I): patients diagnosed with sepsis or septic shock and group (II): normal individuals. Group I was subdivided into two subgroups: subgroup I: included 25 patients with septic shock and subgroup II: included 15 patients with sepsis.

All patients were subjected to: Full history taking, the sources of infection were identified, clinical examination (vital signs), routine laboratory investigations (CRP, white blood cells, d-dimer, serum ferritin, platelets, bilirubin and creatinine), electrocardiogram (ECG), Echocardiography and speckle-tracking echocardiography (STE).

2.2. ECG

The average ECG amplitude reduction for each patient was calculated by adding the percent reduction in the limb lead to the percent reduction in the precordial lead and dividing the result by 2. Statistical analysis was then performed on the averaged value for the QRS amplitude. For septic patients, ECGs from periods when the patients were not septic were compared to tracings during the period of sepsis. If multiple tracings were available when the patient was not septic, the tracing with the lowest QRS voltage was selected to minimize bias.

For control patients, the outpatient ECG closest in time to the hospitalization was selected as baseline. When more than 1 ECG was available for a control patient, the one with the lowest QRS amplitudes or longest QRS duration was selected.

2.3. Echocardiography

All studies were performed using (Philips epiq7 and GE vivid seven cardiac ultrasound phased array system with TDI. All echocardiographic examinations were performed according to the recommendations of ASE [12].

- Conventional echocardiography: The left atrium was be measured in the left parasternal long axis view. LV diameters and wall thicknesses were measured in the left parasternal long axis view at the level of the mitral valve tips, ensuring a measurement perpendicular to the long axis of the ventricle. EF and fractional shortening (FS) were determined using 2D guided M mode echocardiographic tracings at the parasternal long axis view using Teichholz formula. Pulsed wave Doppler was used to record trans-mitral flow at the tips of the mitral leaflets in the apical four-chamber view. Continuous wave Doppler was used to record tricuspid regurge systolic jet velocity in apical four chamber view. Tricuspid regurgitation velocity, pulmonary artery systolic pressure (PASP), LV end-diastolic volume, LV end-systolic volume, left atrial volume index, EF, S-wave, E/A ratio and E/e ratio were calculated.
- Two-dimensional speckle-tracking echocardiography (2D-STE): The LV GLS was calculated in the longitudinal three-chamber, two-chamber, and four-chamber views by 2D-speckle-tracking echocardiography with high-quality ECG gated images. The frame rate was set at between 50 and 90 frames/s, and a minimum of three cardiac cycles were obtained for each loop. The LV endocardial border was manually traced in the end systole. Subsequently, software generates a speckle-tracking region-of-interest (ROI) to include the entire myocardium between the endocardium and the epicardium. The LV was divided into 18 myocardial segments. Longitudinal strains for each segment were recorded and presented as a bull's eye. The strain values for all the segments were recorded and averaged to obtain the GLS. GLS was presented as a percent change (%). Negative values of GLS indicate myocardial contraction. The predefined cutoff for subclinical LV systolic dysfunction in patients with septic shock was defined by a GLS $\geq -15\%$ (less negative than -15%) according to the previous studies [13-15]

2.4. Statistical analysis

Statistical analysis was performed using the SPSS (Statistical Package for the Social Sciences) version 25 (IBM Inc., Chicago, IL, USA).Shapiro-Wilks normality test and histograms were used to test the distribution of quantitative variables to select accordingly the type of statistical testing: parametric or nonparametric. Parametric variables (e.g., age) were expressed as mean and standard deviation (SD) and were compared using F test among the three groups with post hoc (Tukey) test to compare each two groups. Comparison between two variables within the same group was compared by paired T test. Non- parametric variables (e.g., VAS) were expressed as median and interquartile range (IQR) and were analysed using Kruskal-Wallis test; further analysis was performed by Mann–Whitney (U) test to compare each two groups. Comparison between two variables within the same group was compared by Wilcoxon test.

Categorial variables (e.g., sex) were expressed as frequency and percentage and were statistically analysed by Chi-square test. A two-tailed P value ≤ 0.05 was considered statistically significant.

3. Results:

Demographic data were insignificantly different among the three groups. Fever was insignificantly different between both sepsis and septic shock groups, while GCS, MAP, pulse and PF ratio were significantly different among the studied groups (P value < 0.001). GCS was significantly lower in septic shock group than sepsis and normal groups and was insignificantly different between sepsis and normal groups (P value < 0.001). Pulse was insignificantly different between both sepsis and septic shock groups but was significantly higher in septic shock group than normal group (P value < 0.001). MAP and PF ratio were significantly lower in septic shock group than sepsis and normal groups, and significantly lower in sepsis group than normal group (P value < 0.05).

Table (1) Demographic data and clinical examination of the studied group (n = 80)

		Septic shock (n=25)	Sepsis (n=15)	Normal (n=40)	P value
Age (years)		48.56 ± 11.26	41.33 ± 14.56	42.6 ± 12.23	0.109
sex	Male	13(52 %)	7(46.67%)	20 (50%)	0.948
	Female	12(48%)	8(53.33%)	20(50%)	
DM		14 (56%)	5 (33.33%)	16 (40%)	0.299
HTN		17 (68%)	7 (46.67%)	16 (40%)	0.086
Clinical examination					
Fever		15 (60 %)	9 (60%)	14 (35%)	0.082
GCS		11.72 ± 3.54	14.4 ± 1.12	15 ± 0.0	<0.001*
		P1 <0.001*, P2 <0.001*, P3 = 0.595			
MAP (mmHg)		56.68 ± 4.26	74.4 ± 5.99	92.6 ± 7.39	<0.001*
		P1 <0.001*, P2 <0.001*, P3 <0.001*			
Pulse (beats/min)		92.6 ± 15.71	94.07 ± 11.37	81.55 ± 7.98	<0.001*
		P1= 0.585, P2 = 0.01*, P3 = 0.322			
PF ratio		133.24 ± 36.36	243.47 ± 49.94	446.75 ± 29.17	<0.001*
		P1 <0.001*, P2 <0.001*, P3 <0.001*			

Data are presented as mean ± SD or frequency (%). DM: Diabetes milletus, HTN: Hypertension, GCS: Glasgow coma scale, MAP: Mean arterial blood pressure, PF ratio: PaO2/FiO2 ratio, *: significant as P value ≤ 0.05.

Laboratory examinations were significantly different among the studied groups (P value <0.001). CRP was significantly higher in septic shock and sepsis groups compared to normal group (P value <0.001). PCT was significantly higher in both groups compared to normal group (P value <0.05). WBCs was significantly higher in septic shock and sepsis groups compared to normal group (P value <0.05).

D – dimer was significantly higher in septic shock group compared to sepsis and normal groups and significantly higher in sepsis group compared to normal group (P value <0.05). Serum ferritin was significantly higher in septic shock and sepsis groups compared to normal group (P value <0.001). PLT count was significantly lower in septic shock and sepsis groups compared to normal group (P value < 0.05).

Bilirubin was significantly higher in septic shock group compared to both sepsis and normal groups (P value <0.001). Creatinine was significantly higher in septic shock group compared to both sepsis and normal groups and was significantly higher in sepsis group compared to normal group (P value <0.05).

Table (2) Laboratory examination of the studied groups**.**

	Septic shock (n=25)	Sepsis (n=15)	Normal (n=40)	P value
CRP (mg/L)	85.32 ± 81.84	50 ± 39.79	5.68 ± 4.33	<0.001*
	P1 = 0.075, P2 <0.001*, P3 = 0.01*			
PCT (%)	2.28 ± 2.62	1.12 ± 0.71	0.05 ± 0.03	<0.001*
	P1= 0.051, P2 <0.001**, P3= 0.054			
WBCs (*10^{3}cells/mL)	13.32 ± 8.97	13.6 ± 5.22	6.64 ± 1.98	<0.001*
	P1 = 0.988, P2 <0.001*, P3 <0.001*			
D-dimer	723.12 ± 359.62	478.4 ± 139.12	165.83 ± 74.61	<0.001*
	P1 = 0.002*, P2 <0.001*, P3 <0.001*			
Serum ferritin (mcg/L)	313.8 ± 123.94	269.27 ± 76.81	124.33 ± 64	<0.001*
	P1 = 0.282, P2 <0.001*, P3 <0.001*			
PLT (*103cells/mL)	112.84 ± 24.34	108.07 ± 28.34	341.03 ± 75.62	<0.001*
	P1 <0.001*, P2 = 0.005*, P3 <0.001*			
Bilirubin (mg/dL)	6.6 ± 4.89	1.69 ± 0.45	0.65 ± 0.3	<0.001*
	P1 <0.001*, P2 <0.001*, P3 = 0.428			
Creatinine (mg/dL)	3.43 ± 1.49	1.59 ± 0.24	0.64 ± 0.31	<0.001*
	P1 <0.001*, P2 <0.001*, P3 =0.002*			

CRP: C-reactive protein, PCT: Plateletcrit, WBCs: White blood cells, PLT: Platelets, *: significant as P value ≤ 0.05.

Tricuspid regurgitation velocity, PASP, LVEDV and LVESV were significantly different among the studied groups (P value < 0.05) while LAVI, Ef, S Wave, E/A ratio and E/e ratio were insignificantly different among the studied groups. Tricuspid regurgitation velocity was significantly higher in septic shock group compared to both sepsis and normal groups but was insignificantly different between sepsis and normal groups (P value < 0.05). PASP, LVEDV and LVESV were significantly lower in septic shock and sepsis group compared to normal group (P value < 0.05). Table 3

Table (3) Conventional echocardiographic variables of the studied groups.

	Septic shock (n=25)	Sepsis (n=15)	Normal (n=40)	P value
Tricuspid regurgitation velocity (m/s)	2.69 ± 0.39	2.27 ± 0.21	2.37 ± 0.35	<0.001*
	P1 = 0.001*, P2 = 0.001*, P3 = 0.578			
PASP (mmHg)	33.77 ± 10.7	35.23 ± 11.31	28.21 ± 6.18	0.01*
	P1 =0.868, P2 = 0.042*, P3 = 0.028*			
LVEDV (%)	104.08 ± 22.5	105.07 ± 22.67	118.12 ± 11.39	0.006*
	P1 =0.984, P2 = 0.008*, P3 = 0.047*			
LVESV (%)	37.34 ± 9.66	38.63 ± 9.64	51.67 ± 5.1	<0.001*
	P1 = 0.865, P2 <0.001*, P3 <0.001*			
LAVI	23.32 ± 4.37	21.93 ± 4.4	21.1 ± 3.13	0.079
Ef (%)	67.08 ± 3.41	67.87 ± 4.07	67.9 ± 3.56	0.65
S – Wave	9.87 ± 0.56	9.83 ± 0.71	9.79 ± 0.57	0.878
E/A ratio	1.37 ± 0.18	1.32 ± 0.08	1.35 ± 0.14	0.551
E/e ratio	6.11 ± 1.06	6.08 ± 1.38	5.65 ± 1.26	0.26

PASP: pulmonary artery systolic pressure, LVEDV: Left Ventricular End-Diastolic Volume, LVESV: left ventricular end-systolic volume, LAVI: Left atrial volume index, Ef: Ejection fraction, *: significant as P value ≤ 0.05.

Strain echocardiographic variables were significantly different among the studied groups (P value < 0.05). A4C, A3C, A2C and GLS were significantly higher in septic shock group compared to sepsis and normal groups but was insignificantly different between sepsis and normal groups (P value < 0.05). Table 4

Table (4) Strain echocardiographic data in the studied groups**.**

	Septic shock (n=25)	Sepsis (n=15)	Normal (n=40)	P value
A4C (%)	-18.41 ± 3.25	-20.92 ± 2.41	-20.22 ± 7.07	0.001*
	P1 = 0.022*, P2 = 0.001*, P3 = 0.93			
A3C (%)	-16.31 ± 1.89	-18.77 ± 2.28	-20 ± 2.14	<0.001*
	P1 = 0.022*, P2 = 0.001*, P3 = 0.93			
A2C (%)	-18.44 ± 3.23	-21.14 ± 2.36	-23.11 ± 3.03	<0.001*
	P1 = 0.019*, P2 <0.001*, P3 = 0.082			
GLS	-18.01 ± 2.6	-20.16 ± 1.52	-21.45 ± 2.15	<0.001*
	P1 = 0.011*, P2 <0.001*, P3 = 0.137			

A4C: Apical 4-chamber view, A3C: Apical 3-chamber view, A2C: Apical 2-chamber view, GLS: Global longitudinal strain, *: significant as P value ≤ 0.05.

4. Discussion

Sepsis and septic shock are the main reasons for hospitalization and also the leading causes of death and disability in America and are associated with billions in healthcare costs each year [16]. STE has been shown to be a feasible and sensitive quantitative technology for assessing ventricular contractile function in a variety of different cardiovascular diseases such as chemotherapy-induced cardiotoxicity [17], amyloidosis [18], preeclampsia [19] and in a pediatric cohort with severe sepsis **[20]**.

According to the findings of the present study, the demographic data (age, gender, diabetes mellitus and hypertension) were insignificantly different among the three groups.

The results are in agreement with the findings of Hai et al., [16] who carried out a cross-sectional study on 127 consecutive adult patients were diagnosed with septic shock and sepsis, admitted to the intensive care unit (ICU). the results showed that there were no significant differences about age, gender, diabetes mellitus and hypertension.

From the results in the current study, it was observed that Glasgow GCS was significantly lower in septic shock group than sepsis and normal groups and was insignificantly different between sepsis and normal groups. Our results are in the line with Shabanh et al., [21] showed similar results in the prospective observational case-control study, which was recruited to retrieve the prognostic value of LVF assessment using STE among Egyptian adults, who admitted to ICU as a resultant impact of sepsis or septic shock. The results demonstrated that GCS was significantly lower in the septic shock group compared to the sepsis group.

In contrary, Hai et al., [16] explained that MAP was significantly elevated in sepsis group compared to the septic shock group.

In the present study, Pulse was investigated in all participants and reported that there was no statistically significant difference between both sepsis, septic shock groups and sepsis, normal groups but was significantly higher in septic shock group than normal group. Our results come in line with Shabanh et al., [21] who measured pulse in both septic shock and sepsis groups

and demonstrated that pulse was insignificantly different between the studied groups.

In the present study, PaO2/FiO2 ratio (PF ratio) was significantly lower in septic shock group than sepsis and normal groups, and significantly lower in sepsis group than normal group. These results are harmonious with Orde et al., [22] who evaluated the frequency and prognostic value of biventricular function, assessed by STE in patients with severe sepsis or septic shock. Over an eighteen-month period, sixty patients were prospectively imaged by transthoracic echocardiography within 24 hours of meeting severe sepsis criteria. The results exhibited that PaO2/FiO2 ratio was significantly lower in septic shock group in comparison with sepsis and control subjects.

The laboratory investigations in the current study revealed that CRP was insignificantly different between septic shock and sepsis groups but was significantly higher in septic shock and sepsis groups compared to normal group.

Furthermore, Soliman et al., [23] included 3 groups sepsis, septic shock and normal groups. Laboratory investigations, APACHE IV, SAPS II and SOFA scores were calculated. The results demonstrated that CRP was insignificantly different between septic shock and sepsis groups but was markedly increased in septic shock and sepsis groups contrasted to the normal group.

The present study demonstrated that the WBCs count was insignificantly different between septic shock and sepsis group but was significantly higher in septic shock and sepsis groups compared to normal group. Shabanh et al., [21] reported similar results, the WBCs count was insignificantly different between septic shock and sepsis group.

Additionally, the present results revealed that D – dimer was significantly higher in septic shock group compared to sepsis and normal groups and significantly higher in sepsis group compared to normal group. In accordance with the present results, Turak et al., [24] revealed that D- dimer level in sepsis patients was significantly higher than the normal group.

According to the results of the present study, serum ferritin was insignificant between septic shock and sepsis groups but was significantly higher in septic shock and sepsis groups compared to normal group. Our results are confirmed by Florido et al., [25] who carried out a prospective observational cohort study to evaluate iron, transferrin and ferritin serum levels in patients with severe sepsis and septic shock and its association with severity of organ dysfunction. The results revealed that ferritin level was significantly increased in sepsis and septic shock patients compared to the control group.

According to our findings, PLT count was insignificantly different between septic shock and sepsis groups but was significantly lower in septic shock and sepsis groups compared to normal group. Shabanh et al., [21] reported similar results that the PLT count was insignificantly different between septic shock and sepsis group.

The current results illustrated that the Bilirubin was significantly higher in septic shock group compared to both sepsis and normal groups but was insignificantly different between sepsis and normal groups. These results are in agreement with Shabanh et al., [21] who found that total bilirubin in septic shock group was higher than the sepsis group and direct bilirubin was significantly higher in septic shock group compared to sepsis group.

In the present study, the creatinine level showed a statistically significant elevation in septic shock group compared to both sepsis and normal groups and was significantly higher in sepsis group compared to normal group. These results are against Shabanh et al., [21] who reported that creatinine level was insignificantly different between septic shock and sepsis groups.

According to the conventional echocardiography conducted in our study, the tricuspid regurgitation velocity was significantly higher in septic shock group compared to both sepsis and normal groups but was insignificantly different between sepsis and normal groups. The present result is matched with Orde et al., [22] who illustrated that tricuspid regurgitation velocity was significantly higher in septic shock group compared to both sepsis and normal groups.

The present study demonstrated that PASP, left ventricular end-diastolic volume (LVEDV) and LVESV were insignificantly different between septic shock and sepsis groups but was significantly lower in septic shock and sepsis group compared to normal group. In agreement with the present results, Hai et al., [16] reported that differences in LVEDV and LVEDS were not statistically significant between septic shock patients and the control.

Depending on the conventional echocardiographic results, the LAVI, EF, S wave, E/A ratio and E/e ratio were insignificantly different among the studied groups. Our results are comparable to Shabanh et al., [21] who investigated the echocardiographic characteristics of septic shock and sepsis patients in particular, the mean values of EF, E/A ratio and E/e ratio that there were insignificantly different among the studied groups.

Furthermore, the present study used speckle-tracking echocardiography (STE) for investigation the myocardial dysfunction by measuring A4C, A3C, A2C and GLS that were significantly higher in septic shock group compared to sepsis and normal groups but was insignificantly different between sepsis and normal groups. Similarly, Hai et al., [16] used STE for diagnosis of septic shock patients and showed that subclinical LV systolic dysfunction was related to less negative values of longitudinal strain in A3C, A4C, A2C and GLS that appeared markedly in septic shock group compared to sepsis group.

Limitations: The small sample size, repeated imaging and further STE analysis were not performed during hospitalization, so reversibility of LV systolic dysfunction could not be assessed, other speckle tracking parameters to evaluate LV systolic function, such as global circumferential and radial strain, which is showed

to be promising, were not obtained and mortality rate was not evaluated among patients.

5. Conclusions

Speckle-tracking echocardiography can detect early subclinical LV systolic dysfunction via the LV GLS, compared with conventional echocardiographic parameters in patients with septic shock.

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