Research Article

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The effect of dobutamine stress echocardiography on tissue doppler imaging values as a predictor of mortality in patients with septic shock

Abstract

Introduction: Recently Dobutamine Stress Echocardiography [DSE] was used to study the cardiovascular response in patients with septic shock. It was found that the increase in the stroke volume index after DSE most strongly correlated with survival. However, its effect on the Tissue Doppler Imaging [TDI] values in patients with septic shock and its ability to predict the mortality were not well established.

Aim: To study the effect of DSE on Tissue Doppler Imaging values as a predictor of mortality in patients with septic shock.

Methods: This prospective non-randomized interventional study was conducted on adult mechanically ventilated patients admitted to the intensive care unit [ICU] within 24 hours from the diagnosis of septic shock and receiving norepinephrine. Echocardiographic data including TDI values were recorded at baseline and after the start of graded dobutamine infusion with gradual increasing of the dose from 5µg/Kg/min to 15µg/kg/min with 15minutes intervals. TDI values were obtained by placing the pulsed wave TDI at lateral and septal mitral annulus on apical four chamber view and the average value was obtained. All the patients were followed for 28 days to determine ICU mortality, 28 days mortality and weaning of norepinephrine. Patients were divided into survivors who survived the ICU stay and those who did not [non-survivors].

Results: During the period of 14 months, 69 adult septic shock patients were enrolled in the study, of which 18[26.1%] survived the ICU stay while 51[73.9%] did not. At rest, s' wave was significantly lower in survivors [8±2 vs 12±4 cm/s, P<0.001]. After dobutamine, there was no significant difference between the 2 groups [13±3 vs 15±2 cm/sec, P=0.07]. The stress-rest difference was significantly higher in survivors [7±2 vs 1±3 cm/s]. There was no significant difference as regards the e', a' and E/e' ratio. A receiver operator characteristic [ROC] curve of the stress-rest change showed that a cutoff value of>4 cm/s was associated with better survival of the ICU stay with area under the curve [AUC] of 0.939 [95% confidence of interval [CI]=0.871-0.999], sensitivity of 88.2% specificity of 88.9%, PPV of 95.7%, and NPV of 72.7%. Patients with stress-rest s'> 4 cm/s compared to those with ≤4 cm/s showed lower ICU and 28 days mortality [27.7% vs 95.7%, P<0.001], better weaning of norepinephrine [100% vs 19.1%, P<0.001], and lower norepinephrine dose [13.77±3.15 vs 20.15±6.48 µg/min P<0.001].

Conclusion: TDI changes after DSE were able to predict survival in septic shock patients with s' wave stress-rest change of >4 cm/s was associated with lower ICU mortality, 28 days mortality, better weaning of norepinephrine and lower norepinephrine dose.

Keywords: tissue doppler imaging, sepsis, septic shock, dobutamine stress echocardiography, intensive care unit, mortality, septic cardiomyopathy

Volume 11 Issue 1 - 2019

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Received: January 09, 2019 | **Published:** February 06, 2019

Key points

A. Question: How can changes of tissue doppler imaging in response to dobutamine stress predict mortality in patients with septic shock?

B. Findings: Patients with stress-rest change of s'> 4 cm/s compared to those with ≤4 cm/s showed lower ICU and 28 days mortality, better weaning of norepinephrine and lower norepinephrine dose.

C. Meaning: Changes of s' wave in response to dobutamine challenge was able to differentiate between survivors and non-survivors of septic shock.

Abbreviations

DSE, dobutamine stress echocardiography; TDI, tissue doppler imaging; ICU, intensive care unit; APACHE-II score, Acute Physiology and Chronic Health Evaluation II score; AUC, areas under the curve; BSA, body surface area; CI, cardiac index; SOFA, sequential organ failure assessment; ROC, receiver operating characteristic curves; SVI, stroke volume index; SIMD, sepsis-induced myocardial dysfunction; GCS, glasgow coma scale; TTE, trans-thoracic echocardiography; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction

Introduction

Sepsis is considered a major public health problem with a high rate of ICU admission and accounting for high hospital costs in developed countries.[1] A systemic review studied the sepsis burden on the health care service from published national or local population estimates to the global population and showed that about 30 million episodes and 6 million deaths occurred from sepsis.[2] Mortality from sepsis depends on the development of a shock state and number of organs impaired. Survivors from septic shock suffer from impaired quality of life, increased dependence, re-hospitalization, increase healthcare consumption and along with increased mortality; all contribute to the humanistic burden of sepsis.[3] During the pathogenesis of sepsis, the cardiovascular system plays a cornerstone rule. Myocardial dysfunction in sepsis is considered a common finding with about more than half of the patients with septic shock exhibit signs of myocardial dysfunction.[4] A contradiction was found between several studies addressing the impact of myocardial dysfunction and mortality in patients with septic shock. Recently a systemic review showed that diastolic dysfunction was more common among patients with septic shock and associated with higher mortality than patients with isolated systolic dysfunction.[5,6] An experiment performed on animals showed that depression in myocardial function was a feature of early stages of sepsis and this early depression was able to predict the outcomes in septic animals.[7]

Sepsis-induced myocardial dysfunction [SIMD] was a topic of interest for the past 30 years with different studies trying to describe the clinical characteristic of myocardial dysfunction.[8] Parker and Parrillo et al.[9] in 1984, found in about 50% of patients with sepsis, an initial reduction of the systolic function with increase in both end systolic and end diastolic volumes despite preserved or elevated cardiac index. Other studies described SIMD as been reversible reduction of the ejection fraction of both ventricles with ventricular dilation and less response to fluid resuscitation and catecholamines.[9] Recent studies have suggested that SIMD could be defined as impairment in the left ventricular [LV] intrinsic myocardial contractile function either systolic or diastolic of both left and right ventricles.[10,11] Depending on the ejection fraction [EF] or cardiac index [CI] to detect the myocardial dysfunction in septic shock patients revealed inconsistent results as they are considered load-dependent indices that do not reflect the intrinsic myocardial contractile function during sepsis.[11] Recently advanced echocardiographic techniques, as speckle tracking and Doppler Tissue Imaging have been examined as a method for detection of subtle myocardial dysfunction occurring during sepsis.[4]

Tissue Doppler Imaging [TDI] has been recently used to characterize low velocity, high amplitude signals from myocardial motion.[12] The use of TDI has been validated as a tool for detection of LV systolic dysfunction,[13] diastolic dysfunction,[14] right ventricular[15] and atrial function,[16] in various cardiac conditions.[17] Recently, values for TDI at rest has been used in patients with septic shock for 90 days mortality prediction.[18] Several studies have suggested that higher mortality rates occurred in patients with sepsis and septic shock who didn't show appropriate cardiovascular responsiveness to catecholamines.[19,20] Incorporation of TDI with dobutamine stress echocardiography [DSE] is widely used as a tool to detect the myocardial viability in patients with ischemic myocardium and as a predictor to future cardiac events.[21] Although the use of DSE in patients with septic shock is widely accepted as a predictor of mortality, its effect on TDI values as a predictor of mortality was not well evaluated. Therefore, we performed this study to evaluate the effect of DSE on TDI values as a predictor of mortality in patients with septic shock.

Materials and methods

This prospective non-randomized interventional study was conducted on 69 adult patients, who were admitted to the Critical Care Medicine Department of Alexandria Main University Hospital within the first 24 hours from the diagnosis of septic shock. Approval of the Medical Ethics Committee of Alexandria Faculty of Medicine was taken. Informed consent from patients' next of kin was taken before enrollment to the study.

Sample size

After performing a pilot study a sample size of 65 patients diagnosed with septic shock was estimated to determine the predictive ability of TDI for mortality using area under the curve (AUC)=74.9%, using precision of 7%, alpha error=0.05 and droupout rate=10% will provide a power of 80%. The sample size was calculated using the Epi-info 7 software.[22]

Inclusion criteria

1. Patients older than 18 years old.
2. Patients with documented or suspected source of infection and diagnosed with septic shock according to The Third International Consensus Definitions for Sepsis and Septic Shock [Sepsis-3].[23]
   a. Acute change in Sequential Organ Failure Assessment [SOFA] score≥2 points with organ dysfunction consequently to infection. OR Patients with at least two of the clinical criteria of quick SOFA [qSOFA] including respiratory rate≥22/ minute, altered mentation with Glasgow Coma Scale [GCS]≤13 and systolic blood pressure≤100 mmHg.
   b. Septic shock will be identified as persisting hypotension requiring vasopressors to maintain mean arterial pressure≥65mmHg and having a serum lactate level >2 mmol/L [18mg/dL] despite adequate volume resuscitation.
3. Patients with the first episode of septic shock during the same ICU stay.
4. Mechanically ventilated patients.

Exclusion criteria

The following patients were excluded from our study:

1. Pregnant Females
2. Patients with previous heart disease including: Ischemic heart disease: patients with echocardiography evidence of regional myocardial wall motion abnormalities suggesting regional ischemia or previous infarction, heart failure: by history or available echocardiographic data, arrhythmia, congenital heart disease, moderate to severe valvular heart diseases.
3. Patients with poor echocardiographic window; postthoracic operation.
4. Patients with evidence of mixed shock state with clinically significant cardiogenic, hypovolemic or obstructive [pulmonary embolic] elements were excluded.

Citation: Zaytoun TM, Fayed AM, Elsayed HE, et al. The effect of dobutamine stress echocardiography on tissue doppler imaging values as a predictor of mortality in patients with septic shock. *J of Anes & Cri Open Access*. 2019;11(1):26–35. DOI: 10.15406/jaccoa.2019.11.00407

All patients in our study were subjected to complete history taking and physical examination with recording of the baseline clinical variables, hemodynamic data, GCS, APACHE-II [Acute Physiology and Chronic Health Evaluation], SOFA and norepinephrine dose. All patients were mechanically ventilated using mandatory modes and sedated to avoid the spontaneous breathing effort. Patients were resuscitated with fluids and treated according to the Surviving Sepsis Campaign Guidelines 2016.[24] Trans-thoracic echocardiography [TTE] was performed to all patients within the first 24 hours from the onset of septic shock after ICU admission by using a "General Electric healthcare Vivid 3 machine, Norway; 2008 and a phased array 3.5–5 MHz probe". Baseline echocardiographic values were obtained before the start of dobutamine challenge and included the following: Left ventricular end-diastolic volume [LVEDV], left ventricular end-systolic volume [LVESV], and left ventricular ejection fraction [LVEF] were measured by using the modified biplane Simpson equation in the apical four- and two-chamber views, according to the American Society of Echocardiography Guidelines.[25]

Stroke volume was calculated for all patients by calculating the left ventricular outflow tract cross-sectional area [CSA_{LVOT}]×velocity time integral [VTI_{LVOT}]. The CSA of the LVOT was calculated from the diameter of the LVOT obtained from the parasternal long axis window. Measurement of the diameter was done manually and the CSA was obtained by the following equation: $CSA_{LVOT}=\pi\left[\frac{D}{2}\right]^2$. The LVOT velocity was obtained by placing the pulsed-wave [PW] Doppler sample gate in the LVOT in apical-5-chamber view and VTI_{LVOT} was obtained by manually tracing the Doppler velocity spectrum.[26] Stroke volume index [SVI] was calculated by dividing the stroke volume by the body surface area [BSA].[27]

Mitral inflow was assessed with PW Doppler echocardiography from the apical four-chamber view. The Doppler beam was aligned parallel to the direction of flow, and a 1 to 2 mm sample volume was placed between the tips of mitral leaflets during diastole. From the mitral inflow profile, the E- and A-wave velocity, the E/A velocity ratio and E wave deceleration time were measured. In patients with tachycardia, the fused EA wave was considered an E wave.[14] The systolic [s′], early diastolic [e′] and late diastolic [a′] peak velocities were obtained by PW tissue-Doppler imaging [pwTDI] at lateral and septal mitral annulus on four-chamber apical view, the average value was obtained and LV filling index E/e′ ratio was calculated.[28,29] After baseline values have been obtained, a graded dobutamine challenge was performed. dobutamine infusion through the central venous catheter was initiated at 5μg /kg/min and after 15 minutes the rate of the infusion increased to 10μg/kg/min then after another 15 minutes to 15μg/kg/min minutes. All hemodynamic and echocardiographic variables recorded at baseline were recorded again at the maximum dose of the dobutamine challenge. At any stage of the challenge, if the heart rate of the patient reached≥85% of the maximum predicted heart rate or the patient developed arrhythmia, the study was terminated. After the study completion, dobutamine was tapered gradually over 20 minutes then stopped.

Outcome measures

All the patients were followed for 28 days and they were divided into two groups:

a) survivors: in which they survived the ICU stay and

b) non-survivors: death during the ICU stay

Primary outcome: ICU mortality.

Secondary outcome: Weaning of norepinephrine dose, ICU stay, Hospital stay, 28 days mortality.

Statistical analysis[30]

A sample size of 65 patients was calculated using Epi-Info 7 software at a power of>80 % using precision of 7% and alpha error [p] of 0.05. Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. [Armonk, NY: IBM Corp].[31] Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range [minimum and maximum], mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

Results

The current study was carried on 85 adult patients admitted to the Critical Care Medicine Department in Alexandria Main University Hospital between January 2017 and February 2018. Those patients were assessed within 24 hours from the diagnosis of septic shock. Regarding fulfillment of inclusion criteria, sixteen [18.8%] patients were excluded from the study including patients with a suboptimal echocardiographic view [n=7], severe regurgitations [n=4], and development of tachyarrhythmia during the study [n=5]. As a result, 69 patients were eligible to the study. The study population was classified into survivors and non-survivors according to the survival of the ICU stay. The TDI values at baseline [pre-dobutamine] infusion were compared to the values at the maximum dose of dobutamine challenge, together with the amount of change in these values was correlated to the survival of the patients, and the weaning of norepinephrine. The baseline characteristic data for the study population are shown in Table 1.

Eighteen patients [26.1%] survived the ICU stay and 28 days hospital stay with no reported mortality among survivors after ICU stay. The age of the studied patients ranged from 35-81 years with no significant difference between the two groups. The GCS of the patients ranged from 3-11, with significantly higher values for survivors. The APACHE II and SOFA scores showed a similar finding with significantly lower values for survivors. Survivors showed significantly lower norepinephrine dose. Concerning the source of infection, multiple sources have been found with hospital acquired pneumonia [HAP] being most common representing about 26 [37.6%] of the total cases followed by urinary tract infection as the second most common source (Figure 1).

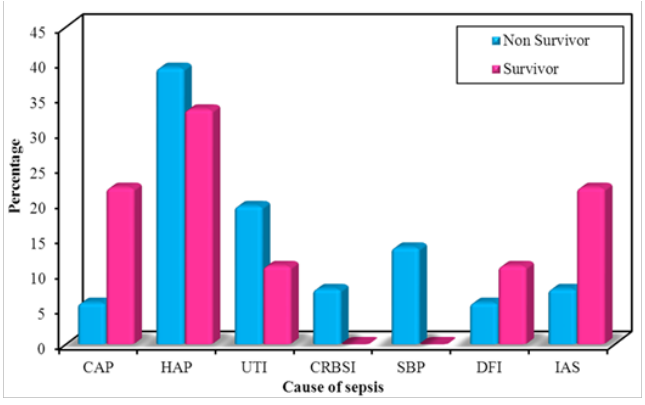

Figure 1 Percentages of different sources of infections.

CAP, community acquired pneumonia; HAP, hospital acquired pneumonia; UTI, urinary tract infection; CRBSI, catheter related blood stream infection; SBP, spontaneous bacterial peritonitis; DFI, diabetic food infection; IAS, intra-abdominal sepsis

Table 1 Baseline characteristic data of the study population

	Non survivors [n=51]	Survivors [n=18]	p
Sex No [%]			
Male	23[45.1]	8[44.4]	0.962
Female	28[54.9]	10[55.6]	
Age [years]			
Min.–Max.	45.0–73.0	35.0–81.0	0.628
Mean±SD.	59.47±8.13	57.56±15.80	
BSA [m2]			
Min.–Max.	1.80–2.10	1.71–2.10	0.034*
Mean±SD.	1.95±0.09	1.90±0.12	
APACHE II Score			
Min.–Max.	17.0–44.0	9.0–29.0	0.012*
Mean±SD.	26.31± 5.17	21.33±7.10	
SOFA Score			
Min.–Max.	11.0–19.0	10.0–14.0	<0.001*
Mean±SD.	14.27± 1.95	12.0±1.37	
PaO2/FiO2			
Min.–Max.	123.0–540.0	146.0–506.0	0.485
Mean±SD.	261.9±101.1	280.0±101.0	
ScvO2 [%]			
Min.–Max.	50.0–92.0	50.0–81.0	0.224
Mean±SD.	73.29±11.07	69.78±8.36	
GCS			
Min.–Max.	3.0– 11.0	6.0–11.0	<0.001*
Mean±SD.	6.59± 2.94	9.33±1.81	
Norepinephrine [µg/min]			
Min.–Max.	13.0–30.0	9.0–18.0	<0.001*
Mean±SD.	19.96± 6.22	12.89±3.01	
WBCs [103/µl]			
Min.–Max.	1.10–43.0	4.30–49.0	0.218
Mean±SD.	19.89±9.79	23.52±11.75	
Creatinine [mg/dl]			
Min.–Max.	0.20– 9.20	1.60–14.0	0.08
Mean±SD.	3.32±2.47	4.84±3.88	
Troponin I [ng/L]			
Min.–Max.	0.01– 0.74	0.01–1.30	0.155
Mean±SD.	0.12± 0.21	0.29±0.43	
CK-MB [mg/dL]			
Min.–Max.	0.90– 35.0	0.20–7.0	0.021*
Mean±SD.	7.86±7.55	4.04±2.39	

p, p value for comparing between non-survivors and survivors

*, Statistically significant at p≤0.05

Table 2 summarized hemodynamic and echocardiographic parameters for the study population. After DSE, survivors showed significantly higher values for the heart rate [123.4±12.22 Vs 111.51±12.39 beats/min, P= 0.001] and higher stress-rest difference [30.67±12.42 Vs 14.94±14.41 beats/min, P <0.001]. Concerning the TDI values, at baseline s' wave was significantly lower in survivors [8±2 Vs 12±4 cm/sec, P <0.001]. After DSE both groups showed significant increase in the s' wave [12±4 Vs 13±3 cm/sec, P=0.007 for non-survivors and 8±2 Vs 15±2 cm/sec, P<0.001 for survivors]. However, there was no statistically significant difference between the two groups after DSE. The stress-rest difference was significantly higher in survivors [7±2 Vs 1±3 cm/sec, P<0.001]. Other TDI values including e', a', and E/e' did not show any statistically significant difference between the two groups.

ROC curve of the stress-rest difference of the s' wave showed that a cutoff value of >4 cm/sec was associated with significant survival of the ICU stay with AUC, sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV] and accuracy of 0.939 [95%CI= 0.871-0.999], 88.24, 88.89, 95.7, 72.7, 88.4% respectively (Figure 2) (Figure 3) (Table 3). We classified the studied population into two groups according to the stress-rest change cutoff value of the left ventricular s' wave [m/sec]. Table 4 Twenty-two patients showed stress-rest change value>4 cm/sec while 47 patients showed a value≤4 cm/sec. We studied the primary and secondary outcomes in this two groups and showed that patients with stress-rest s' wave change≤4 cm/sec had more ICU and 28 days mortality with 45 [95.7%] of the patients died. The same group showed less ICU stay with a mean value of 8.32±5.42 days and less hospital stay with a mean value of 8.62±6.06 days. In addition, 38 [80.9%] patients in the group with a stress-rest change≤4 cm/sec showed failure of weaning of norepinephrine. The norepinephrine dose was higher in the same group with a mean value of 20.15±6.48 µ/min. There was a statistically significant difference between the two groups according to the primary and secondary outcomes.

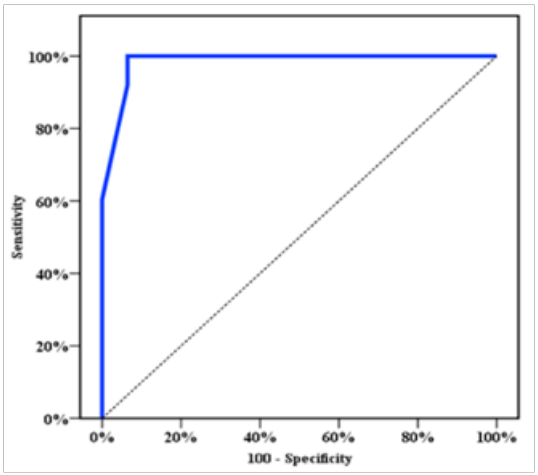

Figure 2 ROC curve for stress-rest change of the left ventricular s' wave [m/sec] to diagnose non-survivor from survivor.

Thirteen patients of the non-survivors group were successfully weaned from norepinephrine. However, those patients died during their ICU stay due to other causes as pulmonary embolism, myocardial infarction, or development of another episode of septic shock. For this reason, we studied the TDI values after classifying the studied population into two groups weaned [n=31] and non-weaned [n=38]

from norepinephrine (Table 5). The s' wave was significantly lower in weaned group. After DSE s' was significantly higher in weaned group with no significant change in non-weaned group [13±4 Vs 13±3 cm/sec, P=0.473]. The stress-rest change showed higher values for weaned than non-weaned group [6±2 Vs 0±3, cm/sec, P<0.001]. ROC curve showed that a cutoff value of >0.02 m/sec [>2 cm/sec] was associated significantly with weaning of the norepinephrine with AUC, sensitivity, specificity, PPV, NPV and accuracy of 0.985 [95% CI= 0.961-1], 92.1, 93.5, 94.6, 90.6, and 92.8% respectively (Table 6) (Figure 4) (Figure 5).

Table 2 Hemodynamic and echocardiographic variable [mean values]

Variable	Non-S at rest	S at rest	P	Non-S after dobutamine	S after dobutamine	P	Stress-rest change for Non-S	Stress-rest change for S	P
Hemodynamic parameters									
MABP [mmHg]	82.06± 17.79	75.78±16.93	0.197	79.41±13.94	73.11±15.32	0.113	-2.65±14.96	-2.67±14.72	0.907
Hart rate [beat/ min.]	96.57± 11.01	92.78±16.38	0.372	111.51±12.39	123.4±12.22	0.001*	14.94±14.41	30.67±12.42	<0.001*
Echocardiographic parameters									
VTILVOT [cm/ sec]	19.75± 5.27	16.82±2.98	0.006*	20.71± 5.51	20.84±4.21	0.923	0.96± 4.53	4.02±2.46	0.002*
SVI [ml/m2]	27.11± 7.14	27.54±5.65	0.503	28.33± 7.18	34.24±7.36	0.024*	1.22±5.94	6.70±4.08	<0.001*
CI [L/min/m2]	2.53± 0.85	2.55±0.60	0.671	3.18± 0.93	4.11±0.65	<0.001*	0.65± 0.75	1.56±0.31	<0.001*
LVEDVI [ml/m2]	26.41± 6.93	43.28±5.46	<0.001*	27.65± 7.89	32.14±5.78	0.009*	1.23± 6.24	-11.14±6.55	<0.001*
LVESVI [ml/m2]	9.79± 5.40	16.25±4.12	<0.001*	7.18±4.79	10.13±3.43	<0.001*	-2.61± 3.0	-6.11±4.78	0.011*
EF %	64.48±13.32	61.94±10.35	0.467	66.51± 9.62	66.27±11.66	0.932	2.03±8.60	4.32±14.0	0.203
E [m/sec]	0.63±0.24	0.78±0.24	0.028*	0.62±0.30	0.68±0.16	0.092	-0.01±0.23	-0.10±0.29	0.345
A [m/sec]	0.78± 0.18	0.70±0.12	0.058	0.79±0.21	0.80±0.30	0.956	0.01±0.19	0.10±0.27	0.381
E/A	0.80±0.26	1.12±0.29	<0.001*	0.77±0.30	0.94±0.36	0.017*	-0.03±0.24	-0.19±0.44	0.049*
s' [cm/sec]	12±4	8±2	<0.001*	13±3	15±2	0.07	1±3	7±2	<0.001*
e' [cm/sec]	7±3	8±5	0.901	7±3	8±4	0.945	0±4	-1±3	0.609
a' [cm/sec]	13±3	11±5	0.216	12±5	13±5	0.376	0±6	3±5	0.072
E/e'	9.80±6.01	11.23±5.17	0.155	9.48±6.20	10.87±5.42	0.11	-0.32± 5.40	-0.36±5.48	0.967

Non-S, non-survivors; S, survivors; LVEDVI, left ventricular end diastolic volume index; LVESVI, left ventricular end systolic volume index; EF, ejection fraction; MABP, mean arterial blood pressure.

p, p value for comparing between non-survivors and survivors

*, Statistically significant at p≤0.05

Table 3 Agreement [sensitivity, specificity] for stress-rest change of the left ventricular s' wave [cm/sec] to diagnose non-survivor from survivor

	Cut off	Survivor [n = 18]	Non survivor [n = 51]	AUC	p	95% C.I		Sensitivity	Specificity	PPV	NPV	Accuracy
						LL	UL					
Change from baseline to after dobutamine [s' cm/sec]	>4	16[88.9%]	6[11.8%]	0.939*	<0.001*	0.871	1	88.24%	88.89%	95.70%	72.70%	88.40%
	≤4	2[11.1%]	45[88.2%]									

Table 4 Outcome measurements

	Change from baseline to after dobutamine [s' cm/sec]		p
	>4	≤4	
	[n = 22]	[n= 47]	
ICU stay days			
Min.–Max.	4.0–18.0	3.0–18.0	0.003*
Mean±SD.	12.45±4.25	8.32±5.42	
Median	14	6	
Mortality			
Survival	16[72.7%]	2[4.3%]	<0.001*
Death	6[27.3%]	45[95.7%]	
28 days mortality			
Survival	16[72.7%]	2[4.3%]	<0.001*
Death	6[27.3%]	45[95.7%]	
Hospital stay			
Min.–Max.	7.0–28.0	3.0–24.0	<0.001*
Mean±SD.	18.18±5.78	8.62±6.06	
Median	17	6	
NE weaning			
Weaned	22[100.0%]	9[19.1%]	<0.001*
Failed	0[0.0%]	38[80.9%]	
NE dose µ/min			
Min.–Max.	9.0–18.0	11.0–30.0	<0.001*
Mean±SD.	13.77±3.15	20.15±6.48	
Median	13.5	19	

NE, noradrenaline; p, p value for comparing between stress-rest change < 4 and > 4 cm/sec; *, statistically significant at p≤0.05

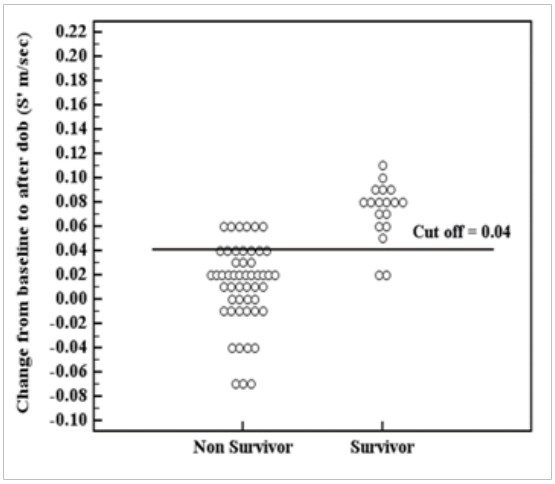

Figure 3 Distribution of the study population according to stress-rest change of the left ventricular s' wave [m/sec] to diagnose non-survivor from survivor.

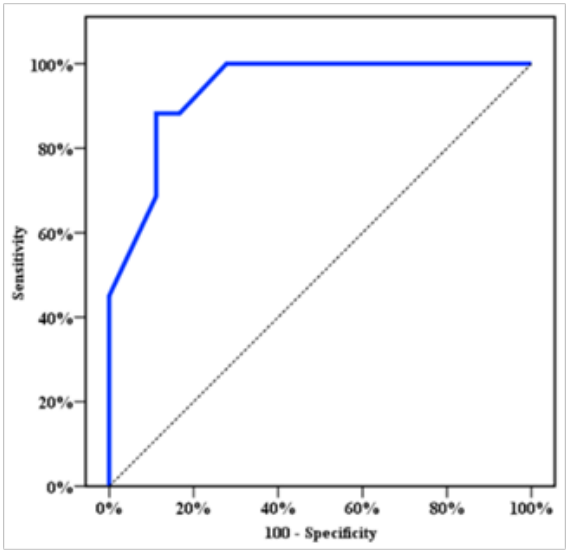

Figure 4 ROC curve for stress-rest change of the left ventricular s' [m/sec] wave to diagnose failed of weaning cases from weaned.

Table 5 TDI values for the study population after classification into non-weaned and weaned from norepinephrine

Variable	Non-weaned at rest	Weaned at rest	P	Non-weaned after dobutamine	Weaned after dobutamine	P	Stress-rest change for Non-weaned	Stress-rest change for Weaned	P
s' [cm/sec]	13±4	9±3	<0.001*	13±3	15±2	0.004*	0±3	6±2	<0.001*
e' [cm/sec]	8±3	8±4	0.184	7±2	8±4	0.808	-1±3	0±4	0.903
a' [cm/sec]	13±4	11±4	0.034*	12±3	13±6	0.856	-1±4	2±7	0.119
E/e'	8.44±3.54	12.30±7.23	0.046*	8.32±3.73	11.72±7.60	0.044*	-0.12±3.41	-0.58±7.16	0.837

Table 6 Agreement [sensitivity, specificity] for stress-rest change of the left ventricular s' wave [cm/sec] to diagnose non-weaned from weaned

	Cut off	Weaned [n= 31]	Failed [n= 38]	AUC	p	95% C.I		Sensitivity	Specificity	PPV	NPV	Accuracy
						LL	UL					
Change from baseline to after dob [s' m/sec]	>0.02	29	3	0.985*	<0.001*	0.961	1	92.10%	93.50%	94.60%	90.60%	92.80%
	≤0.02	2	35									

Citation: Zaytoun TM, Fayed AM, Elsayed HE, et al. The effect of dobutamine stress echocardiography on tissue doppler imaging values as a predictor of mortality in patients with septic shock. *J of Anes & Cri Open Access*. 2019;11(1):26–35. DOI: 10.15406/jaccoa.2019.11.00407

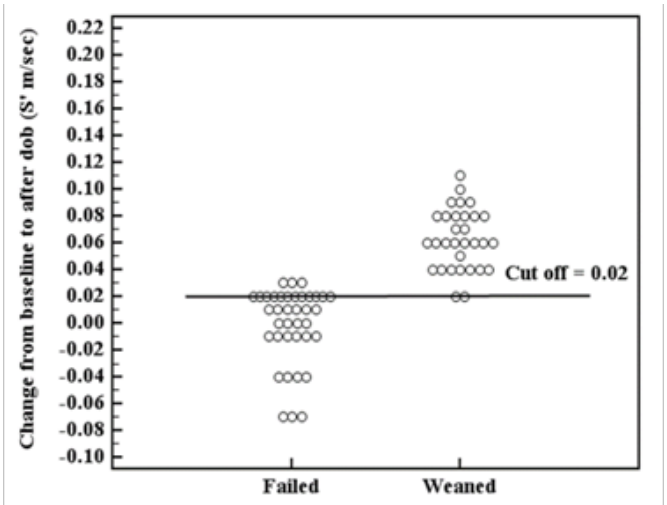

Figure 5 Distribution of the study population according to stress-rest change of the left ventricular s' wave [m/sec] to diagnose non-weaned from weaned.

Discussion

For several years DSE has been widely used as a method to detect myocardial viability in patients with ischemic cardiomyopathy and to determine the contractile reserve in patients with with congestive heart failure [CHF].[32] It has also been shown that the presence of an inotropic response elicited by DSE identifies a subset of patients at a lower risk of death and a high percentage of survival.[33] As mentioned before, DSE has been used in patients with sepsis and septic shock as a predictor of mortality and higher mortality was found to be among patients with failure of cardiovascular response to catecholamines.[19,20] A study by Kumar et al.[20] assessed the cardiovascular and metabolic responses to dobutamine as a correlate of outcome in patients with severe sepsis or septic shock and concluded that survival from severe sepsis and septic shock was associated with increased cardiac performance and contractility indices during dobutamine infusion. Assessment of sepsis-induced myocardial dysfunction in critically ill patients is challenging. Critically ill patients, especially patients with septic shock are subjected to multiple factors as multiple organ failure and different ways of treatment, which affect the loading condition of the heart making traditional echocardiographic indices not suitable for myocardial assessment.[34] Therefore, in the current study, we preferred using pulsed wave TDI values as it is less load dependent and more sensitive in the early detection of subtle myocardial dysfunction.[35]

The major finding of the current study was the change in s' wave after DSE and its ability to predict survival in ICU. In the current study, baseline values of the s' wave were significantly lower in survivors than in non-survivors with a mean value of 12±4 cm/sec for non-survivors and 8±2 cm/sec for survivors. In agreement with our finding, Weng et al.[18] found that the s' wave was significantly lower in the survivors group than in the non-survivors with a mean value of 7.8 [5.5 to 9.0] versus 11.0 [9.1 to 12.5] cm/sec; P<0.0001 respectively, with a mean value of 9.0[6.6 to 11.0] cm/sec for the whole cohort. In this study, a cut-off value of s'>9 cm/sec was associated with significantly higher mortality rate and s' wave was an independent predictor of 90 days mortality in patients with septic shock. Many controversies were found in other studies, Santos et al.[36] who studied the ability of TDI values to detect the disease severity in patients with septic shock newly admitted to the emergency department. He found that s' wave correlated negatively with all three scoring systems (Mortality in Emergency Department Sepsis [MEDS], Sequential Organ Failure Assessment [SOFA], and Simplified Acute Physiology Score [SAPS]) and patients with abnormal values [<10 cm/s] of the s' wave had statistically significant higher severity scores. In the same study, a univariate analysis showed that patients with reduced s' waves had a lower incidence of death [odds ratio [OR] 0.517, 95% confidence interval [CI] 0.344–0.775; p=0.0014]. In addition, Sturgess DJ et al.[37] who studied TDI and cardiac biomarkers ability to predict hospital outcome septic shock patients. The s' wave showed higher values in survivors of septic shock [survivor 13±3.7 cm/s, non-survivor 8.6±4.1cm/s; P=0.03]. The reason for these results may be related to the nature of the study population, which included 21 patients with nine patients having cardiac diseases as myocardial infarction and post-cardiothoracic surgery. The presence of cardiac diseases in the study population may have influenced the results.

Unlike patients with septic shock in whom a lower s' was associated with a higher survival rate as shown in our study, non-survivors of cardiovascular diseases showed lower s' wave. Several studies examined this finding in patients with cardiac diseases. Wang et al.[38] performed echocardiography with TDI measurements for 538 patients, 353 of them were cardiac and 165 patients were normal. After 2 years of following the patients, deaths due to cardiac causes were determined. They found that all TDI values were significantly lower in non-survivors and concluded that TDI was a reliable predictor of cardiac mortality in comparison to clinical data and standard echocardiographic measurements. In a study by Yu C et al.[39] it was found that s' was a more sensitive marker than LVEF for estimation of systolic function in patients with cardiovascular disease. They also showed that s' was able to predict clinical outcome in a more sensitive manner than could the LVEF. Similarly Nagueh SF et al.[40] who performed a study on hypertrophic cardiomyopathy, TDI revealed myocardial contractive abnormalities before any clinical presentations. This may explain the finding in our results, as there was no statistically significant difference between non-survivors and survivors as regards the EF although the s' wave showed a significant difference. As a conclusion, s' appeared to be a more sensitive predictor of mortality than was the ejection fraction.

A proposed explanation for lower values of s' in survivors, is the theory of myocardial depression in septic shock.[41,42] However, most of them could not explain why survivors exhibited more marked myocardial depression. Levy et al.[43] demonstrated a myocardial hibernation in sepsis by different imaging modalities as magnetic resonance imaging. Myocardial hibernation limits the oxygen and energy consumption by cardiac myocytes. This will preserve the myocardium, prevent cell-death pathway activation and allow the future recovery of cardiac myocytes. The slightly increased cardiac biomarkers in the study population also support that physical myocardial injury is negligible. In other words, we can say that the heart is injured "functionally". The explanation of our finding could be related to the presence of vasoplegia. In a study by Robotham et al.[44] it was found that EF values may not correspond to intrinsic LV contractility. For instance, an EF of 55% may be associated with severely depressed intrinsic LV contractility when low vascular tone is present. It is expected to find relatively normal or supernormal s' in non-survivors in our study, which reflected a hyperkinetic state associated with persistent and profound vasoplegia that in turn could be a marker of sustained cytokine release. This profound vasoplegia was greatly related to high mortality rate, which was consistent with our findings.

In our study non-survivors required higher doses of norepinephrine in comparison with survivors [19.96± 6.22 Vs 12.89±3.01 µg/min, P<0.001] which might explain the higher degree of vasoplegia in non-survivors. Non-survivors in our study showed a higher baseline heart rate than survivors did. This together with higher s' wave support the hypothesis that non-survivors have a more severe disease state and a higher level of cardiovascular stress with sympathetic nerve over-stimulation due to elevated endogenous catecholamine levels.[45] After DSE, s' values increased significantly in both studied groups in comparison to baseline with a mean value of 13± 3 cm/sec for non-survivors and 15±2 cm/sec for survivors. However, there was no statistically significant difference between the two groups. The absence of a significant difference between the two groups after dobutamine may be explained by the presence of 13 patients in the non-survivors who were successfully weaned from norepinephrine with the resolution of septic shock. We found that those patients who were successfully weaned from norepinephrine but did not survive the ICU stay had characteristics similar to that of survival group. For this reason, we classified our study population into two groups according to the weaning of norepinephrine so we can clarify this issue.

At baseline, s' of those patients, showed a similar finding as that found when we classified the patients into non-survivors and survivors. The s' was significantly lower in weaned group than failed. After DSE, weaned group showed significantly higher values of s' [13±3 cm/sec for failed weaning Vs 15±2 cm/sec for weaned, P=0.004]. The group who failed weaning of norepinephrine did not show any significant increase in s' wave after dobutamine. We believe that those patients, who showed a failure of norepinephrine weaning, suffered from a severe form of illness with a higher degree of vasoplegia and an excessive amount of endogenous catecholamine with no response to exogenous catecholamine as dobutamine. In our study, failed weaning group showed significantly higher norepinephrine dose than the weaned group [21.32±6.49µg/min for failed weaning Vs 14.19±3.31 µg/min for weaned, P<0.001], this support the previously mentioned hypothesis. Similarly to our finding, Weng et al.[18] found the same pattern for norepinephrine where non survivors had a higher dose of norepinephrine as compared to survivors [0.6 Vs 0.3µg/kg/min; *p*=0.007], attributing this to the severity of the septic shock and severity scores for non survivors. In addition to a study by Sturgess et al.[37] where the mean value of norepinephrine dose was 0.147±0.11µg/kg/min for non-survivors and 0.115±0.123 µg/kg/min for survivors. However, this difference was not statistically significant [P= 0.58].

The effect of DSE on TDI values in patients with septic shock has not been adequately studied. However, its effect in cases with ischemic cardiomyopathy and viability determination was a topic of interest for many researchers.[46,47] In agreement with our finding, Ciampi Q et al.[48] who studied 64 patients with heart failure [HF] and assessed the relationship between the s' change during DSE, contractile reserve, and aerobic exercise capacity in HF patients. In this study s' wave at rest and stress showed mean values of 4.47+1.31 cm/sec and 7.00+4.21 cm/sec respectively with a statistically significant difference between them [P<0.001]. They demonstrated that the change of the s' during DSE was related to myocardial contractile reserve and exercise tolerance in patients with dilated cardiomyopathy. Similar results were found by Mostafa SA et al.[47] who studied the effect of DSE in evaluating LV functional improvement after elective Percutaneous Coronary Intervention [PCI]. Sixty patients performed DSE before elective PCI and TDI values were recorded. After 1 month, a follow-up study was done and patients were classified into two groups: 18 patients [30%] had non-recovered global myocardial function [Group I] and 42 patients [70%] had recovered myocardial function globally [Group II]. Both groups showed a significant increase in the value of s' wave after DSE from baseline. However, [Group II] showed a significantly higher value [16.02±3.82 Vs 11.97±2.36 cm/sec] and they concluded that s' wave was the only predictor for the global functional recovery.

From the previous studies, we can conclude the effect of DSE on s' wave can be used to detect the contractile reserve and global systolic function in ischemic cardiomyopathies. Our study showed similar results, as the effect of DSE on s' wave was able detect patients with better cardiac reserve in cases of septic cardiomyopathy. Patients with s' wave stress-baseline difference of>4 cm/sec showed lower ICU mortality and 28 days mortality. The s' stress-baseline difference in patients with septic shock was not addressed in previous studies, however; it was the point of interest for patients with heart failure. Ciampi Q et al.[48] found a value of 2.02cm/s was the best value for diagnosing the myocardial contractile reserve assessed by systolic pressure/end-systolic volume index ratio [SP/ESVi ratio]. [AUC 0.69 (95%CI 0.56–0.80), sensitivity 69% (95% CI 54–81), specificity 80% (95% CI 45–97)]. They found that patients with s' rest–stress >2.02 cm/sec change during DSE, compared with patients with rest–stress change≤2.02, showed better cardiac reserve and aerobic exercise capacity in HF patients.

From our results together with the previous study, we can conclude that the change of the s' wave in response to dobutamine was able to detect cardiac reserve, weaning from norepinephrine and survival of patients with septic shock in a similar way as detecting the cardiac reserve in ischemic heart failure. In our study, the majority of patients with s' stress-rest change≤4 cm/sec were non-survivors. They showed significantly lower ICU stay and hospital stay. This may be explained by the severe illness for the non-survivor group and non-responsiveness to the medical treatment that led to rapid death. Non-survivors group had significantly higher APACHE II score with a mean value of 26.31± 5.17 and expected mortality about 56%. The SOFA score was also significantly higher in non-survivors with a mean value of 14.27± 1.95 and expected mortality 50-60%. On the other side, patients with s' stress-rest change>4 cm/sec were mainly survivors and showed significantly higher ICU stay and hospital stay. This may be explained by the less severity of illness and the need for more care for complete recovery.

Unfortunately, the s' stress-rest change and its relation to the ICU and hospital stay in patients with septic shock was not addressed in previous researches. However, in partial agreement with our result, a study by Weng et al.[18] survivors with a baseline s' wave<9 cm/sec had a longer hospital stay in comparison to non-survivors [29 Vs 17, P=0.150], although there was not any statistically significant difference between survivors and non-survivors as regard the ICU stay and the hospital stay. In this study, this may be attributed to the non-significance between the two groups as regards the APACHE IV and SOFA scores. In addition, the population sample included septic shock patients with other comorbidities as coronary heart disease, which was excluded from our study.

Study limitations

During the conduction of this single centered study, several limitations have been encountered. This allows conducting future studies and research tackling specific points of research and avoiding these limitations.

The primary endpoint in our study was the ICU mortality, including all-cause mortality and non-survivors constituted about 51 patients [73.9%] of this study population. However; this may not reflect the actual mortality rate for septic shock in our center. Out of the 51 non-survivors, 13 patients were successfully weaned from norepinephrine with resolution of septic shock but they died from other causes than sepsis. Using cause-specific mortality rather than all-cause mortality would have resolved this issue. All patients with any cardiac abnormalities were excluded from the study. However, diastolic dysfunction is very common especially in the age population of the current study. Therefore, whether the diastolic dysfunction, especially when it is an isolated pattern, was already present or sepsis-induced was doubtful. During the conduction of our study, five patients developed tachyarrhythmia during the graded dobutamine challenge and the study was terminated. This may limit the future use of this method as a determinant for septic shock mortality as it may put some patients at risk for tachyarrhythmias and other complication of dobutamine as hypotension. As regard to reproducibility, the inter-observer and intra-observer variability for echocardiographic data were not statistically tested, as only one echocardiographer performed all the cases and there was no follow-up. Echocardiography was performed during the first 24 hours of diagnosing septic shock. A major limitation was that there was no follow-up echocardiography after resuscitation to detect whether the initial myocardial changes and their response to dobutamine were persistent or changed. In addition, impact of this on the adequacy of resuscitation and on ICU mortality. However, this may be addressed in future researches.

Conclusion

DSE can be used to detect the cardiac reserve and predict the mortality in patients with septic shock in a similar way as its use in predicting cardiac events in cardiac patients. The cornerstone finding of our study is that the stress-rest change of>4 cm/s of the LV s' wave was able to predict lower ICU and 28 days mortality.

Acknowledgment

The Authors are thankful to the entire stuff member at the Critical Care Department, Faculty of Medicine, and Alexandria University for their help providing the advice and cooperation required for research advancement.

Funding

This research was not funded by any grants from any authority. No funding agency was involved in the study design, data collection, analysis and interpretation, or in writing and submitting the manuscript.

Statement of interest

None declared.

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