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Prognostic value of ventricular function assessed by speckle tracking echocardiography in patients with sepsis

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Summary

Background. The prognostic value of left ventricular dysfunction in patients with sepsis is unknown. Speckle tracking echocardiography (STE) is a novel, sensitive method for assessing ventricular function, capable of unmasking myocardial dysfunction not detected with conventional echocardiography. We assessed STE in patients with sepsis to determine whether it is associated with mortality.

Material and methods. Between April 2015 and March 2016, patients aged ≥ 18 years admitted to the intensive care unit with the diagnosis of sepsis and without previous cardiomyopathy were prospectively imaged using transthoracic echocardiography. Left ventricular function was assessed using conventional methods and STE. Mortality was assessed over 30 days.

Results. Eighteen patients were included and the 30-day mortality rate was 27.7%. The ejection fraction (EF) estimated using the Simpson method was similar between patients who died and those who survived; however, the ventricular function determined using STE in the 4-chamber view was significantly lower in patients who died ($-14\% \pm 5$ vs $-17\% \pm 2$, $p=0.028$). No significant differences were observed in the 2-chamber view (alive: -16 ± 3 , dead: -14 ± 5 , $p=0.182$), long apical axes view (alive: -17 ± 2 , dead: -15 ± 4 , $p=0.434$) or global strain (alive: -17 ± 2 , dead: -14 ± 4 , $p=0.118$).

Conclusion. In patients with sepsis, ventricular function assessed with STE in the 4-chamber view was more sensitive than EF in detecting dysfunction and better predicted 30-day mortality. Larger trials will be necessary to corroborate these findings.

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Keywords: Speckle tracking - Echocardiography - Strain - Sepsis - Myocardial dysfunction

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Resumo

Valor prognóstico da função ventricular avaliada por ecocardiografia com speckle tracking em pacientes com sepse

Introdução. O valor prognóstico da disfunção ventricular esquerda em pacientes com sepse é desconhecido. O ecocardiograma com speckle tracking (ST) é um novo método sensível para avaliar a função ventricular, capaz de desmascarar disfunção miocárdica não detectada com ecocardiografia convencional. Nós avaliamos ST em pacientes com sepse para determinar se ele está associado com mortalidade.

Material y métodos. Entre Abril de 2015 e Março de 2016, pacientes ≥ 18 anos foram admitidos na unidade de terapia intensiva com diagnóstico de sepse e sem cardiomiopatia, visualizados prévia prospectivamente por ecocardiografia transtorácica. A função ventricular esquerda foi avaliada utilizando métodos convencionais e ST. A mortalidade foi avaliada ao longo de 30 dias.

Resultados. Dezoito pacientes foram incluídos e a taxa de mortalidade de 30 dias foi de 27,7%. A fração de ejeção (FE) estimada pelo método de Simpson foi semelhante entre os pacientes que morreram e os que sobreviveram. Entretanto, a função ventricular determinada usando STE na visão de 4 câmaras foi significativamente menor nos pacientes que morreram ($-14\% \pm 5$ vs $-17\% \pm 2$; $p=0,028$). Não foram observadas diferenças significativas na visão de 2 câmaras (vivos: 16 ± 3 ; mortos: 14 ± 5 ; $p=0,182$), visão de eixos apicais longos (vivos: 17 ± 2 ; mortos: 15 ± 4 ; $p=0,434$) ou strain global (vivos: 17 ± 2 ; mortos: 14 ± 4 ; $p=0,118$).

Conclusão. Em pacientes com sepse, a função ventricular avaliada com ST na visão de 4 câmaras foi mais sensível do que a FE na detecção de disfunção e melhor predisse a mortalidade em 30 dias. Ensaios maiores serão necessários para corroborar esses achados.

Palavras-chave: Speckle tracking - Ecocardiografia - Strain global - Sepse - Disfunção miocárdica

Resumen

Valor pronóstico de la función ventricular evaluada mediante ecocardiografía con speckle tracking en pacientes con sepsis

Introducción. El valor pronóstico de la disfunción ventricular en pacientes con sepsis es desconocido. La ecocardiografía con speckle tracking (ST) es un método nuevo y sensible para valorar la función ventricular, capaz de detectar la disfunción ventricular no observada por ecocardiografía convencional. Nosotros evaluamos los valores de ST en pacientes con sepsis y su impacto en la mortalidad.

Material y métodos. Entre Abril de 2015 y Marzo de 2016, pacientes ≥ 18 años fueron admitidos en la terapia intensiva con sepsis y sin cardiopatía conocida y prospectivamente evaluados por ecocardiografía transtorácica. La función ventricular izquierda fue cuantificada por métodos convencionales y ST. Se evaluó la mortalidad a los 30 días.

Resultados. Se incluyeron 18 pacientes, con una mortalidad a los 30 días del 27,7%. La fracción de eyección estimada por el método de Simpson no difirió entre vivos y muertos; sin embargo, la función ventricular izquierda por ST en 4 cámaras fue menor para los pacientes que fallecieron (vivos: $-17\% \pm 2$; muertos: $-14\% \pm 4$; $p=0,028$). No encontramos diferencias significativas en las proyecciones de 2 cámaras (-16 ± 3 vs -14 ± 5 ; $p=0,182$), eje largo apical (-17 ± 2 vs -15 ± 4 ; $p=0,434$) o con strain global (-17 ± 2 vs -14 ± 4 ; $p=0,118$).

Conclusiones. En pacientes con sepsis, la función ventricular evaluada con ST en la proyección de 4 cámaras fue más sensible en detectar disfunción ventricular que con el método de Simpson, y también predijo mejor la mortalidad a los 30 días. Ensayos más grandes son necesarios para corroborar estos hallazgos.

Palabras clave: Speckle tracking - Ecocardiografía - Strain - Sepsis - Disfunción miocárdica

Introduction

Sepsis is a common condition characterized by an abnormal hemodynamic state, suboptimal tissue oxygenation, multiple organ dysfunction, and increased risk of mortality. In the United States, 751,000 new cases of sepsis and 210,000 sepsis-related deaths are reported annually¹.

The cardiovascular repercussions of sepsis include increased cardiac output, decreased peripheral vascular

resistance, and decreased preload due to increased capillary permeability. In addition, a state of global myocardial ischemia develops due to microvascular dysfunction and direct myocardial dysfunction². In this condition, cardiovascular assessment is generally performed with a Swan-Ganz catheter³.

Echocardiography has become an important tool, which allows both qualitative and quantitative evaluation of the cardiac morphology and function in patients with sepsis^{4,5}. The new modalities, such as second harmonics,

3D echocardiography, tissue Doppler, and speckle-tracking echocardiography (STE), are effective for the evaluation of cardiac mechanics at a cellular level and provide insight into prognosis and possible therapeutic options^{6,7}. In daily practice, myocardial function is frequently assessed based on ejection fraction (EF), utilizing 2D echocardiography or M mode echocardiography⁸. This method has several limitations, such as low reproducibility because the results are influenced by afterload, preload, and heart rate. The strain and strain rate (SR) derived from tissue Doppler are validated methods for the evaluation of myocardial deformity⁹. STE allows objective, quantitative evaluation of global left ventricular (LV) function, with its accuracy independent of the insonation angle. The objective of this study was to compare the LV function assessed with conventional echocardiography vs. STE in patients with sepsis and to determine the association of each with the 30-day survival.

Material and methods

Selection and description of participants

We prospectively studied patients aged ≥18 years who were admitted to the intensive care unit with a diagnosis of sepsis or septic shock. Treatment was provided as per the international guidelines of sepsis¹⁰ as defined by the SCCM/ESIMC/ACCP/ATP/SIS criteria set forth by the Surgical Infection Society¹¹. Major exclusion criteria included history of cardiomyopathy, valve disease or reduced EF, surgical or percutaneous revascularization in the previous year, or need for an urgent coronary angiography.

Procedures

Transthoracic echocardiography was performed within 24 hours of meeting sepsis diagnosis using a Vivid 9

echocardiography machine and 2.5 MHz transducer (GE Medical Systems, Milwaukee, WI, USA) by sonographers experienced in echocardiography and strain imaging. Images were obtained at 50-70 frames/s and analyzed using M-mode and 2D mode echocardiography, and STE (Echo Pac PC, version 113). Routine laboratory workup and cultures were performed and troponin T levels were obtained for all patients. Noninvasive imaging was performed at the discretion of the treating physician.

Statistical analysis

For continuous variables, data were expressed as mean ± standard deviation (SD) or median (25th-75th percentile). Differences were compared using the t-test or Wilcoxon test, as appropriate. Categorical variables were expressed as percentages and were compared using the chi-square test or Fisher test, as appropriate. P-values <0.05 were considered significant.

Results

Between April 2015 and March 2016, 42 patients were diagnosed with sepsis. Twelve patients were excluded because of previous cardiomyopathy, 8 because of known reduced EF, and 4 because of known coronary artery disease. The remaining 18 patients were included in the study. The baseline characteristics of patients who died within 30 days compared to those who survived are depicted in Table 1. There were no differences in sex distribution, length of stay, and APACHE II scores between both groups. The only significant difference was the lower rate of mechanical ventilation in those who survived (23% vs 100%). The most frequent cause of sepsis was respiratory infection. Other sources included urinary tract, gastro-intestinal, bile-pancreatic, and subcutaneous tissue infection and one case of meningitis.

Table 1. Baseline characteristics of patients with sepsis				
	All (N=18)	Non-survivors (N=5)	Survivors (N=13)	p
Age (years)	62 ± 12	58 ± 16	63 ± 10	0.41
Male sex (%)	72.20	60	77	0.47
Total mortality (%)	28			
Number of in hospital days	17 ± 14	25 ± 17	14 ± 11	0.13
Number of ICU days	12 ± 12	22 ± 18	9 ± 6	0.03
Hours from admission to Echocardiography	17 ± 7	15 ± 7	18 ± 8	0.51
Mechanical ventilation (%)	44.4	100	23	0.003
APACHE II Score	15 ± 8	15 ± 8	13 ± 6	0.65
Infection source (%)				
Lungs	50			
Bile-Pancreatic	11			
Urinary	11			
Subcutaneous tissue	11			
Digestive system	11			
Meningitis	6			

Table 2. Hemodynamic variables

	All	Non-survivors	Survivors	p
Heart rate (beats/min)	112 ± 14	114 ± 20	112 ± 12	0.76
Systolic arterial pressure (mm Hg)	105 ± 23	101 ± 18	107 ± 25	0.64
Mean arterial pressure (mm Hg)	61 ± 13	57 ± 12	63 ± 13	0.38
Central venous pressure (cm H ₂ O)	11 ± 5	12 ± 4	11 ± 5	0.74
Noradrenaline requirement (%)	50	100	31	0.009
Dobutamine/Dopamine requirement (%)	22	80	0	<0.001

Hemodynamic parameters

There were no differences in heart rate, systolic or mean blood pressures, and central venous pressure. Vasopressors such as noradrenaline were required in all patients who died, whereas only 31% of those who survived required vasopressors ($p=0.009$). Dopamine and/or dobutamine were used in 80% of the patients who died and were not required among those who survived (Table 2).

Laboratory data

The group of patients who died during hospitalization had higher levels of lactic acid, BUN, and sodium. They also had lower oxygen saturation levels and plasma prothrombin activity. There was a tendency of lower levels of troponin T in the group of patients who died; however, this difference was not statistically significant. The APACHE II score¹², which includes many of these parameters, was similar between both groups (Table 3).

Echocardiographic parameters

Echocardiograms were obtained at an average of 17 hours after the diagnosis of sepsis. Both groups did not differ by EF, LV diastolic diameter, left atrial volume index, and LV mass index; however, LV strain was significantly lower among survivors

(-17% vs. -14%, $p=0.028$). Six patients showed mild valvular abnormalities such as tricuspid, mitral, and aortic insufficiencies. The intra- and inter-observer coefficients of variation in 4-chamber, 2-chamber, and APLAX views were 15%, 17%, 14% and 12%, 12% and 15% respectively (Table 4 and Figures 1-4).

Discussion

In the present study, we compared LV function using conventional echocardiography and STE between patients with sepsis and without previous cardiomyopathy who survived vs. those who died at 30-day follow-up. The principal finding was that non-survivors had a significant reduction of LV function compared to the survivors when assessed with STE in the 4-chamber view; this decrease in LV function was not evident when assessed using the Simpson method. STE in 2C and APLAX views showed a tendency of lower LV function; however, this difference did not reach statistical significance.

It is important to take into account that the normal values for STE are not yet universally defined but a value of -15 has been shown to predict a decrease in LV function^{13,14}.

There were no significant differences in the APACHE II scores between those both groups, suggesting that the severity of sepsis on admission was similar between both groups.

Table 3. Laboratory data

	All	Non-survivors	Survivors	p
WBC Count (WBC/mm ³)	18000 ± 7000	21000 ± 12000	17000 ± 4000	0.341
Hemoglobin (g/dL)	10 ± 3	9 ± 3	11 ± 2	0.093
Platelets (thousands/mm ³)	167 ± 112	102 ± 46	191 ± 121	0.136
Urea (mg/dL)	139 ± 107	242 ± 122	100 ± 73	0.007
Creatinine (mg/mL)	2.7 ± 2.2	3.4 ± 0.9	2.4 ± 2.5	0.412
Lactic acid (mmol/dL)	3.5 ± 2	5.2 ± 2.9	2.8 ± 1.2	0.023
PO ₂ (mm Hg)	69 ± 20	53 ± 11	76 ± 19	0.027
PCO ₂ (mm Hg)	38 ± 10	38 ± 10	39 ± 10	0.917
Bicarbonate	20 ± 6	16 ± 2	22 ± 7	0.087
Sodium (Meq/L)	144 ± 10	156 ± 12	140 ± 5	0.001
Potassium (Meq/L)	4 ± 1	4.2 ± 2	3.9 ± 0.5	0.628
APP (%)	76 ± 22	55 ± 20	84 ± 18	0.009
KPTT (seg)	31 ± 10	39 ± 15	29 ± 5	0.055
Troponin (ng/ml)	74 ± 95	136 ± 120	47 ± 73	0.08

WBC: white blood cells.

Table 4. Echocardiographic parameters

	All	Non-survivors	Survivors	p
Ejection fraction (Simpson method) (%)	59 ± 6	57 ± 5	59 ± 6	0.52
Left ventricle diastolic diameter (mm)	50 ± 5	51 ± 7	50 ± 4	0.18
Left atrium volume index (ml/m ²)	26 ± 4	28 ± 6	25 ± 3	0.30
LV mass index (g/m ²)	102 ± 14	100 ± 15	102 ± 12	0.54
Any mild valvulopathy (%)	33			
Mild mitral insufficiency (%)	16			
Mild aortic stenosis (%)	11			
Mild tricuspid insufficiency (%)	28			
Strain (%)				
4 C view	-16 ± 3	-14 ± 4	-17 ± 2	0.028
2 C view	-16 ± 4	-14 ± 5	-16 ± 3	0.182
Long axis view	-16 ± 3	-15 ± 4	-17 ± 3	0.434
Global	-16 ± 3	-14 ± 4	-17 ± 2	0.118

LV: left ventricle. 4C: four chambers. 2C: two chambers.

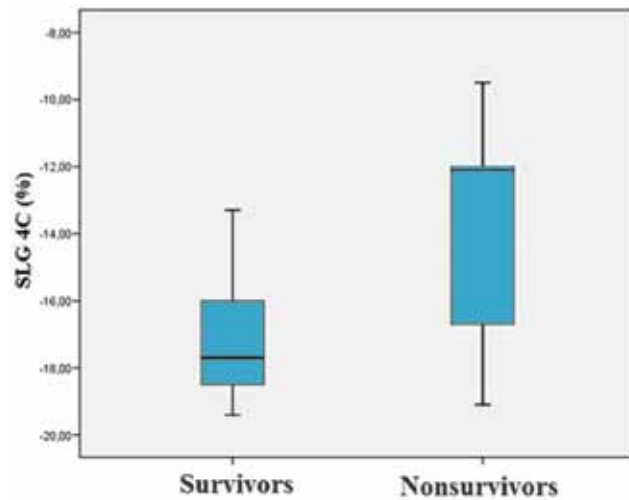


Figure 1. Strain in survivors and non-survivors with sepsis: 4C view (p=0.028).
SLG: global longitudinal strain. 4C: 4 chambers.

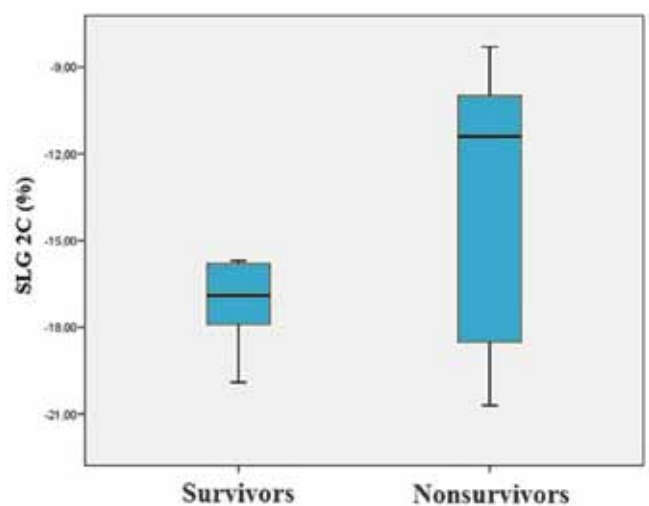


Figure 2. Strain in survivors and non-survivors with sepsis: 2C view (p=0.12).
SLG: global longitudinal strain. 2C: 2 chambers.

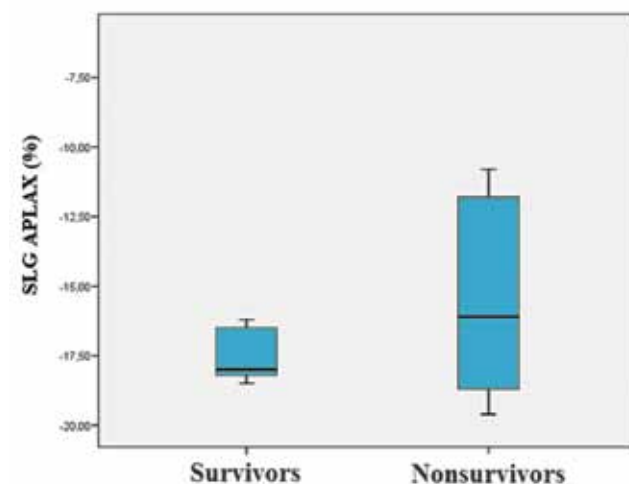


Figure 3. Strain in survivors and non-survivors with sepsis: APLAX view, (p=0.43).
SLG: global longitudinal strain. APLAX: apical long axis.

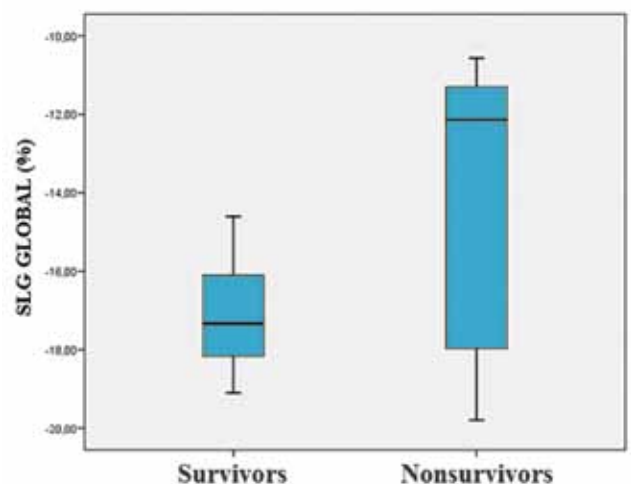


Figure 4. Global strain in survivors and non-survivors with sepsis (p=0.11).
SLG: global longitudinal strain.

Patients who died had a significantly lower LV function assessed with STE in the 4C view. The 2C, APLAX views, and the global strain showed a tendency of lower values but did not reach statistical significance. Recently, Dalla et al.¹⁵ showed that patients with septic shock have a lower strain rate compared to patients admitted with trauma and controls, despite no significant differences in EF. Similar findings have been described in children with septic shock¹⁶.

Orde et al. showed that in patients with sepsis and early septic shock, STE was a more sensitive predictor for myocardial dysfunction than conventional 2D echocardiography¹⁷. Our findings are similar for STE in the 4-chamber view. The small number of patients included in our study possibly explains the lack of significant differences in the other views. Larger studies will be necessary in this regard¹⁸.

A study including of 44 elderly adults with septic shock and higher comorbidities than the patients in our study showed a correlation between longitudinal global LV strain and EF ($r=0.70$)¹⁹⁻²². These findings cannot be extrapolated to our results because we included relatively healthy subjects with normal cardiac structures who became acutely ill. Recently, several reviews and research studies have been published regarding the prognostic value of echocardiography and STE in patients with sepsis¹⁹⁻²².

A previous study on the association between LV dysfunction and inflammatory response syndrome suggested that fluid management should be guided by echocardiography; however, this study did not evaluate the association between LV dysfunction and sepsis²³. Furthermore, there are no human studies on the association between STE and inflammatory response syndrome.

While our study did not include a control group or patients with other causes of systemic inflammation, mechanisms of generalized inflammation in sepsis and other causes of inflammatory response syndrome are similar, if not identical²⁴⁻²⁶. Trials quantifying cytokines, endothelial adherence factors, bacterial molecules, as well as pro- and anti-inflammatory factors are necessary to clarify this issue.

Increased troponin levels in patients with sepsis are associated with worse prognosis²⁷. We found that the group of patients who died had higher troponin levels than those who survived but the difference was not statistically significant. This may be attributed to the small number of patients included, which is an important limitation of this study.

We excluded patients with known cardiomyopathy to demonstrate that the inflammatory response caused by the infection is responsible for the early signs of LV dysfunction detected with STE. Studies with larger numbers of patients will be necessary to confirm our findings. Detection of early signs of LV dysfunction with STE in patients with sepsis could guide therapy and potentially reduce the morbidity and mortality in sepsis.

Conclusion

LV dysfunction detected with STE in the 4-chamber view in patients with sepsis was associated with increased mortality; however, LV dysfunction on 2C and APLAX views and decreased EF did not demonstrate this association. Early evaluation with STE of patients with sepsis may help identify those with worse prognosis, guiding therapeutic measures for these patients. Larger studies will be necessary to confirm these findings.

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Statement of competing interests

The authors report no competing interests.

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