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Impact of Bi-ventricular Systolic Function on Mortality in Patients with Sepsis and Septic Shock

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ABSTRACT

Introduction: We aimed to evaluate left ventricular (LV) and right ventricular (RV) systolic performance in patients with sepsis or septic shock and possible functional alteration on in-hospital mortality.

Patients and Methods: Thirty-seven consecutive patients with the diagnosis of sepsis or septic shock were included in the study. All patients underwent comprehensive transthoracic echocardiographic examination. Data of patients discharged from the intensive care unit was compared with data of patients who died in the hospital.

Results: Fifteen patients (40.5%) survived, while 22 patients were died in the hospital (59.5%). A significant difference was detected between survivor and non-survivor groups regarding before discharge or death level of inflammatory markers such as CRP (p= 0.05) and procalcitonin (p= 0.03) besides BNP (p= 0.01) and SOFA (p= 0.009) score. There were two patients (5.4%) with EF value less than %50 in the study population. Eight patients (21.6%) displayed hypokinesia on the apical segment, and four patients (10.8%) had TAPSE values below 17 mm. One patient (6.6%) in the survivor group, but seven patients (31.8%) in the non-survivor group had apical hypokinesia with a trend towards significance (p= 0.068). One patient in the survivor group (6.6%) and three patients (13.6%) in the non-survivor group had RV systolic dysfunction (p= 0.51).

Conclusion: We found a much lower rate of LV and RV systolic dysfunction in patients with sepsis or septic shock compared with previous studies. None of the myocardial dysfunction types was associated with in-hospital mortality. Apical hypokinesia was also more prevalent in non-survivors despite borderline significance.

Key Words: Mortality; left ventricular function; right ventricular function; sepsis.

Sepsis ve Septik Şoklu Hastalarda Biventriküler Sistolik Fonksiyonun Mortalite Üzerine Etkisi

ÖZ

Giriş: Bu çalışmanın amacı, sepsis veya septik şoklu hastalarda sol ventrikül (LV) ve sağ ventrikül (RV) sistolik performansını ve hastane içi mortalitede olası fonksiyonel değişikliği değerlendirmektir.

Hastalar ve Yöntem: Çalışmaya sepsis veya septik şok tanısı alan ardışık 37 hasta dahil edildi. Tüm hastalara kapsamlı transtorasik ekokardiyografik inceleme yapıldı. Yoğun bakım ünitesinden taburcu edilen hastaların verileri hastanede ölen hastaların verileriyle karşılaştırıldı.

Bulgular: On beş hasta (%40.5) hayatta kalırken, 22 hasta (%59.5) hastanede ölmüştür. BNP (p= 0.01) ve SOFA (p= 0.009) yanında CRP (p= 0.05) ve prokalsitonin (p= 0.03) gibi enflamatuvar belirteçlerin taburculuk veya ölüm öncesi düzeyleri açısından sağ kalan ve ölen gruplar arasında anlamlı fark saptanmıştır. Çalışma popülasyonunda EF değeri %50'nin altında olan iki hasta (%5.4) tespit edilmiştir. Sekiz hastada (%21.6) apikal segmentte hipokinezi, dört hastada (%10.8) 17 mm'nin altında TAPSE değerleri bulunmuştur. Sağ kalan grupta bir hastada (%6.6), ancak ölen gruptaki yedi hastada (%31.8) anlamlılığa doğru bir eğilim gösteren apikal hipokinezi belirlenmiştir (p= 0.068). Sağ kalan grupta bir hastada (%6.6) ve ölen grupta üç hastada (%13.6) RV sistolik disfonksiyonu saptanmıştır (p= 0.51).

Sonuç: Sepsis veya septik şoklu hastalarda önceki çalışmalara göre çok daha düşük LV ve RV sistolik disfonksiyon oranı bulunmuştur. Miyokardiyal disfonksiyon tiplerinin hiçbiri hastane içi mortalite ile ilişkili saptanmamıştır. Apikal hipokinezi, sınırda önemli olmasına rağmen, hayatta kalmayanlarda daha yaygın bulunmuştur.

Anahtar Kelimeler: Mortalite; sağ ventriküler fonksiyon; sepsis; sol ventriküler fonksiyon.

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INTRODUCTION

Myocardial dysfunction in sepsis has been suggested to be an important complication of sepsis and septic shock[1]. The proposed pathophysiology of myocardial dysfunction in these patients is complex and involves dynamic adaptation of the cardiovascular system to the disease process, host response, and resuscitation[2].

Different types of myocardial dysfunction have been shown in septic patients as left ventricular (LV) systolic dysfunction, LV diastolic dysfunction and right ventricular (RV) dysfunction[3-5]. Despite the presence of numerous studies in the literature related with cardiac dysfunction in patients with sepsis, there is lack of consensus regarding the frequency and prognostic significance of this entity[1,2]. Although there is no consensus on definition of myocardial dysfunction in sepsis at the moment, most commonly accepted definition is an LV ejection fraction (LVEF) of less than 45% to 50% in the absence of cardiac disease that demonstrates reversibility upon remission[2,6,7].

The aim of the present study was to evaluate LV and RV performance with transthoracic echocardiography in patients with sepsis or septic shock. We also intended to see the effect of any kind of possible functional alteration on in-hospital mortality.

PATIENTS and METHODS

Patient

Patients were screened for sepsis or septic shock defined by the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock[8]. Inclusion criteria were identified as ≥ 18 years of age, sepsis or septic shock. Exclusion criteria were identified as a history of congestive heart failure and myocardial infarction; primary diagnosis of acute coronary syndrome; presence of significant organic valvular disease, pericardial tamponade, severe pulmonary hypertension and lack of sinus rhythm during initial echocardiogram. In total, 37 patients were included from January 2014 to January 2015. To assess severity of illness, APACHE II score and Sequential Organ Failure Assessment (SOFA) score were calculated on admission and daily till discharge or death. C-reactive protein (CRP), procalcitonin values were also recorded daily. All-cause in-hospital mortality and ICU-days for all enrolled patients were determined.

Transthoracic Examination

Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters were determined with M-mode echocardiography under two-dimensional guidance in the parasternal long-axis view, according to the recommendations of the American Society of Echocardiography[9]. Pulsed wave tissue Doppler imaging (TDI) was performed to assess both LV and RV longitudinal functions. In apical four-chamber view, a 5 mm pulsed Doppler sample volume was placed on the mitral annulus at the septal and lateral sites and on the tricuspid annulus at the place of attachment of the anterior leaflet of the tricuspid valve. To minimize the angle between the beam and the direction of annular motion, care was taken to keep the ultrasound beam perpendicular to the plane of the annulus. Peak systolic (S'), early and late diastolic myocardial velocities (E' and A') were recorded. Left ventricular mean E' value was calculated by using E' velocities obtained from septal and lateral mitral annular sites. Left ventricular mean E' value was used for calculation of LV E/E' ratio.

An acute left ventricular systolic dysfunction characterized by transient wall motion abnormalities, most commonly in the form of apical ballooning with relative sparing of the basal segments, detected by 2D echocardiography in apical 4 and 2 chamber views was defined as apical hypokinesia as shown previously. Right ventricular systolic dysfunction was defined as a TAPSE value lower than 17 mm or tricuspid annulus tissue Doppler peak systolic velocity (RVs) below 9.5 cm/s as suggested[10].

Statistical Analysis

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 11.0 was used for data analysis. Distribution of data was assessed by using one-sample Kolmogorov-Smirnov test. Values displaying normal distribution were expressed as the mean ± SD while values not displaying normal distribution were expressed as median (interquartile range). Significance of difference between groups regarding numeric variables with normal distribution was tested with independent samples Student's t-test. Significance of difference between groups regarding numeric variables without normal distribution was tested with Mann-Whitney U test. For comparison of categorical variables or percentages, we used Chi-square test. A p value less than 0.05 was considered significant.

RESULTS

Data of 37 patients were used in the analysis (21 male, 16 female, mean age: 61.7 ± 18.3 years). Among study population 15 patients (40.5%) survived and discharged from intensive care unit, while 22 patients were died in the hospital (59.5%). Demographic characteristics and laboratory findings reflecting sepsis is shown on Table 1.

Significant difference was detected between survivor and non-survivor groups regarding before discharge or death level of inflammatory markers such as CRP (106 ± 117 mg/L vs. 187

Table 1. Comparison of demographics and laboratory findings of sepsis patients who survived to discharge and those who died in the hospital

	Survivors (n= 15)	Non-survivors (n= 22)	p value
Age (years)	60.3 ± 16.4	62.7 ± 19.8	0.47
Gender (female, %)	4 F, 26.6%	12 F, 54.5%	0.09
Basal BNP level (pg/mL)	3406 ± 5646	6961 ± 7291	0.06
Final BNP level (pg/mL)	2131 ± 2878	6504 ± 5549	0.01
Basal CRP level (mg/L)	216 ± 143	195 ± 121	0.77
Final CRP level (mg/L)	106 ± 117	187 ± 128	0.05
Basal procalsitonin (ng/mL)	32 ± 43	17 ± 29	0.67
Final procalsitonin (ng/mL)	5 ± 7	25 ± 32	0.03
SOFA score	10.9 ± 4.5	12.9 ± 3.8	0.009
APACHE score	19 ± 6.4	23.3 ± 8.5	0.16

BNP: Brain natriuretic peptide, CRP: C-reactive protein, SOFA: Sequential organ failure assessment, APACHE: Acute physiology and chronic health evaluation score.

± 128 mg/L, p= 0.05) and procalcitonin (5 ± 7 ng/mL vs. 25 ± 32 ng/mL, p= 0.03) besides BNP (2131 ± 2878 pg/mL vs. 6504 ± 5549 pg/mL, p= 0.01) and SOFA (10.9 ± 4.5 vs. 12.9 ± 3.8, p= 0.009) score.

There were 2 patients (5.4%) with EF value less than %50 in the study population. Global hypokinesia on all myocardial segments was observed for both of these patients. Eight patients (21.6%) displayed hypokinesia on apical segment and 4 patients (10.8%) had TAPSE values below 17 mm whereas none of the patients had right ventricular peak systolic velocity below 9.5 cm/s.

Comparison of conventional echocardiographic M-mode, 2D, Doppler mitral inflow and tissue Doppler parameters between sepsis patients who survived to discharge and those who died in the hospital is displayed on Table 2 and Table 3.

There were no significant differences between survivors and non-survivors regarding any measured parameters. There was also no significant difference between groups regarding the ratio of patients who display LV systolic dysfunction on echocardiographic examination. One patient (6.6%) in the survivor group and 1 patient (4.5%) in the non-survivor group had LVEF value below 50% (p= 0.62). One patient (6.6%) in the survivor group but seven patients (31.8%) in the non-survivor group had apical hypokinesia with a trend towards significance (p= 0.068). There was also no significant difference between survivor and non-survivor groups regarding the ratio of patients who displayed right ventricular systolic dysfunction based on decreased TAPSE (< 17 mm) and RVs (< 9.5 cm/s) values. One patient in the survivor group (6.6%) and 3 patients (13.6%) in the non-survivor group had RV systolic dysfunction (p= 0.51).

Table 2. Comparison of conventional echocardiographic M-mode, 2D, and Doppler mitral inflow parameters between sepsis patients who survived to discharge and those who died in the hospital

	Survivors (n= 15)	Non-survivors (n= 22)	p value
LV end-diastolic diameter (mm)	46.6 ± 4.6	45.9 ± 4.3	0.80
LV end-systolic diameter (mm)	28 ± 5	28.5 ± 4.9	0.58
LV Ejection fraction (%)	68.9 ± 6.5	63.8 ± 11.5	0.27
Left atrial diameter (mm)	28.5 ± 7.5	31.9 ± 4.6	0.30
Septum Diameter (mm)	10.6 ± 1.3	10.8 ± 2.0	0.88
Posterior wall (mm)	9.7 ± 1.1	10.1 ± 1.4	0.45
E wave velocity (cm/s)	0.70 ± 0.16	0.81 ± 0.17	0.09
A wave velocity (cm/s)	0.79 ± 0.19	0.76 ± 0.21	0.82
EDT (msec)	200 ± 63	201 ± 45	0.86
Transmitral E/A ratio	0.97 ± 0.43	1.14 ± 0.45	0.29
TAPSE (mm)	21.3 ± 4.0	20.5 ± 3.8	0.50
Apical hypokinesia (n, %)	7 (31.8)	1 (6.6)	0.068

LV: Left ventricle, TAPSE: Tricuspid annular plane systolic excursion, EDT: Deceleration time of E wave.

Table 3. Comparison of tissue Doppler derived parameters between sepsis patients who survived to discharge and those who died in the hospital

	Survivors (n= 15)	Non-survivors (n= 22)	p value
Septal S' (cm/s)	8.5 ± 2.7	9.2 ± 2.3	0.43
Septal E' (cm/s)	7.3 ± 3.5	8.2 ± 3.8	0.51
Septal A' (cm/s)	9.0 ± 3.8	8.8 ± 3.3	0.98
Lateral S' (cm/s)	9.7 ± 2.8	11.6 ± 3.8	0.14
Lateral E' (cm/s)	9.7 ± 4.0	9.5 ± 4.7	0.59
Lateral A' (cm/s)	10.8 ± 4.2	10.6 ± 3.5	0.84
RV S' (cm/s)	16.4 ± 2.7	16.6 ± 3.2	0.92
LV E/E' ratio	8.7 ± 2.4	10.7 ± 5.5	0.48

LV: Left ventricle.

DISCUSSION

Prevalence of LV systolic dysfunction was 5.4% and RV systolic dysfunction was 10.8% in our study. None of these types of myocardial dysfunction was associated with in-hospital mortality. Mortality was found to be primarily related with the severity of disease and unresponsiveness to the therapy as reflected by lack of improvement in parameters such as CRP, procalcitonin and BNP. There was also a trend of increased mortality in patients with apical hypokinesia.

Previous studies have reported myocardial depression rates up to 60% of patients with septic shock[6,7,11]. It has also been suggested that sepsis induced myocardial depression affects both ventricles simultaneously with similar pattern of dysfunction. The underlying mechanisms of sepsis induced myocardial depression could not be fully elucidated so far; however, cytokines as tumor necrosis alpha, nitric oxide, reactive free oxygen radicals, endothelial dysfunction and cardiomyocyte apoptosis have been suggested to be involved in the pathogenesis[1,12,13].

There are discrepant findings in the literature related with the association of various types of myocardial dysfunction with prognosis in patients with sepsis. In an early study, Parker et al. reported that patients with LV dilation and depressed EF had better prognosis[6]. However, many other studies have reported that impaired EF is associated with a poor prognosis[13]. Reversible compensatory LV dilation has also been suggested to be associated with better prognosis even in patients with similar EF values[11]. There was no significant difference between survivors and non-survivors in our patient group regarding LV EF values, LV diameters and ratio of patients with LV systolic dysfunction. However, more patients with apical hypokinesia were detected in the non-survivors despite borderline statistical significance. It has been suggested that sepsis is a trigger of takotsubo syndrome by the way of acute cardiac sympathetic disruption with noradrenaline spill-over[14]. Reversibility of apical hypokinesia could not be demonstrated for any patient and none of them had ischemia-like electrocardiographic changes which are characteristic findings of takotsubo syndrome. Higher frequency of apical hypokinesia in non-survivors might be related with the proposed pathophysiological link between sepsis and takotsubo syndrome.

Right ventricular dysfunction has also been suggested to be related with prognosis however, there were again no differences between survivors and non-survivors related with measures of RV dysfunction in our study[11]. Two recent studies have evaluated echocardiography-based indices of myocardial function in patients with sepsis and septic shock. Furian et al. reported RV dysfunction rate of 30%[11]. LV non-dilation and RV dysfunction were found to be associates of poor prognosis in that study. Pulido et al. reported RV systolic dysfunction rate of 31% in their study population[2]. They could not find any difference of mortality between patients with normal myocardial function and those with any kind of ventricular dysfunction. Our findings regarding prognosis are also in agreement with the results of latter publication.

CRP and procalsitonin are serological diagnostic markers that help to evaluate the presence of infection and sepsis in critically ill patients in the ICU[15,16]. Procalsitonin is demonstrated as a better serologic marker than CRP in detecting the severity of infection[17]. Although plasma procalsitonin levels correlate closely with higher SOFA score levels, CRP did not show strict correlation with SOFA score[18]. A significant difference in procalsitonin levels between survivors and non-survivors in the ICU patients was also demonstrated recently[19]. In our study we also demonstrated significant difference between survivor and non-survivor groups regarding levels of inflammatory biomarkers (procalsitonin and CRP) and SOFA score. It was shown that SOFA score has better discriminatory power than APACHE II in predicting mortality in the ICU[20]. In our study, there was a significant difference in SOFA scores between survivors and non-survivor groups, however APACHE II scores were identical.

CONCLUSION

We found much lower rate of LV and RV systolic dysfunction in patients with sepsis or septic shock compared with previous studies. None of the myocardial dysfunction types was associated with in-hospital mortality. Apical hypokinesia was also more prevalent in non-survivors despite borderline significance. Based on these observations it may be speculated that there are still more questions than answers related with cardiac effects of sepsis and its consequences. Results of large scale, prospective and standardized studies are necessary to clarify this issue.

Ethics Committee Approval: The approval for this study was obtained from Marmara University Hospital Ethics Committee (Decision No: 09.2021.559, Date: 26.05.2021).

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