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Original Article

Diastolic Dysfunction and Mortality in Early Severe Sepsis and Septic Shock - A Prospective Echocardiography Study

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***ABSTRACT*:**
Background: Severe sepsis or septic shock is suggested to be a cause of significant cardiovascular dysfunction. Left ventricular diastolic dysfunction is common in septic patients. **Aim:** To evaluate the incidence of the diastolic dysfunction estimated by transthoracic echocardiography (TTE) and its related mortality rate in patients with severe sepsis or septic shock. **Methods:** We carried a prospective study on 80 patients with severe sepsis or septic shock. All the patients underwent TTE within 6 hours of ICU admission, after 18 to 32 hours and after resolution of shock. The study was carried out from January 2017 to December 2017 at Prathima Institute of Medical Sciences, Karimnagar, Telangana State, India. Left ventricular (LV) diastolic dysfunction was defined according to modified American Society of Echocardiography 2009 guidelines using E, A, and e' velocities; E/A and E/e'; and E deceleration time. Systolic dysfunction was defined as an ejection fraction<45%. **Results:** The mean age of the patients was 50.6 ± 18.3 years. Out of 80 patients, 45 were female and 35 male. The mean Acute Physiology And Chronic Health Evaluation II (APACHE II) score was 21.6 ± 8.1. Initial echocardiogram revealed that 30 (37.5%) of patients had diastolic dysfunction, while 50 patients (62.5%) had diastolic dysfunction on at least one echocardiogram. Total mortality was 16 %. Grade I diastolic dysfunction, but not grades II and III, was associated with increased mortality. **Conclusion:** Left ventricular diastolic dysfunction is frequent in septic patients. There is a possible role for TTE in sepsis resuscitation.
Keywords: Diastolic dysfunction, Echocardiography, Sepsis, Shock.

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INTRODUCTION:

Sepsis is a common condition that can lead to shock and mortality. The host response to sepsis is controlled by inflammatory mediators, which transmit, amplify and maintain the generation of the host response. Left ventricle (LV) is a muscular contractile chamber which pumps blood into the systemic circulation to perfuse and oxygenate the vital organs. The clinical picture of early sepsis is a patient with a low systemic vascular resistance (SVR) and a normal or increased cardiac output, although the heart is compromised by poor contractility. Although the stroke volume may be maintained, there is an increase in left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) and very often a decrease in the ejection fraction (EF), with cardiac output maintained by an increase in heart rate. There is also diastolic dysfunction with decreased left ventricular compliance and a subsequent increase in left ventricular end-diastolic pressure (LVEDP).[1-3]

Diastolic dysfunction occurs when the left ventricular myocardium is non-compliant and not able to accept blood return in a normal fashion from the left atrium. Echocardiography is the gold standard to diagnose diastolic dysfunction. There are four grades of diastolic dysfunction.[4, 5]

1. **Grade I (impaired relaxation):** This is a normal finding and occurs in nearly 100% of individuals by the age of 60. The E wave velocity is reduced resulting in E/A reversal (ratio < 1.0). The left atrial pressures are normal. The deceleration time of the E wave is prolonged measuring > 200 ms. The e/e' ratio measured by tissue Doppler is normal.
2. **Grade II (pseudonormal):** This is pathological and results in elevated left atrial pressures. The E/A ratio is normal (0.8 ± 1.5), the deceleration time is normal (160-200 ms), however the e/e' ratio is elevated. The E/A ratio will be < 1 with Valsalva.
3. **Grade III (reversible restrictive):** Significantly elevated left atrial pressures. Also known as a "restrictive filling pattern", the E/A ratio is > 2.0,

the deceleration time is < 160 ms, and the e/e' ratio is elevated. The E/A ratio changes to < 1.0 with Valsalva.

4. **Grade IV (fixed restrictive):** This indicates a poor prognosis and very elevated left atrial pressures. The E/A ratio is > 2.0, the deceleration time is low and the e/e' ratio is elevated. The major difference distinguishing grade III from grade IV diastolic dysfunction is the lack of E/A reversal with the Valsalva maneuver (no effect will be seen with Valsalva).

Much less is known about LV diastolic dysfunction in severe sepsis and septic shock. Previous studies on LV diastolic dysfunction in patients with severe sepsis and septic shock have employed various definitions and have not yielded a stable estimate of incidence.[5, 6]

Some reports suggest that the presence of LV diastolic dysfunction may be associated with poor outcome. While others suggest no effect on outcomes. The natural evolution of diastolic dysfunction and its clinical implications during the course of sepsis and septic shock are also not well characterized.[7]

Non-invasiveness and instantaneous diagnostic capability are prominent features of the use of echocardiography in critical care. Sepsis and septic shock represent complex situations where early hemodynamic assessment and support are among the keys to therapeutic success. Echocardiography can play a key role in the critical septic patient management, by excluding cardiac causes for sepsis, and mostly by guiding hemodynamic management of those patients in whom sepsis reaches such a severity to jeopardize cardiovascular function. In recent years, there have been both increasing evidence and diffusion of the use of echocardiography as monitoring tool in the patients with hemodynamic compromise.[6-8]

We prospectively evaluated the incidence of the diastolic dysfunction estimated by transthoracic echocardiography and its related mortality rate in patients with severe sepsis or septic shock.

MATERIALS AND METHODS:

We carried a study on 100 patients who have been admitted in the MICU, RICU, SISU & ER IN PL at Prathima Institute of Medical Sciences, Karimnagar, Telangana State, India, over a period of one year from January 2017 to December 2017. We followed the methodology of **Brown et al (2012)** in our sample.[1]

Inclusion Criteria:

1. Patients of at least 14 years of age,
2. Patients with a suspected infection,
3. Patients who had two or more systemic inflammatory response syndrome criteria,
4. Patients either had severe sepsis or septic shock.

Exclusion criteria:

1. Primary diagnosis of acute coronary syndrome or major cardiac dysrhythmia,
2. Presence of pericardial tamponade, presence of mitral stenosis, known diagnosis of severe pulmonary hypertension,
3. Lack of sinus rhythm during initial echocardiogram,
4. Contraindication to central venous catheterization
5. Hypertension, Diabetes

Patients were treated according to the Surviving Sepsis Guidelines.[9]

Transthoracic echocardiography:

First TTE was done within the first 6 hours of admission to the ICU, the second at 18–32 hours after admission, and the third at least 24 hours after cessation of vasoactive medications or resolution of severe sepsis in patients who did not require vasoactive medications.

We assessed diastolic function by measuring E and A peak velocities using spectral Doppler of mitral inflow and e' and a' velocities using tissue Doppler of the septal mitral annulus in the apical four-chamber view. Each data point represents the average of measurements from three consecutive cardiac cycles. Mitral deceleration time (DT) and left atrial (LA) area at end systole were also measured.

We evaluated the definition of diastolic dysfunction proposed by Sturgess et al.[6] LV systolic dysfunction was defined as an LV ejection fraction (EF)<45%.[2] We assessed the incidence of LV diastolic dysfunction on first or subsequent TTE as well as the relationship between LV diastolic dysfunction on the initial TTE and 28-day out- comes. Our primary outcome was 28-day mortality, with secondary outcomes of ventilator-free days and ICU-free days.

STATISTICAL ANALYSIS:

Central tendencies were compared using Fisher's exact test, Student's t test, Wilcoxon rank-sum, and Kruskal-Wallis test.

RESULTS:

Demographic findings:

The mean age of the patients was 50.6 ± 18.3 years. Out of 80 patients, 45 were female and 35 male. The mean APACHE II score was 21.6 ± 8.1. Initial echocardiogram revealed that 30 (37.5%) of patients had diastolic dysfunction, while 50 patients (62.5%) had diastolic dysfunction on at least one echocardiogram. Total mortality was 15%. Grade I diastolic dysfunction was associated with increased mortality. (**Table 1 and 2: Graph 1**).

Table 1 Demographic Details of the Sample

CHARACTERISTIC	VALUE
Number of patients	80
Mean Age	50.6 ± 18.3
Gender	Female=45: Male=35
Mean APACHE II	21.6 ± 8.1

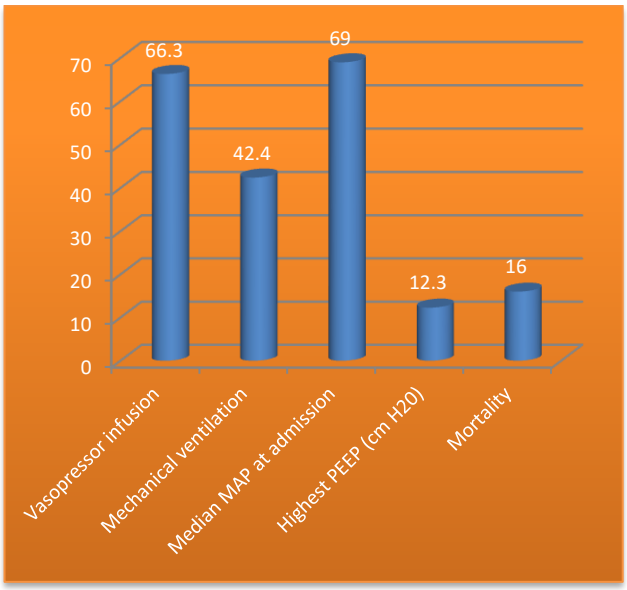
APACHE II, Acute Physiology

Table 2: Clinical Findings of the Sample

Clinical Findings	Percentage Of Patients
Received vasopressor infusion	66.3 %
Received mechanical ventilation	42.4 %
MAP at admission (mmHg, median, IQR)	69 (63–78)
Highest PEEP (cm H20)	12.3
Mortality	16 %

MAP, mean arterial pressure; PEEP, positive end-expiratory pressure

Graph1: Bar Graph showing Clinical Findings of the Sample



The major source of infection was thorax (pneumonia) in 36.25 % patients followed by urinary tract (13.75%) (**Table 3, Graph 2**)

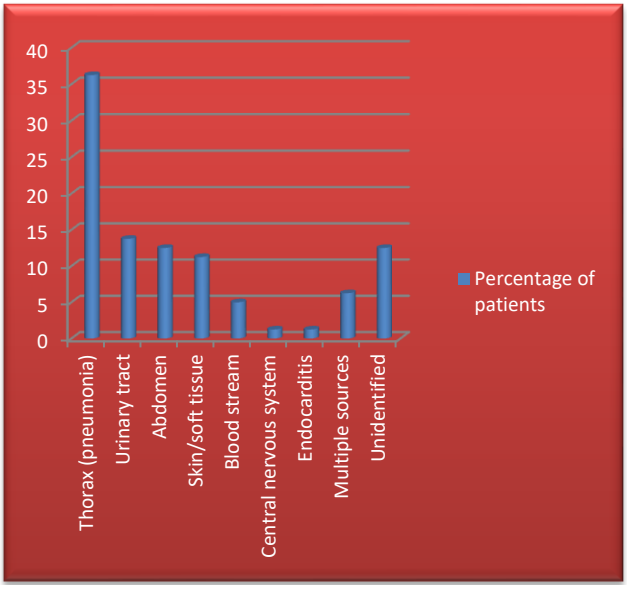
Table 3: Source of infection of the Sample

Source Of Infection	Percentage Of Patients
Thorax (pneumonia)	36.25 %
Urinary tract	13.75%
Abdomen	12.5%
Skin/soft tissue	11.25%
Blood stream	5.0%
Central nervous system	1.25%
Endocarditis	1.25%
Multiple sources	6.25%
Unidentified	12.5%

Incidence of diastolic dysfunction

Initial echocardiogram revealed that 30 (37.5%) of patients had diastolic dysfunction, while 35 patients (43.75%) had LV diastolic dysfunction on the final echocardiogram, 20 (25%) were newly diagnosed with diastolic dysfunction on second and third occasion, a whole 50 patients (62.5%) had diastolic dysfunction on at least one echocardiogram. Total mortality was 15 %. Grade I diastolic dysfunction (11 of 12 cases), but not grades II (one case) and III, was associated with increased mortality.

Graph 2: Bar Graph showing Percentages of patients and Source of infection



DISCUSSION:

Diastolic dysfunction occurs when the left ventricular myocardium is non-compliant and not able to accept blood return in a normal fashion from the left atrium. During sepsis, excessive NO is produced, which causes ventricular dysfunction by three methods; it decreases both calcium trafficking during systole (leading to decreased contractility) and calcium flux during diastole (which leads to abnormal cardiac filling). In these circumstances, cardiac force is compromised by the resulting abnormalities of fibre length. This diastolic dysfunction can be seen globally as increased LVEDP.[1, 10]

The mean age of the study sample was 50.6 ± 18.3 years. Patients whose initial LV diastolic dysfunction improved by the third echocardiogram were younger than patients whose LV diastolic dysfunction persisted (36 years vs 62 years, $p<0.01$), and this effect became significant after controlling for age greater than 50 years. We also found that Patients with grade I diastolic dysfunction had similar CVPs compared to patients with grade II or higher diastolic dysfunction. Systolic dysfunction was recorded in 20 (25%) of patients. The above findings are similar to Brown et al (2012).[1]

Our findings of 37.5% of patients having diastolic dysfunction on initial echocardiogram and 62.5% having diastolic dysfunction on at least one echocardiogram with a total mortality of 16 % are similar to Brown et al (2012) and in contrast to Sturgess et al (2010), who found a worse outcome with more severe LV diastolic dysfunction.[1, 6] The reason for this discrepancy may be related to patient population, treatment algorithms, timing of the TTE, or definition of diastolic dysfunction employed.

68 out of 80 patients recovered from diastolic dysfunction. When mortality between echocardiography's was estimated, it was found that 3 patients died between first and second and 2 patients died between second and third Echo.

Rivers et al (2001) pivotal study of early aggressive optimization of oxygen delivery in patients with severe sepsis or septic shock suggested that initial resuscitation was crucial to outcome.[11] In our study, the mean CVP among those patients with grade I diastolic dysfunction was the same as that among patients with grade II or III diastolic dysfunction. Our study suggests that there may exist a group of patients with grade I diastolic dysfunction on TTE who would benefit from further volume expansion despite an elevated CVP. While small numbers in the subgroup of patients with grade I diastolic dysfunction limit generalizability, the higher mortality and lesser volume expansion prior to ICU admission suggest that further volume resuscitation in this group may improve survival. APACHE II scoring system is commonly used in the intensive care population to prognosticate outcome. Among patients with diastolic dysfunction grade I diastolic dysfunction was associated with higher mortality, even after receipt of vasoactive medications, and APACHE II score upon admission, similar to Brown et al (2012).[1]

Our study also highlights the need to establish a consistent, reproducible definition of LV diastolic dysfunction among critically ill patients, especially those with severe sepsis or septic shock.

In a retrospective review of 94 general ICU patients, Sturgess et al reported an incidence of LV diastolic dysfunction equal to 67%. Applying Sturgess et al definition to our cohort, we found a relatively consistent incidence of LV diastolic dysfunction on the initial echocardiogram of 61.7%.[6]

In a small study of 35 patients with septic shock requiring mechanical ventilation, Etchecopar-Chevreuil et al. found that LV diastolic dysfunction occurred in 20% of patients.[8]

Bouhemad et al reported a 20% incidence of isolated LV diastolic dysfunction in 54 post-operative patients with septic shock using transesophageal echocardiography.[12]

The association of worsening outcome with the less severe form of diastolic dysfunction could suggest the deleterious effect of inadequate volume expansion at the time of ICU admission. Future studies with classification of patients by age and grade of diastolic dysfunction should help clarify the evolution and clinical implication of LV diastolic dysfunction in severe sepsis and septic shock.

Limitations of the study

1. Smaller sample size
2. Our study being observational in nature.
3. Clinicians were blinded to the research TTEs, but the clinical TTEs may have influenced clinical management.
4. Diastolic dysfunction was measured by the ASE 2009 guidelines, which were not developed for patients with sepsis.

The strength of our study was its prospective nature and even though had limited sample, but was one of the largest studies to date of critical care echocardiography.

CONCLUSION:

LV diastolic dysfunction occurs frequently during severe sepsis and septic shock. Grade I diastolic dysfunction is associated with increased mortality when compared to either patients with normal filling patterns or those with grade II or III diastolic dysfunction. Our findings suggest that TTE may identify patients who require further fluid resuscitation during severe sepsis and septic shock.

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