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Cardiac dysfunction in septic conditions: Insights from echocardiographic evaluation and mortality associations

Frantisek Golas[1], Rastislav Cikrai[2], Jurina Sadlonova[3], Milan Dragula[3], Monika Kulinova[4], Andrea Cikraiova[4]

[1]The Jessenius Faculty of Medicine in Martin, Comenius University Bratislava, Hospital with Policlinic, Department of Internal Medicine, Zilina, Slovakia

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Abstract. *Introduction:* In septic cardiomyopathy, changes manifest as systolic and diastolic dysfunction of both the left and right ventricles and dilation of cardiac chambers. The aim of this study was to determine whether left ventricular dysfunction as well as the right ventricular dysfunction were associated with 30-day mortality.

Patients and methods: Using established criteria for sepsis and septic shock (SEPSIS.3, The third international consensus definitions for sepsis and septic shock, SOFA score), a total of 65 patients (41 males, 24 females) were enrolled for observation from January 1, 2020, to January 1, 2023. The overall mean age of the patients was 62.5±15.2 years old. Subsequently, transthoracic and, if necessary, transesophageal echocardiographic examinations were performed.

Results: Systolic dysfunction (EF ≤ 55%) was observed in 35/65 (53.8%) patients on the first day of observation. Comparison using the log-rank test did not show a significant difference in survival time between patients with EF ≤ 55% and those with EF > 55%. Diastolic left ventricle dysfunction (LV) was present in 50/65 (76.9%) patients on the first examination day. We confirmed a strong association between diastolic dysfunction of the LV and mortality. Right ventricular (RV) dysfunction was present in 22/65 (33.8%) patients on the first day. RV dysfunction was significantly associated with higher mortality compared to the control group.

Conclusion: In our study, we investigated the relationship between systolic and diastolic dysfunction of the left ventricle (LV), as well as the systolic dysfunction of the right ventricle (RV) in patients with sepsis/septic shock, focusing on the 30-day mortality rate. We identified a significant association between left ventricular diastolic dysfunction and 30-day mortality. Similarly, right ventricular systolic dysfunction was significantly correlated with 30-day mortality. Conversely, left

From [1]The Jessenius Faculty of Medicine in Martin, Comenius University Bratislava, Hospital with Policlinic, Department of Internal Medicine, Zilina, Slovakia, [2]Faculty of Medicine of the Comenius University, National Institute of Cardiovascular Diseases, Clinic of Cardiac Surgery, Bratislava, Slovakia, [3]The Jessenius Faculty of Medicine in Martin, Comenius University, University Hospital Martin, Cardiology department, Martin, Slovakia and [4]Hospital with Policlinic, Department of Internal Medicine, Zilina, Slovakia

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Address for correspondence: Frantisek Golas, MD, Faculty of Medicine of the Comenius University, Hospital with Policlinic, Department of Internal Medicine, Zilina, Vojtecha Spanyola 43, 012 07 Zilina, Slovakia, e-mail: frantisekgolas@yahoo.com

ventricular systolic dysfunction (EF ≤ 55%) did not demonstrate an impact on 30-day mortality compared to patients with preserved left ventricular systolic function (EF > 55%). Fig. 4, Tab. 4, Ref. 40, on-line full text (Free, PDF), www.cardiologyletters.sk
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Introduction

Septic shock stands as the foremost cause of patient hospitalization in intensive care units. This life-threatening condition necessitates prompt recognition and immediate initiation of treatment to achieve adequate tissue oxygen utilization (1). Despite the advances in modern medicine, encompassing antibiotics, vaccination, and organ support, a substantial challenge endures in the form of persistently high mortality rates associated with septic conditions and septic shock. Unfavourable statistics have been validated by the European SOAP study (Sepsis Occurrence in Acutely Ill Patients), wherein sepsis was observed in as many as 35% of intensive care unit patients, with mortality rates reaching up to 27% (2, 3, 4). The progression of sepsis to septic shock is characterized by mitochondrial dysfunction and dysregulation of the immune response, ultimately leading to multi-organ dysfunction and, in the absence of treatment, hemodynamic instability and subsequent mortality (5, 6, 7). The heart is frequently one of the organs most severely affected (8, 9). Depending on the definition, which lacks uniformity, the prevalence of sepsis-induced cardiomyopathy ranges between 10% and 70% (10, 11, 12, 13). Sepsis-induced cardiac injury results in a wide spectrum of cardiac dysfunction, ranging from asymptomatic courses to cardiac chamber dilation, diastolic dysfunction, and even systolic failure with a reduction in the ejection fraction (EF) of the left ventricle (LV) (14, 15). The abnormalities in cardiac kinetics can manifest in various forms, including global hypokinesia or segmental hypo-akinesia, sometimes in the presence of preserved myocardial function in the basal segments of the LV (16, 17). Every patient presenting with suspicion of septic shock should undergo echocardiographic examination immediately upon admission to the Intensive Care Unit (ICU) and subsequently at least once daily, contingent on the patient's overall clinical condition (15, 16, 18).

The aim of this study is to report a grade of cardiac dysfunction during sepsis/septic shock and its impact on mortality.

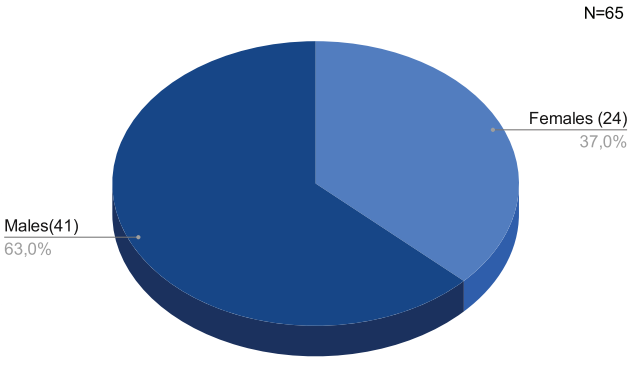

Figure 1 Gender

Patients and methods

Over the course of three years (January 1, 2020, to January 1, 2023), a total of 65 subjects (41 males, 24 females) were enrolled in the clinical study (**Figure 1**).

The overall mean age of the patients was 62.5±15.2 years old (**Figure 2**).

These subjects were admitted to the Intensive Care Unit of the Internal Department (59 patients) and to the Critical Care Unit of the Anesthesiology and Intensive Care (6 patients) at the University Hospital in Žilina. They met the inclusion criteria, including suspected infection and SOFA score ≥ 2, and their voluntary consent to participate in the study (as indicated by their informed consent form). The representation of individual diseases in the dataset is clearly illustrated in **Figure 3**.

From the provided dataset, 24 out of 65 (37%) patients required artificial lung ventilation (invasive or non-invasive), 63 out of 65 (97%) patients required

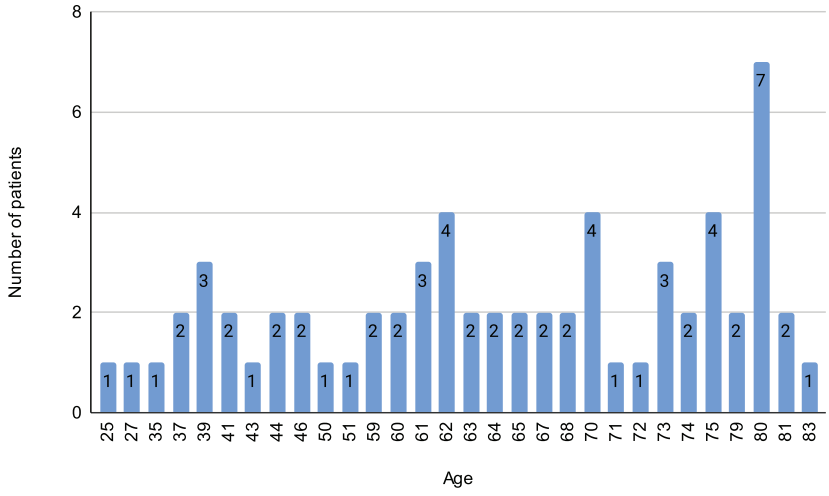

Figure 2 Age distribution

vasopressor and inotropic support, and 21 out of 65 (32%) patients experienced sepsis-induced renal failure necessitating acute hemodialysis (**Figure 4**).

To focus on specific population, and maintain a more homogeneous sample, we excluded from the study patients with a history of severe systolic dysfunction (EF LV ≤ 40%), whether due to ischemic heart disease or dilated cardiomyopathy, as well as patients with echocardiographically confirmed severe aortic stenosis (AVA ≤ 1 cm^2). Including patients with pre-existing severe LV dysfunction might have confounded the mortality results, as their cardiac function could be primarily influenced by their pre-existing conditions rather than sepsis (Risk of Bias). Transthoracic and, when necessary, transesophageal echocardiographic examinations were performed on the first, seventh, and thirtieth days. Left ventricular systolic function was assessed using Simpson's method of discs and longitudinal myocardial velocity at the mitral annulus level (TDI-S' LV), while right ventricular function was evaluated through fractional area change (FAC). Left ventricular diastolic function was assessed using tissue Doppler and measurements of left atrial size/volume. The data were subjected to statistical analysis using the R software environment (R Core Team, 2020) and the JASP program (JASP Team, 2022).

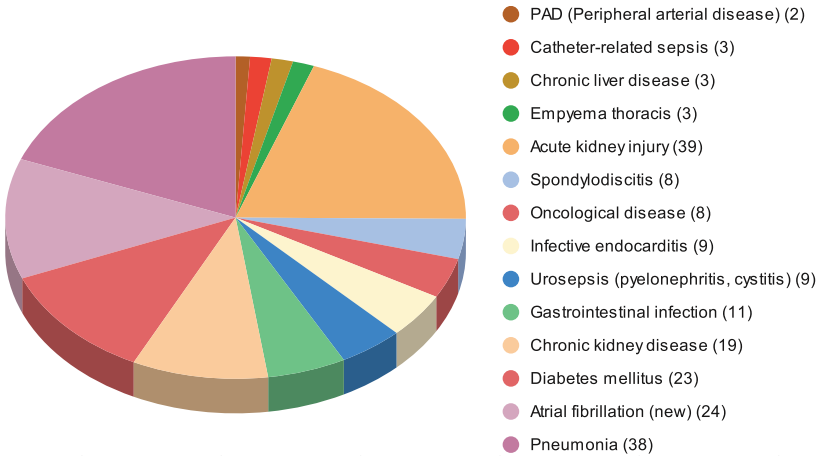

Figure 3 Characteristics before and after ICU admission in patients with suspected sepsis

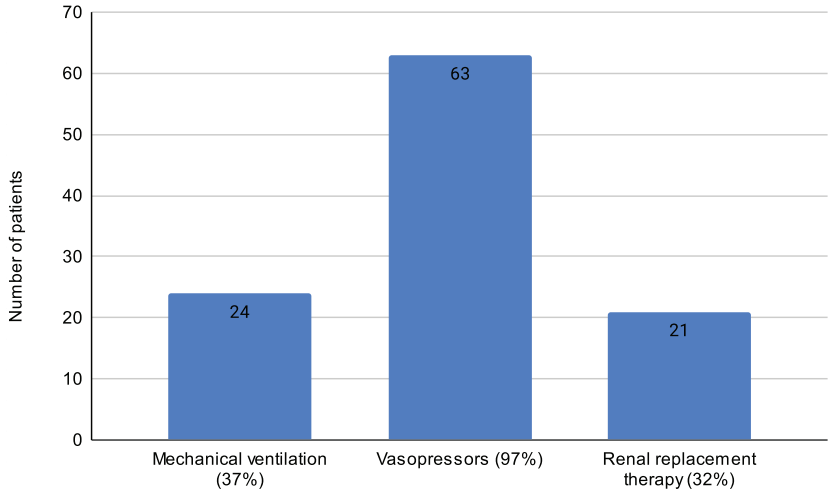

Figure 4 Organ support

Results

Within the observed cohort, patients were categorized into two distinct groups: those with a normal range EF (> 55%), and those with reduced EF (≤ 55%). Systolic dysfunction (EF ≤ 55%) was observed in 35 patients on the first day of monitoring. Comparison using the log--rank test revealed no significant difference in survival time between patients with EF ≤ 55% and patients with EF > 55%. The probability of survival with EF > 55% and EF ≤ 55% is shown in **Table 1**. This conclusion was also supported by the result of Cox regression, β = 0.14, SE = 0.42, H-R = 1.15 [95% CI: 0.51; 2.63], p = .736.

We also did measurements by tissue Doppler, (TDI--S′ LV ≤ 8 cm/s; TDI S′ LV > 8 cm/s) on the 1st day compared to the rest of the cohort. The probability of survival over 30 days again did not significantly differ between groups, log-rank test: $\chi 2(1) = 2.89$,

p = .100. This result was also confirmed by the Cox regression model, β = 0.69, SE = 0.42, H-R = 1.99 [95% CI: 0.87; 4.55], p = .101. (**Table 2**).

Regarding left ventricular diastolic dysfunction, on the 1st day of examination 50 patients had this condition, on the 7th day 40 patients, and during the outpatient follow-up on the 30th day, 24 patients still exhibited diastolic dysfunction. Mortality among patients with diastolic dysfunction showed the steepest increase in the first 10 days (**Table 3**), with the survival probability curve demonstrating a gradual decline, reaching a 46% mortality rate by the end of the observation period. The log-rank test indicated a statistically significantly shorter

Table 1 The probability of survival with EF > 55% and EF ≤ 55%

Day	EF > 55% (norm; *n* = 30)			EF ≤ 55% (dysfunction; *n* = 35)		
	Deaths	NoP	PoS (95% CI)	Deaths	NoP	PoS (95% CI)
5	2	29	93% (85; 100)	3	34	91% (83; 100)
10	4	24	80% (67; 96)	6	27	74% (61; 90)
15	1	24	77% (63; 93)	1	25	71% (58; 88)
20	1	22	73% (59; 91)	0	25	71% (58; 88)
25	2	20	67% (52; 86)	1	24	69% (55; 86)
30	0	20	67% (52; 86)	2	22	63% (49; 81)

NoP – Number of patients at risk, PoS – Probability of survival with a 95% confidence interval

Table 2 Probability of survival when assessing the longitudinal systolic function of the left ventricle using TDI-S′ (measured on the lateral annulus)

Day	TDI(S′)-LV > 8 cm/s (norm; *n* = 37)			TDI(S′)-LV ≤ 8 cm/s (dysfunction; *n* = 28)		
	Deaths	NoP	PoS (95%CI)	Deaths	NoP	PoS (95% CI)
5	2	36	95% (88; 100)	3	27	89% (78; 100)
10	4	31	83% (73; 96)	6	20	68% (53; 88)
15	1	31	81% (69; 95)	1	18	64% (49; 85)
20	1	29	78% (66; 93)	0	18	64% (49; 85)
25	2	27	73% (60; 89)	1	17	61% (45; 82)
30	0	27	73% (60; 89)	2	15	54% (38; 76)

NoP – Number of patients at risk, PoS – Probability of survival with a 95% confidence interval

survival time in patients with (median survival ~ 30 days) compared to patients without left ventricular diastolic dysfunction, $\chi2(1) = 11.90$, $p < .001$.

In our dataset, we also compared patients with right ventricular dysfunction, assessed using right ventricular fractional area change (FAC-RV ≤ 35%; n = 22), with patients having normal right ventricular function (FAC--RV > 35%; n = 43). Right ventricular dysfunction was significantly associated with higher mortality compared to the control group, $\chi2(1) = 19.70$, $p < .001$ (**Table 4**).

The risk of mortality on any given day during the observation period was substantially higher in patients with right ventricular dysfunction (Hazard Ratio [H-R] = 5.7 [95% Confidence Interval: 2.40; 13.6]) in comparison to patients with normal right ventricular function, $\beta = 1.75$, $SE = 0.44$, $Z = 3.96$, $p < .001$.

Discussion

Four decades ago Parker and colleagues published findings that introduced the concept of LV dilation and LVEF depression in a subset of patients with sepsis that reversed to normal within two weeks as patients recovered (19, 20). In those studies, patients with ventricular dilation and lower LVEF had lower mortality compared to patients without these features. This was a very interesting suggestion. The prognostic value of low LV EF (< 55%) and normal LV EF (55-70%) on survival has yielded mixed results with respect to outcomes. Some studies found that decreased LV EF was associated with increased mortality (21), others reported improved survival (22), and others found no difference in survival based on LV EF (23). A 2013 meta-analysis did not establish a relationship between LV EF and mortality (24). In our observed cohort, we also did not observe an influence of lower LV EF (< 55%) on survival. A challenge associated with the utilization of LVEF lies in its reliance on preload and afterload conditions. In instances of substantial contractile dysfunction, a patient may exhibit a seemingly normal LVEF in the presence of hypovolemia or low mean arterial pressure, common occurrences in sepsis. The dynamic and substantial fluctuations of LVEF in response to variations in arterial pressure and volume status may not accurately reflect changes in the true contractility of the myocardium. Thus it is not surprising that studies, based in LVEF, have demonstrated considerable variability in prognostication. It remains unclear whether a lower LVEF is cardioprotective or represents a deleterious state.Within our cohort, there was a small subgroup of 7 patients which displayed a "hyperdynamic" EF (> 70%), on the initial day of observation, resulting in the mortality of 4 within the first 7 days. It appears that a higher left ventricular ejection fraction (LV EF, termed "hyperdynamic" LV) may be associated with increased mortality in septic patients when compared to those with a normal LV EF (25, 26). Hyperdynamic cardiac function may serve as a compensatory mechanism for vasoplegia or inadequate intravascular volume, but it can also manifest in a hyperadrenergic state resulting from an excess of endogenous or exogenous catecholamine stimulation. Paonessa and colleagues conducted a retrospective, single-centre study involving 2867 patients admitted to the intensive care unit. They found that 8.6% of the patients had a higher LV EF (> 70%). When compared to patients with a normal LV EF, those with

Table 3 Survival analysis results in patients with diastolic dysfunction within a 30-day interval

Day	Number of deaths	Number at risk	Probability of survival	L-95%	U-95%
5	5	48	90%	82.1%	98.7%
10	10	36	70%	58.4%	83.9%
15	2	34	66%	54.1%	80.5%
20	1	32	64%	52.0%	78.8%
25	3	29	58%	45.8%	73.4%
30	2	27	54%	41.8%	69.7%

The number at risk represents the remaining count of patients after a given time (day). L- and U-95% are the lower and upper bounds of the 95% confidence interval for the point estimate of survival probability.

Table 4 Probability of survival in normal and right ventricular dysfunction

Day	FAC-PK > 35% (norm; *n* = 43)			FAC-PK ≤ 35% (dysfunction; *n* = 22)		
	Deaths	NoP	PoS (95%CI)	Deaths	NoP	PoS (95% CI)
5	1	42	97% (93; 100)	4	21	82% (67; 99)
10	3	40	91% (82; 99)	7	11	50% (33; 76)
15	1	39	88% (79; 98)	1	10	45% (29; 72)
20	1	37	86% (76; 97)	0	10	45% (29; 72)
25	2	35	81% (71; 94)	1	9	41% (25; 68)
30	0	35	81% (71; 94)	2	7	32% (17; 59)

NoP – Number of patients at risk, PoS – Probability of survival with a 95% confidence interval

a higher LV EF experienced increased mortality on the 28th day. In the mentioned study, "hyperdynamic" LV was associated with female gender, higher age, obesity, and concomitant oncological diseases (27). Ultra-short--acting beta blockers (landiolol, esmolol) may represent a potential therapy for hyperdynamic LVEF but further research is warranted. There is concern that beta blockade can suppress compensatory tachycardia in the setting of low preload, causing a drop in CO and worsening hemodynamics (28, 29). Unfortunately, patients with a "hyperdynamic" EF (> 70%) are less relevant for the primary objectives of our study, as it focused on assessing and comparing patients with normal and reduced EF, where more significant changes in clinical outcomes were anticipated.

There are many factors that affect RV during sepsis: hypoxia, hypercarbia, and acidosis can contribute to pulmonary vasoconstriction (30, 31). Right ventricular dysfunction was significantly associated with higher mortality compared to the control group in our study. In the case of a patient experiencing acute respiratory distress syndrome (ARDS), the impact on right ventricular function is even more pronounced. Hypoxemia and mechanical lung ventilation increase the afterload of the right heart, elevating pulmonary vascular resistance, which can lead to an increase in right atrial pressure and subsequently result in right-to-left shunting through a patent foramen ovale (32). The incidence of right-to-left shunting through a patent foramen ovale in patients with ARDS is reported to be between 15-19%. In the case of acute cor pulmonale, the incidence increases to as much as 33% (33). RV dysfunction has therapeutic implications as well. While fluids are advised in sepsis to sustain sufficient preload, intensivists must exercise caution in administering fluids, given that a dilated RV with compromised systolic function and elevated afterload may struggle to adapt to increased volume. RV dysfunction is a demonstrated predictor of a lower probability of fluid responsiveness, so high volume fluid resuscitation is likely less helpful in these patients' supporting prioritization of vasopressors in this population. Norepinephrine is the first line vasopressor recommended in sepsis. Norepinephrine increases RV systolic function without a detrimental effect on pulmonary vascular resistance which is a favourable profile for use in patients with RV dysfunction (34).

In patients who exhibit left ventricular diastolic dysfunction (defined by tissue Doppler as a low e' value and a high E/e' ratio), appropriate left ventricular filling depends on adequate preload, sinus rhythm with an appropriate heart rate, and the absence of arrhythmias. In the septic state, we commonly observe patients who are hypovolemic, tachycardic, and often afflicted with atrial fibrillation (35, 36). For example, new-onset atrial fibrillation occurs in 6 to 46% of septic shock patients and significantly increases the risk of ischemic stroke and mortality (37, 38). In our studied cohort, 24 probands (16 males, 8 females) exhibited new-onset atrial fibrillation. Mortality among patients in our dataset with diastolic dysfunction showed the steepest increase in the first 10 days, and we have confirmed a strong relationship between left ventricular diastolic dysfunction and mortality. In line with meta-analyses (39, 40), we have confirmed a strong relationship between left ventricular diastolic dysfunction and mortality. Patients with diastolic dysfunction are particularly prone to worsening hemodynamics in the setting of tachycardia and reduced filling time. This group may benefit from heart rate control and precise assessment of fluid responsivness.

Conclusion

There is no universal definition of septic cardiomyopathy. Sepsis-induced myocardial dysfunction is generally characterized as an acute process that is not caused by acute coronary syndrome and is typically reversible in seven to ten days. It manifests as biventricular systolic and/or diastolic dysfunction with left ventricular dilation which is poorly responsive to fluid and catecholamines. In studies conducted so far, values of LV EF < 40-50% define systolic LV dysfunction, and an e' value of less than 8 cm/s measured by tissue Doppler defines LV relaxation impairment. The absence of a definition for septic cardiomyopathy and the need for recommended guidelines for its evaluation will certainly be a challenge for both intensive care and cardiology working groups. We need more direct methods of contractile assessment, such as strain and speckle tracking, three-dimension echocardiography, and which are less dependent on loading conditions and

are potentially more reflective of intrinsic myocardial function and have higher reproducibility to compare with 2D echocardiography.

Study limitation

The single-centre study and the small number of patients are the main limitations of the present study.

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