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Gap CO2 in septic patients to predict septic cardiomyopathy

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Abstract

Introduction:

Cardiocirculatory failure in septic patients contributes to a significantly increased mortality, ranging from 40–70%. Septic cardiomyopathy, a reversible myocardial depression observed in sepsis, typically manifests within the first 24 hours and is associated with a decrease in left ventricular ejection fraction (LVEF) < 40%.

Despite advances in treatment, the outcomes for patients with septic shock remain poor, with the condition often leading to further cardiac dysfunction. This study aims to explore the pathophysiology, risk factors, and treatment of myocardial failure during sepsis and septic shock.

Materials and Methods:

This observational study, conducted at Mohammed VI University Hospital of Oujda from January 2022 to May 2023, included 98 patients diagnosed with sepsis or septic shock. Patients were monitored via echocardiography and pulse wave contour analysis, focusing on those with LVEF < 40%. Exclusion criteria involved patients with non-sepsis-related cardiac conditions, incomplete records, or those who died within 48 hours. Data were analyzed using SPSS, employing both descriptive and inferential statistics to assess risk factors and associations with mortality.

Results and Discussion:

The study found that patients with septic cardiomyopathy had significantly lower cardiac output and cardiac index compared to those without myocardial involvement. The median cardiac output was 3.3 L/min in affected patients, compared to 6 L/min in those without dysfunction. Additionally, 76.5% of patients with cardiac involvement exhibited a $\Delta PCO2 \geq 6$ mmHg, suggesting its potential as a prognostic marker. Mortality rates were higher in patients with myocardial dysfunction (73.7%) compared to those without (46.8%). These findings align with previous studies, which suggest that cardiac dysfunction in sepsis is associated with higher mortality and longer hospital stays. Notably, patients with a low cardiac index (< 2.2 L/min/m²) had poorer outcomes.

Conclusion:

The study emphasizes the significant impact of myocardial dysfunction on outcomes in septic shock. Septic cardiomyopathy is linked to increased mortality and prolonged hospitalization, with low cardiac output and elevated $\Delta PCO2$ being key indicators of cardiac involvement. While echocardiography remains essential for diagnosis, pulse wave contour analysis presents a valuable alternative in challenging cases. Further multicenter studies are needed to confirm these findings and refine management strategies for septic patients with cardiac dysfunction.

INTRODUCTION

Cardiocirculatory failure occurs in 40% of sepsis cases, leading to a mortality increase from 20-30% in sepsis without cardiovascular dysfunction to 40-70% in septic shock. These percentages have seen little variation in recent years despite significant advancements in the fields of antibiotic therapy and resuscitation techniques [1].

The hemodynamic profile observed during septic shock is complex and dynamic: initially characterized by vasoplegia and high cardiac output, it can evolve towards cardiac failure involving both systolic and diastolic dysfunction.

Septic cardiomyopathy was first described by McLean et al. in 1967 [2], where diagnostic criteria for identifying heart failure (HF) included a low cardiac index (CI). Subsequently, in 1984, Parker et al. [3], using radionuclide cineangiography, characterized septic cardiomyopathy as a reversible myocardial depression due to sepsis and septic shock [4], defined by a decrease in the initial left ventricular ejection fraction (LVEF) <40% with an increase in end-diastolic and end-systolic volumes (EDV, ESV) [5].

Myocardial dysfunction observed during sepsis is typically most pronounced within the first 24 hours. Complete reversal is usually observed within seven to ten days in survivors [6]. In non-survivors, left ventricular function continues to deteriorate despite inotropic support, often contributing significantly to the patient's demise.

A precise understanding of its pathophysiology should, in the near future, enhance the therapeutic management of this myocardial impairment.

The objective of this study was to investigate the pathophysiology and treatment of myocardial failure during sepsis/septic shock. To achieve this, we conducted the following studies:

1. Objectifying the presence of cardiac involvement during septic shock.

2. Identifying the risk factors for cardiac involvement during septic shock and prognostic factors for cardiac involvement in septic shock.

3. Understanding the mechanisms of septic myocardial dysfunction (SMD)

4. Monitoring cardiac involvement during septic shock.

5. Treatment of SMD and therapeutic perspectives.

ETHICS APPROVAL:

Data collection was carried out in accordance with global ethical principles concerning the confidentiality and protection of patient-specific data and was confirmed by the our ethics committee of biomedical research of Oujda (CERBO) under approval number NCT06326762.

CONSENT TO PARTICIPATE:

All participants involved in this study provided informed consent prior to participation. Participation was voluntary, and participants were informed of the purpose of the study and their right to withdraw at any time.

MATERIALS AND METHODS

•Materials:

- Study Type:

This is an observational cross-sectional study with a descriptive and analytical purpose.

- Study Location and Duration:

The study was conducted at the Mohammed VI University Hospital in Oujda, specifically in the intensive care unit. The study spanned a period of 17 months, from January 2022 to May 2023.

- Study Population:

We included patients diagnosed with sepsis/septic shock admitted at various points in time to the intensive care unit of the Mohammed VI University Hospital in Oujda.

- Inclusion Criteria:

Patients admitted to the intensive care unit presenting with sepsis or septic shock, who underwent at least one echocardiogram and were monitored by pulse wave contour analysis, with a minimum stay of 48 hours in the intensive care unit.

Patients with cardiac involvement were defined by a left ventricular ejection fraction (LVEF) <40%.

- Exclusion Criteria:

Patients excluded from the study were those whose echogenicity did not allow for a high-quality echocardiogram, thoracic trauma patients, individuals with atrial fibrillation or non-sinusoidal heart rhythm, patients with pre-existing cardiac conditions (such as paced heart rhythm, aortic or mitral valve pathology, prosthetic valve, myocardial trauma, known coronary artery disease with left ventricular dysfunction and Q waves of necrosis on ECG), post-operative patients from cardiac and thoracic surgeries.

Patients without sepsis or septic shock.

Patients with COVID-19.

Patients who died within 48 hours of hospitalization.

Cases with incomplete medical records or patients not monitored.

•Study Methods and Data Collection:

This study comprised 98 observations, and the collection of anamnestic, clinical, and biological data was conducted utilizing the hospitalization records from the Department of Anesthesiology and Intensive Care at the Mohammed VI University Hospital in Oujda.

Imaging data, specifically echocardiography, were acquired within the Intensive Care Unit of the same hospital, employing the same ultrasound equipment.

Echocardiography is routinely performed in the unit as part of standard practice.

Statistical Analysis:

The data were stored and analyzed at the Laboratory of Epidemiology, Clinical Research, and Public Health at the Faculty of Medicine and Pharmacy in Oujda. Data entry and statistical analysis were performed using SPSS version 21.0.

Descriptive analysis was conducted, presenting quantitative variables as means and standard deviations, median [25th percentile - 75th percentile], while qualitative variables were represented by frequencies and percentages.

Subsequently, to identify factors associated with cardiac involvement and mortality, a univariate analysis was conducted. The Chi2 test or Fisher's exact test was employed for comparing percentages (for qualitative variables), and t-tests and non-parametric tests were used (for quantitative variables) after verifying the normality of variables using the Kolmogorov-Smirnov test; a significance threshold of $p < 0.05$ was considered.

RESEARCH FUNDING AND CONFLICT OF INTEREST:

We declare no conflicts of interest regarding this project, and the project is not financially supported.

RESULTS

I. Epidemiological Data:

· Age :

The average age in patients with dysfunction was 61.04 years ($p = 0.38$).

· -Gender :

In our study, men were more represented than women, with a percentage of 68.4% compared to 31.6%.

II. Comorbidities

· Diabetes :

The diabetic patients accounted for 28,9% in patients with myocardial dysfunction compared to 13,3% in patients with no myocardial dysfunction (p = 0.05).

· Hypertension :

Hypertensive patients accounted for 21.4% in patients with myocardial dysfunction compared to 18.6% in patients with no myocardial dysfunction (p = 0.74).

III. Clinical findings :

· Arterial pressure :

At admission, patients with myocardial dysfunction had a mean systolic blood pressure of 80 mmHg compared to 78 mmHg in patients without dysfunction (p = 0.98).

The mean diastolic blood pressure was 40 mmHg in the myocardial dysfunction group and 42 mmHg in the no dysfunction group (p = 0.54).

Similarly, the mean arterial pressure was 53 mmHg among patients with myocardial dysfunction versus 53 mmHg among those without dysfunction (p = 0.89).

· SOFA score :

The mean SOFA score at admission was significantly higher in patients with myocardial dysfunction compared to those without dysfunction, with values of 13.41 versus 10.22 respectively (p < 0.05).

IV. Paraclinical Data

· In terms of biological/gasometric aspects:

- The mean Ph level (ABG) at admission was lower in patients with myocardial dysfunction compared to those without dysfunction, with values of 7,29 versus 7,36 respectively (p = 0.22).

- The mean lactate level (ABG) at admission was slightly higher in patients with myocardial dysfunction compared to those without dysfunction, with values of 2,85 versus 2,80 (p = 0,49)

- The mean bicarbonate level (ABG) at admission was lower in patients with myocardial dysfunction compared to those without dysfunction, with values of 15,90 versus 18,45(p = 0,15)

- The mean CRP level at admission was quietly similar in both groups (212 in patients with dysfunction and 203 in patients without); p = 0,81

- The median APACHE II Score at admission was slightly higher in patients with dysfunction compared to those without (17 versus 15); p = 0,20

- The delta PCO2 percentage was calculated, and the findings were as follows: A value greater than 6 was observed in 76.5% of patients with myocardial dysfunction compared with 23.5% of patients without dysfunction. Conversely, a value$_2$ less than 6 was found in 7.4% of patients with myocardial dysfunction and 92.6% of those without dysfunction. (p<0,05)

- The mean cardiac output was significantly lower in patients with myocardial dysfunction compared with those without dysfunction, at 3.3 L/min versus 6 L/min, respectively ($p < 0.05$).

· On the echocardiography side:

- The mean subaortic velocity–time integral (VTI) was significantly lower in patients with myocardial dysfunction compared with those without dysfunction, at 10 cm versus 15 cm respectively ($p < 0.05$).

- Regarding cardiac index, 64.3% of patients with myocardial dysfunction had a cardiac index lower than 2.2 L/min/m², compared with 38.7% of patients without dysfunction. In contrast, a cardiac index greater than 2.2 L/min/m² was observed in 11.9% of patients with myocardial dysfunction and 88.1% of those without dysfunction ($p < 0.05$).

V. Evolution and mortality :

-Patients with myocardial dysfunction had a longer mean duration of hospitalization compared with those without dysfunction, with hospital stays of 14.2 days versus 7.26 days, respectively ($p < 0.05$).

- Mortality was also significantly higher among patients with myocardial dysfunction, occurring in 73.7% of cases compared to 46.8% in patients without dysfunction ($p < 0.05$).

The following table summarizes the findings listed above. (Table 1)

Table 1: Clinical and paraclinical findings summarized

k	Myocardial Dysfunction		P value
	YES (n=19)	NO (n=79)	
Arterial pressure			
Systolic Blood Pressure	80	78	0.98
Diastolic Blood Pressure	40	42	0.54
Mean Arterial Pressure	53	53	0.89
SOFA Score at admission	13.41	10.22	<0.05
Biological and gasometric aspects			
Arterial Blood Gas - pH	7.29	7.36	0.22
Arterial Blood Gas - Lactate	2.85	2.80	0.49
Arterial Blood Gas - Bicarbonate	15.90	18.45	0.15
C-reactive Protein	212	203	0.81
APACHE II Score	17	15	0.20
DELTA PCO2			<0.05
	76.50	23.50	
-Higher than 6 (%)	7.40	92.60	
-Less than 6 (%)			
Cardiac Output(L/min)	3.3	6	<0.05
Echocardiographic aspects			
Subaortic VTI	10	15	<0.05
Cardiac Index (L/min/m2) :			<0.05
-Less than 2.2 (%)	64.3	38.7	
-More than 2,2 (%)	11.9	88.1	
Evolution			
Hospitalization days	14.2	7.26	<0.05
Mortality (%)	73.7	46.8	<0.05

DISCUSSION

In this study, we elucidated the profile of patients afflicted with septic cardiomyopathy. Firstly, our investigation underscored echocardiography as the primary hemodynamic monitoring tool. This examination is routinely conducted at the patient's bedside in our intensive care unit, a practice substantiated by numerous studies confirming its preeminent role as the primary monitoring modality in critical care [7].

For medical history, our study revealed that 28.9% of patients with myocardial dysfunction were diabetic with a P-value of 0.05. However, our results regarding other comorbidities were inconclusive.

The ΔPCO2 appears to be a marker of cardiac dysfunction, as 76.5% of our patients with cardiac involvement had a ΔPCO2 ≥ 6 mmHg. This aligns with the findings of the study by F. Bagate in 2020, which advocates the clear recommendation of using ΔPCO2 with central venous PCO2 measurement to assess the adequacy of cardiac output to general metabolic conditions. It can serve as a prognostic marker and, more importantly, a therapeutic target for fluid management and vasopressor administration, especially dobutamine. However, these results are inconsistent in cardiac surgery (a patient profile excluded from our study). The use of this approach (rapid, cost-effective, and readily available) should be complemented by echocardiography or other monitoring techniques to better explore hemodynamic disorders in shock states. Additionally, the SOFA score is significantly higher in patients with cardiac involvement compared to those without, with a P-value <0.05 [8].

Cardiac output (CO) is one of the determinants of ΔPCO2 = (k x VCO2)/cardiac output, where k represents the factor defining the relationship between CCO2 and PCO2. Therefore, a decrease in cardiac output increases ΔPCO2 9. In our study, the median cardiac output calculated by pulse contour analysis in patients with myocardial dysfunction was 3.3 L/min compared to those without myocardial dysfunction, which was 6L/min with a P-value <0.05. However, Margaret Parker's study indicates that normal cardiac output does not rule out the existence of impaired ventricular systolic performance due to various compensatory mechanisms (tachycardia, reduced afterload), which sometimes contribute to its maintenance [4].

The cardiac index, a hemodynamic parameter reflecting the quantity of blood ejected by each of the heart's ventricles per minute and per square meter of body surface area, showed that 64.3% of our patients with dysfunction had a cardiac index (< 2.2 L/min/m2), while only 11.9% had a cardiac index (≥ 2.2 L/min/m2) (P < 0.05) based on pulse contour analysis. Our study suggests that hemodynamic monitoring using this technique could serve as a diagnostic tool for septic cardiomyopathy and potentially be a reliable alternative in patients for whom echocardiographic evaluation is challenging or in cases of persistent shock after initial resuscitation.

Our results align with the study by François Bagate, which found that the cardiac index is significantly lower in patients with myocardial involvement, with a value of 2,3 in patients with dysfunction compared to 3,3 in those without. (p <0,01) [8].

A recent study by Pierre-Louis Jacquemet reported that this type of monitoring has already proven its effectiveness in estimating cardiac output (CO). It is also a good indicator of left ventricular (LV) preload, especially in septic shock, and allows for the assessment of response to vascular filling. Its use to estimate cardiac index and LV systolic function shows a good correlation with echocardiography, both in absolute values and in variations. This correlation is particularly strong in patients with septic shock, making them good candidates for the use of these tools, both for diagnosis and monitoring. These tools can be used in conjunction with transthoracic or transesophageal echocardiography to monitor right cardiac function [10,11]

Our single-center study (n=98 patients) significantly demonstrates that the mortality rate is high in patients with septic cardiomyopathy (73.7%) compared to those without cardiac involvement (46.8%) with a (P<0.05). Additionally, the length of hospitalization, with an average of 14.2 days for patients with myocardial dysfunction, is higher than that of patients without cardiac dysfunction, whose average was 7.26 days, with a (P<0.05). Indeed, cardiocirculatory failure increases mortality from 20–30% in sepsis without cardiovascular dysfunction to 40–70% in septic shock [12].

Our results confirm several studies reporting high mortality when there is myocardial depression, a decrease in ejection fraction (FEVG), and an increase in the duration of hospitalization. This can be explained by more extensive vascular filling and a more frequent need for pressor agent treatment [13–15] . However, older studies from the 1980s suggested that patients in septic shock with initial LV systolic dysfunction had a better prognosis [4]. These initial findings were not later confirmed, as summarized by a recent meta-analysis including 762 patients with severe sepsis and septic shock, which found no statistically significant link between the presence of LV systolic dysfunction, primarily evaluated by echocardiography (FEVG), and mortality [16]. Simultaneously, several small-scale studies reported increased mortality in the subgroup of septic shock patients with elevated cardiac output, indicative of profound arterial vasoplegia reducing LV afterload [4,17]. These results can be explained by the pathophysiology of cardiocirculatory failure in septic shock. The presence of early LV systolic dysfunction may reflect relatively preserved arterial vasoreactivity, while a hyperkinetic profile (high cardiac output) might reflect profound vasoplegia secondary to an intense systemic inflammatory response, itself linked to severe causal infection [4,17].

These paradoxical results prompt us to conduct further studies using other techniques than FEVG due to its low reproducibility, operator-dependence, and susceptibility to errors. Studying cardiac function through two-dimensional (2D) speckle tracking is more sensitive than conventional echocardiography for detecting both systolic and diastolic cardiac dysfunctions [18,19], and it is recognized for its speed and reproducibility. Speckle tracking analyzes LV deformation by tracking cardiac motion from image

intensities [20]. However, this promising technique is currently challenging to apply routinely in critically ill patients [21].

STUDY LIMITATION:

The limitations of our study are the same as those of various monitoring techniques. In fact, each hemodynamic monitoring technique has limitations in interpreting results, which unfortunately reduced our sample size.

Moreover, in our study, we primarily relied on the assessment of LV systolic dysfunction, using FEVG as the criterion for selecting patients with septic myocardial dysfunction. However, both diastolic function and right ventricular systolic dysfunction (RV) may also be impaired. Studies using thermodilution and echocardiography have reported right ventricular systolic dysfunction during severe sepsis and septic shock [22,17,23], as well as thermodilution [23,24].

The prognostic impact of myocardial dysfunction during septic shock remains to be confirmed by large multicenter studies before considering potential therapeutic trials and practice modifications.

CONCLUSION

This study highlights the significant impact of myocardial dysfunction in patients with sepsis and septic shock. Our findings confirm that septic cardiomyopathy is associated with increased mortality and prolonged hospitalization. Specifically, patients with myocardial dysfunction demonstrated markedly lower cardiac output and cardiac index compared to those without such dysfunction. The significant association between elevated ΔPCO2 and cardiac involvement further underscores the value of ΔPCO2 as a prognostic marker and potential therapeutic target in managing septic shock.

The data suggests that while echocardiography remains a crucial tool for diagnosing and monitoring septic cardiomyopathy, pulse wave contour analysis offers a valuable alternative, especially when echocardiographic assessment is challenging. The high mortality rate observed in patients with septic cardiomyopathy reaffirms the need for improved early identification and targeted therapeutic strategies to manage myocardial impairment in sepsis.

Our study also highlights the importance of considering additional diagnostic and monitoring modalities beyond traditional echocardiography, as well as the necessity for larger, multicenter studies to validate these findings and refine treatment approaches. Future research should focus on exploring the underlying mechanisms of septic myocardial dysfunction, evaluating the efficacy of new diagnostic tools, and developing targeted therapies to improve outcomes in septic patients with cardiac involvement.

Declarations

CONSENT TO PARTICIPATE:

All participants involved in this study provided informed consent prior to participation. Participation was voluntary, and participants were informed of the purpose of the study and their right to withdraw at any time.

Author Contribution

• Pr. Younes Oujidi: wrote the article and managed the patients.• Dr Zahrou Imane: revised and edited the manuscript• Dr. Soufyane Kadiri: participated in patient care and revised the manuscript.• Dr. Marouane Boukroute: supervised and edited the article.• Pr. Bensaid Amine: led patient management and finalized the article.• Pr. Houssam Bkier: supervised the research and contributed to the article.• All authors approved the final version of the manuscript.

Data Availability

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality and hospital policy.

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