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Research Article

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Echocardiographic Assessment of Cardiac Function After Fluid Resuscitation and Norepinephrine Therapy in a Porcine Model of Septic Shock

Rizki Ading Anugrah[1], Gunanti[2], Deni Noviana[2], Deny Setyo Wibowo[3], Aridamuriany D. Lubis[4], Andriamuri P. Lubis[5], Arni Diana Fitri[2*], Dwi Utari Rahmiati[2], Bintang Nurul Iman[6], Farid Ikram kamil[1], Shellia Calista Samosir[1]

[1]Postgraduate Student, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, Indonesia
[2]Division of Surgery and Radiology, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, Indonesia
[3]Division of Internal Medicine, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, Indonesia
[4]Department of Pediatric, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[5]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[6]Staff of The Veterinary Teaching Hospital, IPB University, Bogor, Indonesia

*Corresponding author: arnifi@apps.ipb.ac.id

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ABSTRACT

Background: Septic shock induces systemic vasodilation, endothelial dysfunction, and impaired cardiac filling, necessitating interventions that restore tissue perfusion.

Aims: This study aimed to evaluate the effects of crystalloid fluid resuscitation and norepinephrine on echocardiographic indices of cardiac function in a porcine model of septic shock.

Methods: A controlled experimental design was conducted using nine male pigs (40 – 60 kg) aged 12 -16 weeks divided into three groups: control (G0), fluid resuscitation (G1; Ringer-lactate 30 mL/kg with protocolized repeats), and norepinephrine titration (G2; starting at 0,05 µg/kg, adjusted to Mean Arterial Pressure ≥ 65 mmHg). M-mode echocardiography was used to measure systolic and diastolic structural measures (interventricular septum in systole and diastole, left ventricular internal dimension in systole and diastole, left ventricular posterior wall in systole and diastole), volumes (End Diastolic Volume, End Systolic Volume, Stroke Volume, Cardiac Output) and cardiac function (Ejection Fraction, Fractional Shortening, Heart Rate). Data were analyzed using two-way ANOVA ($\alpha = 0.05$).

Results: Septic shock over time resulted in decreased in ventricular dimensions (LVIDd), EDV, SV and CO during shock, with partial recovery after therapy. Interventricular septal thickness in systole (IVSs) increased significantly over time ($p = 0.01$), while treatment effects and treatment-time interactions were not statistically significant for most parameters. Post-therapy, norepinephrine significantly improved ejection fraction and fractional shortening, whereas fluid resuscitation primarily restored end-diastolic volume and stroke volume.

Conclusion: Fluid resuscitation and norepinephrine administration have different physiological effects on cardiac function in septic shock. Fluid resuscitation primarily increases preload and intravascular volume, while norepinephrine predominantly improves systolic function through inotropic and vasoconstrictor mechanisms.

INTRODUCTION

Sepsis in animals is characterised by a systemic response involving both the inflammatory and coagulation systems. During sepsis, the host mounts a pronounced response to infectious agents, leading to hemodynamic and capillary damage, increased coagulation, and organ perfusion disturbances that may progress to multiple organ failure. Sepsis represents organ dysfunction that can lead to hemodynamic instability due to an uncontrolled immune response to infection (Evans et al., 2021). Severe infection may result in sepsis, severe sepsis, or septic shock (Hadinegoro et al., 2016; Kissoon & Carapetis, 2015; Weiss et al., 2020).

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Escherichia coli is the etiological agent of colibacillosis, a disease that can cause sepsis in pigs (Fairbrother & Nadeau, 2019).

Septic shock is indicated by significant alterations in the cardiovascular system at both the macrocirculation and microcirculation levels. Macrocirculation abnormalities include hypovolemia, reduced vascular tone, and myocardial dysfunction. Hemodynamic disturbances ultimately result in tissue hypoxia and multiple organ failure (Teboul, 2023). In sepsis, systemic vasodilation, endothelial dysfunction, and reduced vascular tone contribute to hypotension and decreased mean arterial pressure (MAP). Conversely, myocardial depression, reduced contractility, and decreased intravascular volume lead to a lower cardiac index (CI).

Cardiac ultrasound, commonly referred to as echocardiography, is the most widely used diagnostic tool for cardiovascular disease in both humans and animals. Echocardiography enables rapid assessment of cardiac function, intravascular volume status, and structural heart changes (Anderson & Morrow, 2017). This technique employs high-frequency sound waves to generate images of cardiac morphology and structure, including myocardial size and thickness, myocardial and valvular motion, and blood flow within the vessels (Noviana et al., 2018).

The primary objective in the management of septic shock is to maintain mean arterial pressure and cardiac output until the underlying infection is controlled (George et al., 2019). Initial resuscitation involves fluid administration, followed by vasopressor therapy if the patient does not respond adequately to fluids (Ospina-Tascón et al., 2023). The goal of fluid resuscitation is to restore intravascular volume and optimise cardiac output during shock. Norepinephrine, also known as noradrenaline, is a vasopressor that increases blood pressure by inducing vasoconstriction (Xu et al., 2024). Research on septic shock therapy continues to be a significant focus within the medical community. Nevertheless, the limitations associated with animal studies remain a challenge.

Given the paucity of controlled experimental data on cardiac responses to these interventions in porcine models, this study aimed to evaluate the impact of septic shock on cardiac function and to assess the therapeutic effects of crystalloid fluid resuscitation and norepinephrine therapy.

MATERIALS AND METHODS

The research was conducted over three months, from March to June 2025. The research was conducted at the Veterinary Teaching Hospital of the School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, Indonesia.

The study commenced with the preparation of quarantine pens upon the animal's arrival at the research facility, followed by an acclimatisation period to standardise their health and physiological status.

The animal subjects utilized in this study were pigs (*Sus scrofa domestica*). Nine male pigs, each weighing between 40 and 60 kg, were allocated into three groups. Each animal subject was induced with ketamine 20 mg/kg BW and xylazine 2 mg/kg BW, and propofol 10 mg/kg BW was administered for anaesthetic induction and maintenance and supported by volume-controlled mechanical ventilation, adjusted according to blood gas analysis readings. For maintenance, a 0.9% physiological NaCl infusion of 3 mL/kg/hour was administered. After 1 hour of stabilization, echocardiographic parameters were measured. The right femoral artery was prepared using aseptic technique, and a thermistor-tip transpulmonary thermodilution catheter (PiCCO, PULSION Medical Systems SE, Munich, Germany) was placed in the right femoral artery for invasive hemodynamic monitoring. Endotoxin infusion of E. coli (lipopolysaccharide 0111:B4, Difco Laboratories, Detroit, MI) was initiated at a rate of 0.25 mcg/kg/h. Sepsis was defined as the presence of organ damage, with a SOFA score ≥ 2; lactate level ≥ 2 mmol/L (Rutai et al., 2022). To induce septic shock, the endotoxin infusion rate was gradually increased over 1–3 hours to achieve septic shock (MAP < 60 mmHg) (Martikainen et al., 2004; Zurek-Leffers et al., 2023). The total duration of endotoxin infusion varied between animals depending on the hemodynamic response and ranged from 1 to 3 hours until the septic shock criteria were achieved. All animals successfully reached septic shock conditions, although the time required to achieve the target MAP was not identical among individuals due to biological variability in endotoxin response. Echocardiography was performed after sepsis was achieved. Group 0 (G0) served as the positive control and did not receive therapeutic treatment. Group 1 (G1) received crystalloid fluid resuscitation therapy (Ringer's lactate R) at a dose of 30 mL/kg/hour, while Group 2 (G2) was administered norepinephrine therapy starting at a minimum dose of 0.05 µg/kg. After receiving therapy, echocardiography examinations were performed. At the end of the in vivo experiment, all animals still under the influence of anesthesia were then terminated by exsanguination.

Echocardiographic Examination

Echocardiography was performed with the patient in dorsal recumbency. The transducer was placed for long

axis (LA) views at a frequency of 4 to 8.2 MHz, following palpation of the heartbeat between the fourth and sixth intercostal spaces on the left thorax. The LA transducer position facilitated M-mode imaging and measurement of heart rate, left ventricular internal dimension in systole (LVIDs) and diastole (LVIDd), left ventricular posterior wall in diastole (LVPWd) and systole (LVPWs), interventricular septum in diastole (IVSd) and systole (IVSs), end systole volume (ESV), end diastole volume (EDV), ejection fraction (EF), fractional shortening (FS), cardiac output (CO), and stroke volume (SV). Additionally, echocardiography was utilised to assess blood flow, quantify blood volume, and evaluate myocardial contractility. Image data are subsequently transferred offline following the procedure. Each measurement was performed in triplicate.

Data Analysis

Echocardiography data were assessed for residual normality using the Shapiro–Wilk test and for variance homogeneity using Levene's test. Statistical analysis was conducted using a two-way ANOVA with treatment group (G0, G1, and G2) and observation timepoint (pre-shock, septic shock, and post-therapy) as independent factors. Interaction effects between treatment and timepoint were also evaluated. Because no significant interaction effects were identified for most parameters, post-hoc multiple comparison analysis was not performed. Statistical analysis was conducted using RStudio with a 95% confidence interval, and results were presented as mean ± standard deviation.

RESULTS AND DISCUSSION

Sepsis occurs when organ damage with a SOFA score ≥ 2; lactate level ≥ 2 mmol/L and Mean Arterial Pressure (MAP) ≤ 60 mmHg (Rutai et al., 2022). The results of E. coli endotoxin induction causing septic shock animal models are shown in Table 1.

Table 2 presents left ventricular structural parameters. IVSs increased progressively across all groups, with the most pronounced rise observed in G2 (1.54 ± 0.28 to 2.69 ± 0.83 cm). A comparable trend was noted for IVSd, which increased in all groups throughout the observation period, again most markedly in G2 (1.03 ± 0.30 to 1.75 ± 0.57 cm post-therapy).

LVIDs declined across all groups, with the greatest reduction in G2 (1.96 ± 0.91 to 0.663 ± 0.17 cm). LVIDd decreased modestly in G0 and G2, whereas G1 demonstrated a partial recovery post-therapy (3.21 ± 0.67 to 3.57 ± 1.38 cm). LVPWs increased in all groups, whilst LVPWd remained largely stable, with a marginal increase confined to G2 (1.50 ± 0.44 to 1.89 ± 0.69 cm).

Table 3 summarises left ventricular volume parameters. EDV and ESV declined following induction of septic shock across all groups. Post-therapy, G1 demonstrated a recovery in EDV (36.28 ± 18.53 to 60.12 ± 66.23 ml), whereas G2 showed further reduction (33.38 ± 9.71 to 16.05 ± 14.00 ml). ESV followed a similar pattern, with G1 exhibiting a post-therapy increase (6.97 ± 1.34 to 17.35 ± 27.86 ml) and G2 declining markedly to 0.34 ± 0.20 ml.

Stroke volume (SV) decreased uniformly during the septic shock phase across all groups. Following therapy, SV recovered in G1 (29.31 ± 18.01 to 42.76 ±

Table 1. Mean Arterial Pressure in pigs with septic shock

No	Group	Pre shock (mmHg)	Septic Shock (mmHg)
1	G0P1	115	60
2	G0P3	87	54
3	G0P4	119	60
4	G1P1	129	59
5	G1P4	83	50
6	G1P5	73	54
7	G2P3	146	55
8	G2P4	114	57
9	G2P5	118	54

Description: G0= Group 0 Positive Control; G1= Group 1 Fluid Resuscitation Therapy; G2= Group 2 Norepinephrine Therapy; P1= Pig 1; P3= Pig 3; P4= Pig 4; P5= Pig 5

38.59 ml) but declined further in G2 (29.05 ± 11.77 to 15.71 ± 13.89 ml). Cardiac output (CO) decreased in G0 (3,634.57 ± 752.46 to 2,764.4 ± 316.77 ml/min), with no consistent trend observed in G1 or G2.

Table 4 presents left ventricular systolic function. Both EF and FS declined during the septic shock phase but recovered post-therapy in the treatment groups. The most notable improvement was observed in G2, where EF rose to 96.82 ± 2.89% and FS to 70.75 ± 9.49%. Heart rate increased in all groups during the final observation phase, reaching 121.04 ± 37.43 bpm in G1 and 125.07 ± 7.86 bpm in G2.

Two-way ANOVA (Table 5) revealed that treatment did not significantly affect any echocardiographic parameter ($p > 0.05$). However, observation timepoint exerted a significant effect on IVSs ($p = 0.01$). No significant treatment × timepoint interaction was identified for any parameter ($p > 0.05$).

Statistical analysis indicated that the treatment did not result in significant differences in most echocardiographic parameters. The absence of statistically significant differences in most parameters may also be influenced by the relatively small sample size (n = 3 per group), which potentially reduced the statistical power of the study. Biological variability among animals, particularly in cardiovascular responses during septic shock, may have further contributed to the large standard deviations observed in several variables. Therefore, subtle treatment-related effects may not have been fully detected despite observable trends in echocardiographic changes. However, observation time significantly affected interventricular septal thickness (IVSs) ($p = 0.01$), suggesting that haemodynamic changes during the shock phase and following treatment influenced septal thickness.

In cases of severe sepsis, alterations in ventricular pressure load and impaired myocardial perfusion can modify the septal contraction pattern, as evidenced by changes in IVSs (Vieillard-Baron et al., 2019). The observed difference in IVSs response between fluid therapy and norepinephrine suggests that IVSs is more sensitive to changes in afterload and contractility than to increases in preload alone. These results align with

Table 2. Left ventricular structural parameters (M-mode) in pigs during pre-shock, septic shock, and post-therapy

Parameter	Group	Mean ± SD		
		Pre Shock	Septic Shock	Post Therapy
IVSs (cm)	G0	1.48 ± 0.45	1.69 ± 0.30	1.69 ± 0.30
	G1	1.67 ± 0.25	1.74 ± 0.19	2.14 ± 0.32
	G2	1.54 ± 0.28	1.87 ± 0.38	2.69 ± 0.83
LVIDs (cm)	G0	1.9 ± 0.69	1.77 ± 0.21	1.77 ± 0.21
	G1	2.17 ± 0.26	1.88 ± 0.12	1.89 ± 1.6
	G2	1.96 ± 0.91	1.47 ± 0.55	0.663 ± 0.17
LVPWs (cm)	G0	2.05 ± 0.41	2.18 ± 0.29	2.18 ± 0.29
	G1	1.90 ± 0.34	1.97 ± 0.21	2.12 ± 0.77
	G2	1.83 ± 0.42	2.11 ± 0.15	2.30 ± 0.62
IVSd (cm)	G0	1.04 ± 0.16	1.19 ± 0.24	1.19 ± 0.24
	G1	1.13 ± 0.14	1.25 ± 0.51	1.56 ± 0.23
	G2	1.03 ± 0.3	1.33 ± 0.52	1.75 ± 0.57
LVIDd (cm)	G0	3.47 ± 0.25	3.24 ± 0.33	3.24 ± 0.33
	G1	3.71 ± 0.43	3.21 ± 0.67	3.57 ± 1.38
	G2	3.36 ± 1.09	3.19 ± 0.32	2.36 ± 0.66
LVPWd (cm)	G0	1.75 ± 0.22	1.62 ± 0.18	1.62 ± 0.18
	G1	1.36 ± 0.41	1.52 ± 0.07	1.57 ± 0.59
	G2	1.5 ± 0.44	1.48 ± 0.3	1.89 ± 0.69

Description: LVIDs= Left Ventricular Internal Dimension systole; LVIDd= Left Ventricular Internal Dimension diastole; LVPWd= Left Ventricular Posterior Wall diastole; LVPWS= Left Ventricular Posterior Wall systole; IVSd= Inter Ventricular Septum diastole; IVSs= Inter Ventricular Septum systole

the concept of sepsis-induced myocardial dysfunction, which is heterogeneous and shaped by the interplay of inflammatory mediators, perfusion pressure, and vasoactive therapy (Shvilkina & Shapiro, 2023).

Echocardiographic findings demonstrated that septic shock induced both morphological and functional alterations in the pig heart, including changes in left ventricular dimensions, ventricular volume, and systolic function parameters. During the shock phase, all experimental groups exhibited reductions in left ventricular internal diameter at end-diastole (LVIDd), end-diastolic volume (EDV), stroke volume (SV), and cardiac output (CO) compared to pre-shock values. These reductions suggest impaired ventricular filling resulting from relative hypovolaemia, systemic vasodilation, and increased capillary permeability, which are hallmark features of septic shock (Cecconi et al., 2014; Singer et al., 2016).

In the context of sepsis, endothelial dysfunction and microvascular imbalance lead to plasma leakage, maldistribution of blood flow, and decreased intravascular volume, directly impacting preload and cardiac output (McMullan et al., 2024; Gonzales et al., 2025). Therefore, alterations in echocardiographic parameters during the shock phase reflect systemic haemodynamic disturbances that compromise overall cardiac pump function.

Table 3. Left ventricular volume parameters (M-mode) in pigs during pre-shock, septic shock, and post-therapy

Parameter	Group	Mean ± SD		
		Pre Shock	Septic Shock	Post Therapy
ESV (ml)	G0	8.84 ± 8.82	5.91 ± 2.09	5.91 ± 2.09
	G1	10.53 ± 3.29	6.97 ± 1.34	17.35 ± 27.86
	G2	10.61 ± 9.75	4.33 ± 2.78	0.34 ± 0.20
EDV (ml)	G0	42.4 ± 8.73	34.9 ± 9.96	34.9 ± 9.96
	G1	52.82 ± 17.24	36.28 ± 18.53	60.12 ± 66.23
	G2	45.63 ± 34.11	33.38 ± 9.71	16.05 ± 14.00
SV (ml)	G0	33.57 ± 2.44	28.99 ± 7.87	28.99 ± 7.87
	G1	42.3 ± 14.21	29.31 ± 18.01	42.76 ± 38.59
	G2	35.01 ± 24.4	29.05 ± 11.77	15.71 ± 13.89
CO (ml/min)	G0	3634.57 ± 752.46	2764.4 ± 316.77	2764.4 ± 316.77
	G1	4283.05 ± 809.64	3427.96 ± 2474.42	3918.32 ± 2587.44
	G2	3665.59 ± 2490.16	3352.62 ± 1851.48	1884.77 ± 1930.99

Description: EDV= End Diastole Volume; ESV= End Systole Volume; SV= Stroke Volume; CO= Cardiac Output

Table 4. Left ventricular systolic function on M-mode echocardiography in pigs during pre-shock, septic shock, and post-therapy

Parameter	Group	Mean ± SD		
		Pre Shock	Septic Shock	Post Therapy
EF (%)	G0	83.41 ± 1.38	81.1 ± 15.74	81.1 ± 15.74
	G1	79.89 ± 1.98	74.38 ± 18.71	82.94 ± 18.19
	G2	81.19 ± 9.12	85.23 ± 10.96	96.82 ± 2.89
FS (%)	G0	45.71 ± 1.48	45.9 ± 15.76	45.9 ± 15.76
	G1	41.65 ± 1.9	39.32 ± 14.53	51.59 ± 23.93
	G2	44.02 ± 10.57	53.03 ± 20.33	70.75 ± 9.49
HR (bpm)	G0	80.7 ± 25.67	97.54 ± 17.07	97.54 ± 17.07
	G1	105.11 ± 33.62	85.63 ± 4.76	121.04 ± 37.43
	G2	104.57 ± 22	90.27 ± 19.62	125.07 ± 7.86

Description: EF= Ejection Fraction; FS= Fraction Shortening; and HR= Heart Rate

In the fluid resuscitation group (G1), the post-treatment phase demonstrated increases in end-diastolic volume (EDV) and stroke volume (SV), suggesting improved preload and intravascular volume expansion following crystalloid administration. According to the Frank–Starling principle, increased ventricular filling may enhance stroke volume as long as myocardial fibres remain within the adaptive response range (Piccioni et al., 2025). However, the observed increases in EDV and SV were not consistently accompanied by improvements in ejection fraction (EF) or fractional shortening (FS), indicating heterogeneous cardiac responses to fluid resuscitation. Similar findings were reported by Wang et al. (2025), who demonstrated that only a subset of patients with septic shock exhibited sustained increases in SV following fluid therapy. The substantial variability observed in ESV, EDV, and CO values within the G1 group further suggests that augmentation of preload alone may be insufficient to restore optimal cardiac performance in the presence of sepsis-induced myocardial dysfunction.

Inflammatory mediators, altered catecholamine receptor sensitivity, and pathogenic toxins associated with septic shock may impair myocardial contractility despite the apparent restoration of intravascular volume (Shvilkina & Shapiro, 2023). Furthermore, aggressive crystalloid administration may contribute to hemodilution, vascular leakage, and interstitial edema due to increased capillary permeability during systemic inflammation (Cecconi et al., 2014; McMullan et al., 2024). These pathophysiological alterations may adversely affect tissue oxygenation and cardiac efficiency despite improvements in preload-related parameters.

The relatively high EF observed during the shock phase in G2 may reflect hyperdynamic circulation associated with early distributive septic shock rather than preserved intrinsic myocardial function. Ejection fraction (EF) and fractional shortening (FS) decreased during the shock phase and subsequently increased following therapy, particularly in the norepinephrine-treated group (G2). This trend is consistent with the post-resuscitation hyperadrenergic phenomenon, which is characterised by enhanced myocardial contractility following haemodynamic stabilisation (Vieillard-Baron & Cecconi, 2014). These findings also correspond with the characteristics of sepsis-induced cardiomyopathy, in which myocardial depression caused by cytokine toxicity and impaired catecholamine responsiveness is generally reversible (Shvilkina & Shapiro, 2023).

Table 5. M-Mode echocardiography results based on Two-way ANOVA analysis

Parameter	Treatment (p)	Significant	Time point (p)	Significant	Treatment × Timepoint (p)	Significant
IVSs (cm)	0.13	No	0.01	**Yes**	0.31	No
LVIDs (cm)	0.18	No	0.24	No	0.61	No
LVPWs (cm)	0.79	No	0.42	No	0.96	No
ESV (ml)	0.40	No	0.69	No	0.66	No
IVSd (cm)	0.40	No	0.06	No	0.70	No
LVIDd (cm)	0.30	No	0.39	No	0.65	No
LVPWd (cm)	0.60	No	0.63	No	0.77	No
EDV (ml)	0.38	No	0.61	No	0.72	No
SV (ml)	0.42	No	0.59	No	0.77	No
EF (%)	0.20	No	0.49	No	0.76	No
FS (%)	0.20	No	0.19	No	0.60	No
HR (bpm)	0.37	No	0.41	No	0.56	No
CO (ml/min)	0.49	No	0.48	No	0.89	No

Description: LVIDs= Left Ventricular Internal Dimension systole; LVIDd= Left Ventricular Internal Dimension diastole; LVPWd= Left Ventricular Posterior Wall diastole; LVPWS= Left Ventricular Posterior Wall systole; IVSd= Inter Ventricular Septum diastole; IVSs= Inter Ventricular Septum systole; EDV= End Diastole Volume; ESV= End Systole Volume; EF= Ejection Fraction; FS= Fraction Shortening; CO= Cardiac Output; SV= Stroke Volume; And HR= Heart Rate.

The marked increase in EF observed in G2 was likely associated with the β1-adrenergic inotropic effect of norepinephrine, which enhances myocardial contractility and ventricular emptying (Espinoza et al., 2019; Hamzaoui et al., 2018). Nevertheless, the markedly elevated EF values observed post-therapy should be interpreted cautiously, as EF in septic shock is highly influenced by preload and afterload conditions and may appear preserved or supranormal despite ongoing myocardial dysfunction (Vieillard-Baron & Cecconi, 2014).

Hyperdynamic circulation, reduced afterload, and vasopressor-induced increases in contractility may therefore contribute to apparently elevated systolic performance. In addition, M-mode echocardiographic assessment performed under rapidly changing haemodynamic conditions may have overestimated systolic function, particularly when ventricular chamber dimensions became markedly reduced during vasoconstrictive states. Consistent with these findings, the post-treatment phase in G2 demonstrated reduced left ventricular internal diameter in systole (LVIDs) and end-systolic volume (ESV), accompanied by increased EF and FS, indicating enhanced left ventricular systolic performance. Beyond its vasopressor effect in maintaining mean arterial pressure (MAP), norepinephrine may also improve cardiac performance through augmentation of myocardial contractility and perfusion pressure (Hamzaoui et al., 2010; Hamzaoui et al., 2018).

This study has several limitations. The relatively small sample size may have reduced statistical power and contributed to variability among animals. In addition, echocardiographic assessment was limited to M-mode parameters and short-term haemodynamic observation following therapy. Further studies with larger sample sizes and advanced echocardiographic modalities are required to better characterise myocardial dysfunction during septic shock.

CONCLUSION

Fluid resuscitation and norepinephrine exerted distinct haemodynamic effects on cardiac function during septic shock. Fluid therapy primarily improved preload and intravascular volume expansion, whereas norepinephrine enhanced systolic performance through vasoconstrictive and inotropic mechanisms. These findings highlight the complex and heterogeneous cardiovascular responses that occur during septic shock and support the importance of haemodynamic-targeted therapy guided by echocardiographic evaluation.

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AUTHORS CONTRIBUTION

R.A.A. contributed to the conceptualisation of the study, data collection, echocardiographic examinations, data analysis, and manuscript drafting. G. served as principal investigator and first supervisor, contributing to study design, research supervision, data interpretation, and manuscript review. D.N. contributed to the study design, research supervision, and manuscript review. D.S.W., A.D.L., A.P.L., A.D.F., D.U.R., and B.N.I. participated in the research and contributed to data collection, clinical examinations, and data interpretation. F.I.K. contributed to data analysis and manuscript editing. S.C.S. contributed to manuscript review and final editing. All authors read, reviewed, and approved the final manuscript.

"The author declares that there is no conflict of interest with the parties involved in this research".

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