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Heterogeneous Cardiovascular Responses to Acute Mean Arterial Pressure Augmentation in Septic Shock: The Role of Ventriculo-Arterial Coupling

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Research Article

Keywords:

Posted Date: July 29th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10412124/v1

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Critical Care on September 9th, 2026. See the published version at https://doi.org/10.1186/s13054-026-06317-x.

Abstract

Background

In septic shock, vasopressor-induced mean arterial pressure (MAP) augmentation is commonly used in septic shock to restore tissue perfusion, but patients may exhibit divergent cardiovascular responses despite achieving similar arterial pressure targets. We hypothesized that this heterogeneity reflects differences in ventricular adaptation to the acute increase in arterial load, as assessed by ventriculo-arterial (VA) coupling.

Methods

We conducted a prospective physiological observational study in mechanically ventilated adults with fluid-resuscitated septic shock undergoing transient MAP augmentation from approximately 65 to 85 mmHg. MAP was increased by norepinephrine dose escalation or by adding vasopressin, according to clinical judgment. Comprehensive transthoracic echocardiography was performed immediately before and after MAP augmentation. Patients were classified a priori according to relative changes in cardiac output (CO): flow recruitment (> 15% increase), stable flow (− 15% to + 15%), or flow deterioration (> 15% decrease). Changes in effective arterial elastance (Ea), end-systolic elastance (Ees), VA coupling (Ea/Ees), stroke volume, left ventricular ejection fraction (LVEF), myocardial performance index (MPI), isovolumetric contraction time (IVCT), and perfusion variables were analyzed.

Results

Thirty-two patients were included. Despite comparable increases in MAP, cardiovascular responses were heterogeneous: 10 patients (31%) exhibited flow recruitment, 17 (53%) maintained stable flow, and 5 (16%) developed flow deterioration. Patients with flow deterioration showed a greater increase in Ea and a smaller increase in Ees, resulting in worsening VA coupling (ΔEa/Ees + 0.22 [IQR 0.06–0.43]), whereas VA coupling remained stable or improved in patients with preserved or increased flow ($p = 0.031$). Flow deterioration was accompanied by reduced stroke volume, decreased LVEF, prolonged IVCT, and worsening MPI. Changes in VA coupling correlated with changes in IVCT ($\rho = 0.790$, $p < 0.0001$), MPI ($\rho = 0.599$, $p = 0.0003$), LVEF ($\rho = -0.431$, $p = 0.014$), and stroke volume ($\rho = -0.418$, $p = 0.017$). Tissue perfusion markers changed less consistently across response groups.

Conclusions

Acute MAP augmentation elicits heterogeneous cardiovascular responses in fluid-resuscitated septic shock. Flow deterioration is characterized by impaired ventricular adaptation to increased arterial load, reflected by worsening VA coupling and systolic performance.

Introduction

Septic shock is characterized by profound circulatory heterogeneity in which vasoplegia, relative hypovolemia, and myocardial dysfunction coexist in varying proportions [1]. Consequently, the mean arterial pressure (MAP) required to maintain adequate organ perfusion is unlikely to be uniform across patients [2]. This concept has challenged the traditional "one-size-fits-all" approach to blood pressure targets and has stimulated growing interest in individualized MAP strategies during septic shock resuscitation [3].

Transient MAP augmentation is increasingly used in patients with persistent signs of hypoperfusion after initial resuscitation to assess whether higher perfusion pressures improve tissue perfusion. Clinical studies, including the ANDROMEDA-SHOCK trials, have demonstrated marked heterogeneity in this response, with only a subset of patients exhibiting improvements in peripheral perfusion despite achieving similar increases in MAP [3–5]. These observations suggest that the physiological response to MAP augmentation may provide clinically relevant information beyond the achieved arterial pressure itself. However, the mechanisms responsible for this heterogeneity remain poorly understood.

The cardiovascular response to MAP augmentation is inherently complex because increasing arterial pressure simultaneously modifies multiple determinants of cardiovascular performance. Restoration of vascular tone may recruit stressed blood volume, increase venous return, and augment cardiac output [6]. Conversely, the accompanying increase in arterial load may impair ventricular ejection and reduce forward flow. Accordingly, preservation of forward flow depends not only on the achieved arterial pressure but also on the capacity of the cardiovascular system, particularly the left ventricle, to tolerate the imposed increase in arterial load. This property, which may be conceptualized as afterload tolerance, reflects the ability to maintain stroke volume and forward flow during acute arterial loading. Preserved afterload tolerance implies adequate ventricular adaptation to the increased load, whereas limited afterload tolerance reflects a mismatch between arterial load and ventricular response, leading to impaired ejection and flow deterioration.

Experimental and clinical observations support this concept. Maas et al. demonstrated that norepinephrine-induced MAP augmentation after cardiac surgery produced highly variable cardiac output responses despite similar increases in arterial pressure, with nearly 60% of patients exhibiting a reduction in cardiac output [7]. Although the hemodynamic profile of septic shock differs substantially because of profound vasodilation and markedly reduced arterial elastance, these findings suggest that patients may differ in their capacity to accommodate an acute increase in arterial load [8]. The physiological determinants of this adaptation in septic shock remain unknown.

Ventriculo-arterial (VA) coupling provides a physiological framework to investigate this question because it integrates ventricular contractility and arterial load, thereby describing the mechanical efficiency of the cardiovascular system [9, 10]. During acute MAP augmentation, preservation of forward flow requires ventricular contractility to increase in proportion to the increase in arterial elastance. Failure of this adaptive response may result in ventriculo-

arterial uncoupling, impaired systolic performance, and deterioration of cardiac output [11, 12]. Accordingly, assessment of VA coupling during transient MAP augmentation may help explain why patients exposed to similar increases in arterial pressure exhibit markedly different cardiovascular responses [13].

The vasoactive agent used to increase MAP may further influence these responses. Norepinephrine increases arterial pressure through combined arterial and venous vasoconstriction while maintaining β-adrenergic activity that may support myocardial contractility, whereas vasopressin acts predominantly as a V1 receptor-mediated vasopressor without clinically relevant direct inotropic activity. [14, 15]. Consequently, comparable increases in MAP achieved using different vasopressor strategies may impose distinct arterial loading conditions and elicit different patterns of cardiovascular adaptation.

We hypothesized that transient MAP augmentation would unmask clinically relevant differences in afterload tolerance among patients with septic shock and that these differences would be reflected by changes in VA coupling, systolic performance, and forward flow. Accordingly, the primary objective of this study was to characterize cardiovascular responses to acute MAP augmentation using comprehensive echocardiography and VA coupling as a physiological framework. As a secondary exploratory objective, we evaluated whether different vasopressor strategies were associated with distinct cardiovascular responses.

Materials and Methods

Study design and MAP augmentation protocol

This prospective physiological observational study included mechanically ventilated adult patients with septic shock undergoing transient mean arterial pressure (MAP) augmentation following initial hemodynamic resuscitation.

Transient MAP augmentation was performed in patients with persistent signs of hypoperfusion despite adequate fluid resuscitation and the absence of preload responsiveness. Preload responsiveness was assessed using dynamic indices, including pulse pressure variation, stroke volume variation, and inferior vena cava distensibility; patients were considered non–preload responsive when at least two of the following criteria were absent: pulse pressure variation ≥ 13% [16], stroke volume variation ≥ 12% [17], or inferior vena cava distensibility ≥ 18% [18]. MAP was increased from approximately 65 to 85 mmHg using either norepinephrine dose escalation or the addition of vasopressin at a fixed dose of 0.03 U/min, according to the treating physician's decision. Vasopressor selection was not protocolized and reflected routine clinical practice.

The study was approved by the Human Ethics and Safety Committee of the Pontificia Universidad Católica de Chile in accordance with the Declaration of Helsinki (Protocol ID: 200318004), and written informed consent was obtained from all patients or their legally authorized representatives. Clinical trial registration: Not applicable. This was an observational physiological study without random allocation to a study intervention.

Cardiovascular assessment

Comprehensive transthoracic echocardiography was performed immediately before and after achievement of the target MAP by a certified operator according to current recommendations for advanced critical care echocardiography [19], using a Mindray M9 ultrasound system (Bio-Medical Electronics Co., Shenzhen, China).

The following variables were recorded before and after MAP augmentation: cardiac output (CO), stroke volume (SV), left ventricular ejection fraction (LVEF), heart rate (HR), central venous pressure (CVP), capillary refill time (CRT), arterial lactate concentration, and myocardial performance index (MPI).

Central venous pressure was measured at end-expiration at the base of the A wave [20].

Assessment of ventriculo-arterial coupling

Ventriculo-arterial (VA) coupling was assessed as the ratio between effective arterial elastance (Ea) and left ventricular end-systolic elastance (Ees). Effective arterial elastance was calculated as:

$$\varvec{E}\varvec{a} = \frac{0.9 \times \varvec{S}\varvec{A}\varvec{P}}{\varvec{S}\varvec{V}}$$

where SAP represents systolic arterial pressure.

End-systolic elastance (Ees) was estimated non-invasively using the validated single-beat method described by Chen et al. [21]. VA coupling was calculated as the Ea/Ees ratio.

Isovolumetric contraction time (IVCT) was measured as an additional index of left ventricular systolic performance. Changes in cardiovascular variables were expressed as absolute and relative differences between baseline and post-augmentation measurements.

Classification of cardiovascular responses

Patients were classified according to the relative change in cardiac output following MAP augmentation. Three cardiovascular response groups were defined *a priori*:

1. Flow recruitment: increase in cardiac output > 15%.
2. Stable flow: change in cardiac output between − 15% and + 15%.
3. Flow deterioration: decrease in cardiac output > 15%.

A 15% change in cardiac output was selected *a priori*, consistent with the threshold commonly used to define a clinically meaningful hemodynamic response in studies of fluid responsiveness [17, 22]. Although originally developed to evaluate preload responsiveness, this threshold was applied as an operational criterion to classify the magnitude and direction of the cardiovascular response to MAP augmentation and was not intended to define discrete biological phenotypes.

Statistical analysis

Continuous variables are presented as median (interquartile range [IQR][5]) and categorical variables as counts and percentages.

Baseline characteristics and changes following MAP augmentation were compared among response groups using the Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical variables. Pairwise comparisons were performed using Dunn's post hoc test with Bonferroni correction when appropriate. Within-group comparisons between baseline and post-augmentation measurements were performed using the Wilcoxon signed-rank test.

Associations between changes in VA coupling and indices of ventricular performance (stroke volume, left ventricular ejection fraction, myocardial performance index, and IVCT) were assessed using Spearman's rank correlation coefficients. To account for repeated measurements within individuals, linear mixed-effects models with patient-level random intercepts were fitted. Separate models were constructed for cardiac output, stroke volume, heart rate, left ventricular ejection fraction, myocardial performance index, IVCT, and VA coupling. Fixed effects included time (baseline versus post-augmentation), vasopressor strategy (norepinephrine versus vasopressin), and the interaction between time and vasopressor strategy.

Finally, exploratory analyses were performed to identify baseline cardiovascular characteristics associated with flow deterioration following MAP augmentation.

Results

Study population

Thirty-two mechanically ventilated patients with fluid-resuscitated septic shock undergoing transient mean arterial pressure (MAP) augmentation were included. The median APACHE II score was 20 (IQR 14–26), and pneumonia was the most frequent source of infection (63%). Baseline MAP was 66 ± 4 mmHg while patients were receiving norepinephrine (0.18 ± 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$). MAP augmentation was achieved by norepinephrine dose escalation in 20 patients (63%) and by the addition of vasopressin (0.03 U/min) in 12 (37%). Baseline demographic, clinical, and hemodynamic characteristics are summarized in Table 1.

Cardiovascular responses to acute MAP augmentation

Despite comparable increases in arterial pressure, acute MAP augmentation elicited markedly heterogeneous cardiovascular responses. Based on the predefined changes in cardiac output, three response groups were identified: flow recruitment (ΔCO > 15%; n = 10, 31%), stable flow (ΔCO between − 15% and + 15%; n = 17, 53%), and flow deterioration (ΔCO < − 15%; n = 5, 16%) (Table 2).

Patients with flow deterioration were the only group in whom ventriculo-arterial (VA) coupling worsened following MAP augmentation (ΔVA + 0.22 [0.06–0.43]). In contrast, VA coupling remained stable or improved in patients with stable flow (ΔVA − 0.02 [− 0.33 to + 0.10]) and flow recruitment (ΔVA − 0.12 [− 0.37 to + 0.14]) (Table 2).

Cardiovascular adaptation according to flow response

Compared with patients with preserved or increased cardiac output, those with flow deterioration exhibited a distinct pattern of cardiovascular adaptation during MAP augmentation (Table 3). They developed a significantly greater increase in effective arterial elastance (ΔEa + 0.70 [0.40–0.80] vs + 0.27 [0.17–0.40], p = 0.006), whereas the increase in end-systolic elastance was smaller (ΔEes + 0.27 [− 0.50 to + 0.30] vs + 0.43 [0.12–0.73], p = 0.118). Consequently, the increase in arterial elastance exceeded the increase in ventricular elastance, resulting in significant deterioration of VA coupling (ΔVA + 0.22 [0.06–0.43] vs − 0.05 [− 0.34 to + 0.12], p = 0.031).

Flow deterioration was accompanied by a reduction in stroke volume (ΔSV − 6.21 [− 10.15 to − 5.86] mL vs + 4.96 [1.43–10.57] mL, p < 0.001), a decrease in left ventricular ejection fraction (ΔLVEF − 13.38% [− 16.00 to − 4.14] vs + 3.51% [− 3.88 to + 7.29], p = 0.021), and prolongation of isovolumetric contraction time (ΔIVCT + 9 [0–10] ms vs − 6 [− 16 to + 3] ms, p = 0.045). Myocardial performance index also worsened (ΔMPI + 0.10 [− 0.07 to + 0.24] vs − 0.07 [− 0.16 to − 0.01], p = 0.041), whereas heart rate decreased more markedly (ΔHR − 11 [− 26 to − 8] bpm vs − 1 [− 4 to + 3] bpm, p = 0.012). In contrast, changes in capillary refill time and arterial lactate were similar between groups.

At baseline, patients with flow deterioration tended to exhibit a more hyperdynamic circulatory profile, characterized by higher cardiac output and stroke volume together with lower arterial elastance and lower VA coupling than the remaining cohort (Supplementary Table 1).

Relationship between ventriculo-arterial coupling and ventricular performance

Changes in VA coupling were significantly associated with changes in indices of ventricular performance. Deterioration in VA coupling correlated with reductions in stroke volume ($\rho = -0.418$, $p = 0.017$) and left ventricular ejection fraction ($\rho = -0.431$, $p = 0.014$), worsening myocardial performance index ($\rho = 0.599$, $p = 0.0003$), and prolongation of isovolumetric contraction time ($\rho = 0.790$, $p < 0.0001$) (Fig. 1). No significant associations were observed between changes in VA coupling and changes in cardiac output ($\rho = -0.292$, $p = 0.105$) or mitral annular systolic velocity ($\rho = -0.272$, $p = 0.133$).

Exploratory analyses

Exploratory analyses were performed to identify physiological characteristics associated with flow deterioration following MAP augmentation.

Patients with flow deterioration more frequently underwent MAP augmentation using vasopressin than norepinephrine (80% vs 29.6%; odds ratio 9.5, Fisher's exact $p = 0.053$).

To further evaluate whether the vasopressor strategy influenced cardiovascular responses, linear mixed-effects models were constructed accounting for repeated measurements within individuals. Vasopressin was associated with different trajectories of cardiac output (interaction $\beta = -816$ mL/min, $p = 0.038$) and heart rate (interaction $\beta = -9.58$ bpm, $p < 0.001$) during MAP augmentation. No significant interaction between vasopressor strategy and time was observed for VA coupling.

Discussion

The principal finding of this physiological study is that acute mean arterial pressure (MAP) augmentation elicited markedly heterogeneous cardiovascular responses despite comparable increases in arterial pressure. Although most patients maintained or increased cardiac output, a subset experienced a marked decline despite similar increases in arterial pressure. This response was accompanied by worsening ventriculo-arterial (VA) coupling, impaired systolic performance, and reduced stroke volume. Together, these findings suggest that the cardiovascular consequences of MAP augmentation depend not only on the achieved arterial pressure but also on each patient's capacity to accommodate the accompanying increase in arterial load.

Acute MAP augmentation simultaneously restores perfusion pressure and increases arterial load [6]. Consequently, the net cardiovascular response reflects the balance between restoration of vascular tone and the increase in arterial load imposed on the left ventricle. Patients with preserved or increased forward flow exhibited proportional increases in ventricular elastance relative to arterial elastance, thereby maintaining VA coupling. In contrast, patients with flow deterioration developed a disproportionate increase in arterial elastance that was not matched by an appropriate increase in ventricular elastance, resulting in VA uncoupling and reduced forward flow. These observations are consistent with the physiological framework proposed by Sunagawa and support the concept that cardiovascular performance depends on the interaction between ventricular contractility and arterial load rather than on either component in isolation [9, 11].

Importantly, patients with flow deterioration did not exhibit more severe baseline myocardial dysfunction. Rather, they tended to display a more hyperdynamic and vasoplegic circulatory profile, characterized by higher baseline cardiac output and stroke volume, together with lower arterial elastance and lower baseline VA coupling. Although exploratory, this pattern may be interpreted through two complementary physiological mechanisms. First, these patients may have been operating near the upper range of their recruitable forward-flow reserve. In such a state, acute MAP augmentation may predominantly increase arterial load without providing substantial additional opportunity for stroke volume or cardiac output recruitment; if ventricular contractile adaptation is insufficient to match the imposed load, stroke volume may fall and VA uncoupling may develop. Second, the abrupt increase in arterial load may unmask latent systolic dysfunction that is not apparent under conditions of low afterload, as may occur in sepsis-induced myocardial dysfunction [23]. Thus, flow deterioration after MAP augmentation may reflect either limited residual flow reserve, impaired afterload tolerance, or both. This interpretation provides a plausible physiological explanation for why patients exposed to similar increases in arterial pressure exhibited markedly different cardiovascular responses. These mechanisms are schematically integrated in Fig. 2.

Changes in VA coupling were more closely associated with indices of ventricular mechanics than with cardiac output itself. The strongest association was observed with isovolumetric contraction time (IVCT), followed by myocardial performance index, stroke volume, and left ventricular ejection fraction. Because IVCT reflects the time required for the ventricle to generate sufficient pressure to open the aortic valve, its prolongation likely represents impaired ventricular adaptation to increased arterial load. Although IVCT has not traditionally been used to assess cardiovascular responses during vasopressor therapy, our findings suggest that it may represent a sensitive physiological marker of ventricular intolerance to acute increases in arterial load. This observation warrants prospective validation.

Our findings also have potential implications for individualized blood pressure management in septic shock. Current practice assumes that increasing MAP improves organ perfusion provided conventional pressure targets have not been exceeded [1]. However, patients achieving similar increases in arterial pressure experienced substantially different cardiovascular responses. These findings suggest that the physiological response elicited by transient MAP augmentation may be as informative as the achieved arterial pressure itself. In this context, transient MAP augmentation may provide insight into each patient's cardiovascular reserve and capacity to tolerate additional arterial loading. Whether this physiological information can be used to individualize MAP targets and improve clinical outcomes remains to be determined.

The influence of the vasopressor strategy also deserves consideration. Patients with flow deterioration more frequently received vasopressin, but this observation should be interpreted cautiously because vasopressor selection was not protocolized and the number of events was limited. Physiologically, this association may be consistent with a state of limited residual forward-flow reserve: in patients already operating near their recruitable flow limit, vasopressin may predominantly increase vascular tone and arterial load without providing substantial additional inotropic effect. Under these conditions, insufficient

ventricular adaptation to the imposed load may lead to VA uncoupling and flow deterioration. Whether vasopressin contributed directly to this response or merely identified patients with limited afterload tolerance remains uncertain.

Peripheral perfusion markers evolved less consistently than central cardiovascular variables. Despite marked differences in forward flow, ventricular mechanics, and VA coupling, changes in capillary refill time and lactate were similar across response groups. These findings reinforce the concept that arterial pressure, forward flow, ventricular mechanics, and tissue perfusion represent related but distinct physiological domains. Accordingly, optimization of MAP should probably integrate multiple physiological signals rather than rely exclusively on arterial pressure [2, 3, 5].

This study has several limitations. First, the relatively small sample size, particularly the limited number of patients with flow deterioration, reduced statistical power and precluded robust multivariable analyses. Consequently, analyses exploring predictors of cardiovascular responses should be considered hypothesis-generating. Second, patients were classified according to a pre-specified operational threshold in cardiac output selected to facilitate physiological comparisons. Although this threshold is widely accepted to define clinically meaningful hemodynamic responses in fluid responsiveness studies, its application to MAP augmentation should be considered an operational classification rather than evidence of discrete biological phenotypes. Third, the observational design precludes causal inference regarding the mechanisms underlying the observed cardiovascular responses or the differential effects of individual vasopressors. Fourth, VA coupling was estimated using validated non-invasive single-beat methods, which remain indirect approximations of pressure-volume relationships. Fifth, measurements were obtained immediately after MAP augmentation and therefore reflect short-term physiological responses rather than sustained cardiovascular adaptation during prolonged vasopressor therapy. Finally, these physiological findings cannot be directly extrapolated to long-term clinical outcomes or to the optimal MAP target during septic shock resuscitation.

Conclusion

Acute MAP augmentation elicited markedly heterogeneous cardiovascular responses in fluid-resuscitated patients with septic shock despite comparable increases in arterial pressure. Patients with flow deterioration demonstrated impaired ventricular adaptation to increased arterial load, reflected by worsening ventriculo-arterial coupling, increased arterial elastance, impaired systolic performance, and reduced stroke volume. These findings provide a physiological explanation for the heterogeneous cardiovascular responses to MAP augmentation and support future studies aimed at individualizing MAP targets during septic shock.

Abbreviations

CCE
Critical care echocardiography
ICU
Intensive Care Unit
AVP
Vasopressin
CO
Cardiac output
SV
Stroke volume
CVP
Central venous pressure
Ea
Aortic elastance
LVEF
Left ventricular ejection fraction
MAP
Mean arterial pressure
Pmsf
Mean systemic filling pressure
VPT
Vasopressor test
CRT
Capillary refill time
VRdP
Venous return driving pressure
ΔSV
SV during VPT – SV basal
IVCT
Isovolumetric contraction time
Ees
Left ventricle end systolic elastance

MPI
Myocardial performance index

Declarations

Acknowledgments

We sincerely thank all the nurses and physicians at the participating institutions, and all the patients who contributed to this study.

Ethics declarations

Ethics approval and consent to participate

The study protocol was approved by the appropriate Institutional Review Board (Ethics Committee, Protocol number ID: 200422002). Pontificia Universidad Católica de Chile.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

Funding

This work was supported by FONDECYT ANID Grants N°11201220 and FONDECYT ANID Grants N° 1241463

Authors' contributions

EDV, PM, RC, JR: Contributed to the study conception and design.

EDV, PM, NM and VO contributed to the clinical performance of this study.

EDV, PM, NM, RC, JB, MS and JR contributed to the statistical analysis and interpretation.

EDV, RC, and JR contributed to drafting this manuscript.

All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The data underlying this article will be shared by the corresponding author upon reasonable request.

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Tables

Table 1. Demographic and clinical characteristics

	All **n = 32**	**Flow recruitment ΔCO > +15% (n=10)**	**Stable flow** **−15% ≤ ΔCO ≤ +15% (n=17)**	**Flow deterioration** **ΔCO < −15% (n=5)**	**p** **value**
Age, y.o.	71 ± 9	75 ± 9	72 ± 8	65 ± 10	0.133
Sex, female (%)	16 (50)	5 (50)	9 (53)	2 (40)	0.878
APACHE II score	20 [14-26]	24 [17-27]	20 [14-26]	14 [13-21]	0.247
SOFA score at ICU admission	10 [6-12]	11 [8-12]	9 [6-17]	8 [5-11]	0.265
Duration of Mechanical Ventilation, days	7 [3-15]	7 [3-16]	7 [3-15]	7 [3-22]	0.922
ICU length of stay, days	13 [7- 19]	4 [3-9]	5 [3-15]	8 [4-23]	0.659
Norepinephrine days	5 [3-13]	13 [7-29]	13 [8-17]	11 [4-24]	0.910
AVP use during VPT	12 (38)	3 (30)	5 (29)	4 (80)	0.102
ICU Mortality, n(%)	10 (31)	2 (20)	5 (29)	3 (60)	0.281

Continuous data were expressed as mean ± SD or median [25th–75th percentiles]. Categorical variables expressed as number. APACHE II = Acute Physiology and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; ICU = Intensive Care Unit, AVP = vasopressin; VPT = vasopressor test.

Table 2	Flow recruitment ΔCO > 15% Baseline	Flow recruitment ΔCO > 15% VPT	Δ	Stable flow −15% ≤ ΔCO ≤ 15% Baseline	Stable flow −15% ≤ ΔCO ≤ 15% VPT	Δ	Flow deterioration ΔCO < −15% Baseline	Flow deterioration ΔCO < −15% VPT	Δ	Δ P
CO, ml	4646 (3293–5677)	5722 (3987–6884)	26 % (19–29)	5820 (5014–6427)	5819 (4876–6479)	2 % (-5–6)	7037 (6703–7861)	4422 (3614–6363)	-24 % (-37–-16.)* [f]	<0
VA coupling	1.65 (0.80–2.18)	1.10 (0.74–2.25)	-0.12 (-0.37–0.14)	0.97 (0.64–1.20)	0.87 (0.73–1.00)	-0.02 (-0.33–0.10)	0.67 (0.59–0.71)	1.10 (0.93–1.50)	0.22 (0.06–0.43) [f]	0.
Stroke volume	56.30 (41.02–58.94)	70.62 (50.54–80.59)	11.43 (9.32–13.01)	63.73 (53.85–71.82)	67.66 (54.25–71.79)	2.85 (0.76–5.68)	77.84 (74.87–79.00)	71.62 (53.28–76.91)	-6.21 (-10.15–-5.86)* [f]	<0
IVCT	70.00 (41.75–93.50)	71.50 (41.75–81.50)	-3.00 (-20.75–2.00)	54.00 (45.00–62.00)	47.00 (46.00–54.00)	-7.00 (-15.00–4.00)	49.00 (41.00–51.00)	59.00 (41.00–86.00)	9.00 (0.00–10.00)	0.
Ejection fraction	57 (51–65)	62 (51–74)	2.63 (-1.20–7.17)	63 (58–68)	65 (59–70)	3.98 (-4.26–7.51)	62 (62–63)	58 (54–61)	-13.38 (-16.00–-4.14)*	0.
Ea	1.65 (1.52–1.98)	1.80 (1.67–2.24)	0.20 (0.14–0.26)	1.41 (1.37–1.70)	1.80 (1.69–2.00)	0.30 (0.30–0.50)	1.30 (1.20–1.40)	1.90 (1.70–2.20)	0.70 (0.40–0.80)* [f]	0.
Ees	1.10 (0.72–2.95)	1.50 (0.98–2.83)	0.15 (0.02–0.63)	1.40 (1.30–1.90)	2.20 (2.00–2.50)	0.60 (0.30–0.80)	2.00 (2.00–2.30)	2.30 (1.10–2.60)	0.27 (-0.50–0.30) [f]	0.
Heart rate	87 (72–103)	89 (70–110)	2.50 (-1.50–5.00)	94 (88–100)	93 (82–95)	-3.00 (-5.00–-1.00)	94 (79–101)	80 (76–83)	-11.00 (-26.00–-8.00)* [f]	0.
CRT	3.00 (2.25–4.00)	2.50 (1.62–3.00)	-0.50 (-1.00–0.00)	2.00 (2.00–5.00)	2.00 (2.00–3.00)	0.00 (-0.50–0.00)	2.80 (2.00–8.00)	3.00 (1.50–5.00)	-0.50 (-1.00–-0.50)	0.
Lactate	2.50 (2.17–3.12)	2.45 (1.85–3.73)	0.00 (-0.25–0.40)	4.20 (2.30–4.80)	3.60 (2.10–4.70)	-0.20 (-0.60–-0.10)	2.20 (2.10–4.40)	2.10 (1.60–2.70)	-0.90 (-1.20–-0.10)	0.
Mitral S' wave	10.34 (7.52–14.87)	10.84 (8.11–15.23)	0.30 (-0.73–0.98)	13.00 (10.00–15.17)	12.05 (10.82–16.40)	-0.62 (-1.23–1.00)	13.05 (8.81–13.39)	11.60 (6.95–13.50)	-1.79 (-1.86–0.11)	0.
MPI	0.68 (0.61–0.92)	0.60 (0.49–0.85)	-0.08 (-0.13–-0.03)	0.55 (0.45–0.59)	0.46 (0.40–0.55)	-0.06 (-0.18–0.05)	0.58 (0.48–0.72)	0.58 (0.51–0.68)	0.10 (-0.07–0.24)	0.

Legend. CO = cardiac output; VA coupling = ventriculo-arterial coupling; IVCT = isovolumetric contraction time; Ea = static aortic elastance; Ees = left ventricl systolic elastance; CRT = capillary refill time; IVA = isovolumetric velocity acceleration; MPI = myocardial performance index.(*)Represent significant differer between decrease CO group (**ΔCO < −15%)** vs increase CO group (**ΔCO > +15%**), and ([f]) represent significant difference between decrease CO group vs Neut group (**−15% ≤ ΔCO ≤ +15%**) group

Table 3	Flow recruitment / stable flow (n=27)	Flow deterioration (n=5)	p value
ΔCO	4.84 (-1.92–24.91)	-24.01 (-37.17–-16.24)	<0.001
ΔVA coupling	-0.05 (-0.34–0.12)	0.22 (0.06–0.43)	0.031
ΔSV	4.96 (1.43–10.57)	-6.21 (-10.15–-5.86)	<0.001
ΔIVCT	-6.00 (-16.00–3.00)	9.00 (0.00–10.00)	0.045
ΔEF	3.51 (-3.88–7.29)	-13.38 (-16.00–-4.14)	0.021
ΔEa	0.27 (0.17–0.40)	0.70 (0.40–0.80)	0.006
ΔEes	0.43 (0.12–0.73)	0.27 (-0.50–0.30)	0.118
ΔHR	-1.00 (-4.00–3.00)	-11.00 (-26.00–-8.00)	0.012
ΔCRT	0.00 (-0.50–0.00)	-0.50 (-1.00–-0.50)	0.224
ΔLactate	-0.10 (-0.40–0.10)	-0.90 (-1.20–-0.10)	0.083
Δs wave	-0.10 (-0.98–0.83)	-1.79 (-1.86–0.11)	0.194
ΔIVA	-4.50 (-101.20–111.50)	-118.00 (-202.00–-62.00)	0.071
ΔMPI	-0.07 (-0.16–-0.01)	0.10 (-0.07–0.24)	0.041

Legend. CO = cardiac output; VA coupling = ventriculo-arterial coupling;

IVCT = isovolumetric contraction time; Ea = static aortic elastance;

Ees = left ventricle end systolic elastance; CRT = capillary refill time;

IVA = isovolumetric velocity acceleration; MPI = myocardial performance index.(*)

Figures

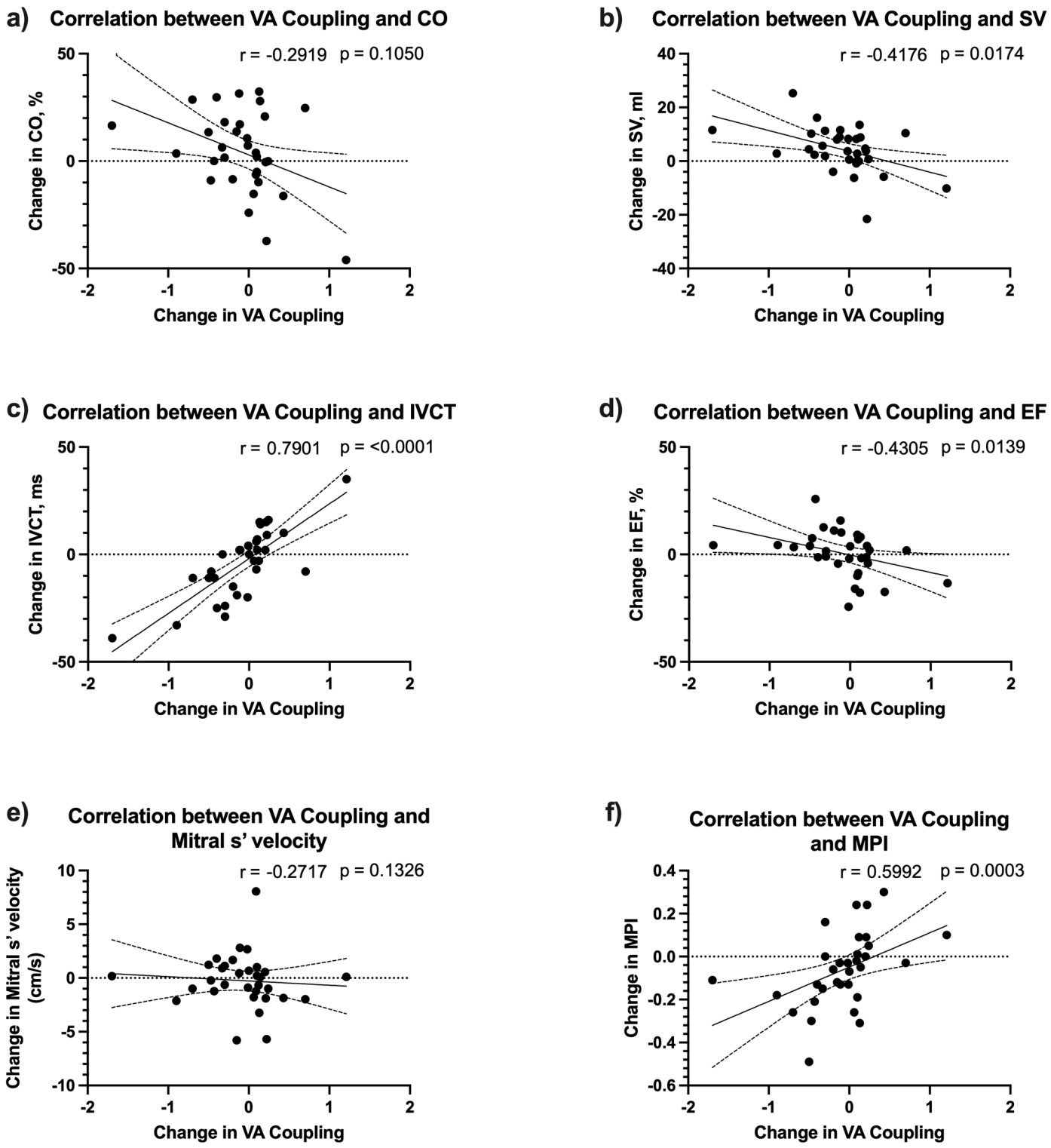


Figure 1

Association between changes in ventriculo-arterial coupling and changes in ventricular performance during acute MAP augmentation.

Scatter plots showing the relationship between changes in ventriculo-arterial (VA) coupling and changes in cardiac output (panel a), stroke volume (panel b), isovolumetric contraction time (panel c), left ventricular ejection fraction (panel d), mitral annular s' velocity (panel e), and myocardial performance index (panel f) after acute mean arterial pressure (MAP) augmentation. Each point represents one patient. VA coupling was expressed as the ratio between effective arterial elastance and end-systolic elastance (Ea/Ees); therefore, an increase in VA coupling reflects worsening ventriculo-arterial coupling. Worsening VA coupling was significantly associated with reductions in SV and EF, prolongation of IVCT, and increase in MPI, whereas no significant association was observed with CO or mitral annular s' velocity. Solid lines represent fitted linear regression lines and dashed lines represent 95% confidence intervals. Dotted horizontal lines indicate no change from baseline. Correlation coefficients and p values are shown in each panel. **Abbreviations:** VA,

ventriculo-arterial; MAP, mean arterial pressure; CO, cardiac output; SV, stroke volume; IVCT, isovolumetric contraction time; EF, ejection fraction; MPI, myocardial performance index; Ea, effective arterial elastance; Ees, end-systolic elastance.



Figure 2

Ventricular adaptation determines the cardiovascular response to acute afterload increase in septic shock.

Schematic representation of the proposed physiological mechanisms underlying heterogeneous cardiovascular responses to acute mean arterial pressure (MAP) augmentation in septic shock. The upper panel illustrates a pressure–volume framework of ventriculo-arterial coupling during MAP augmentation. In patients with adequate ventricular reserve, the acute increase in arterial elastance (Ea) is accompanied by a proportional increase in end-systolic elastance (Ees), preserving ventriculo-arterial coupling and maintaining or increasing stroke volume. In contrast, in patients with limited ventricular reserve, the increase in Ea is not matched by an adequate increase in Ees, resulting in ventriculo-arterial uncoupling and a fall in stroke volume.

The lower panel summarizes the proposed transition from arterial loading to clinical phenotype. When ventricular adaptation is adequate, VA coupling remains preserved and forward flow is maintained or recruited. When ventricular adaptation is insufficient, VA uncoupling develops and cardiac output deteriorates. The central dashed box highlights the exploratory baseline profile observed in patients with flow deterioration, characterized by a more hyperdynamic/vasoplegic pattern with higher baseline cardiac output and stroke volume, lower baseline Ea, and lower VA ratio.

Pressure–volume loops are schematic and not derived from individual patient data.
Abbreviations: CO, cardiac output; Ea, effective arterial elastance; Ees, end-systolic elastance; EDV, end-diastolic volume; ESP, end-systolic pressure; ESV, end-systolic volume; LV, left ventricle; MAP, mean arterial pressure; SV, stroke volume; VA, ventriculo–arterial.

Supplementary Files

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- Supplementarytable1.docx