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ORIGINAL ARTICLE

Physiologic cardiovascular studies among patients with treated septic shock and persistent hyperlactatemia

Dujrath Somboonviboon[1], Waraporn Tiyanon[2], Petch Wacharasint[1]

[1]Division of Pulmonary and Critical care Medicine, Phramongkutklao Hospital, Bangkok, Thailand
[2]Division of Cardiology, Phramongkutklao Hospital, Bangkok, Thailand

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Corresponding author:
Petch Wacharasint
Division of Pulmonary and Critical Care Medicine, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand 10400
Tel: (+66) 2-763-9300
Fax: (+66) 2-763-9300
E-mail: Wacharasint@hotmail.com

ABSTRACT:

Background: In early phase septic shock, both ventriculo-arterial (VA) coupling and venous return (VR) are altered. We hypothesized that among patients with normotensive septic shock already receiving both vasopressor and fluid resuscitation but still presenting hyperlactatemia, VA coupling remains altered and giving more fluid or more vasopressor dosage may improve VA coupling and VR-related parameters.

Methods: We performed a prospective experimental study among patients with septic shock admitted to a medical intensive care unit and still presenting hyperlactatemia even receiving initial resuscitation to maintain mean arterial pressure (MAP) >65 mmHg. All patients received incremental doses of norepinephrine (NE) to increase MAP, then NE was titrated to baseline dosage and after 15 min, then fluid bolus was given. VA coupling-related parameters [i.e. arterial elastance (Ea), left ventricular end-systolic elastance (Ees), left ventricular stroke work (SW), potential energy (PE), stroke volume (SV), and Ea/Ees], as well as VR-related parameters [i.e. central venous pressure (CVP), mean systemic pressure analogue (Pmsa), venous return pressure (Pvr)] were measured at 4 time points including 1) pre-increased NE phase (baseline-1), 2) postincreased NE phase, 3) prefluid bolus phase (baseline-2), and 4) postfluid bolus phase. Primary outcome was average of Ea/Ees. Secondary outcomes differed in VA coupling-related parameters and VR-related parameters between pre- vs. postinterventions, and survivors vs. nonsurvivors.

Results: At baseline, all 20 patients were normotensive [MAP 74 (66-80) mmHg] with elevated blood lactate [2.7 (2.4-3.6) mmol/L]. Average Ea/Ees was 0.89 (0.61-1.16). Compared with baseline-1, incremental doses of NE raised MAP, CVP, SV, SW, PE, Pmsa, and Pvr. Likewise, compared with baseline-2, fluid bolus raised MAP, CVP, SV, Ees, SW, Pmsa, and Pvr. No difference in Ea/Ees was observed from baseline after receiving both interventions. Compared with survivors, nonsurvivors had a trend toward a higher Ea/Ees (1.18 vs. 0.84, p=0.075) and higher Ea (1.96 vs. 1.57 mmHg/mL, p=0.09).

Conclusion: Among patients with normotensive septic shock receiving initial resuscitation and still presenting hyperlactatemia, we found an average Ea/Ees of 0.89. Increasing NE dosage or fluid bolus increased most VA coupling-related parameters and VR-related parameters, but not Ea/Ees. Compared with survivors, nonsurvivors had a trend toward a higher Ea/Ees. A further large study is warranted to validate these findings.

Keywords: Sepsis, Ventriculo-arterial coupling, Venous return, Lactate

INTRODUCTION

While sepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection, septic shock is a subset of sepsis presenting particularly profound circulatory, cellular and metabolic abnormalities [1]. Both syndromes need urgent awareness and treatment. Despite a substantial amount of research has increased the speed of recognition and treatment over the past 30 years, sepsis remains the most common cause of death among critically-ill patients worldwide [2,3]. In the early phase of septic shock, many inflammatory cytokines are released causing arterial vasodilatation. However, hemodynamic response of patients with septic shock may manifest differently such as hyperdynamic state, typically increased stroke volume and decreased systemic vascular resistance, or cardiomyopathy in which cardiac contractility is suppressed. Initial management as recommended by Surviving Sepsis Campaign International (SSC) Guidelines focuses on source control, early initiation of appropriate antimicrobial therapy, restoration of tissue perfusion with fluid bolus, and vasopressor to maintain tissue perfusion [2,4]. However, even early initial resuscitation, sepsis-induced cardiomyopathy still occurred [5,6]. Related studies have demonstrated that mortality among septic patients with cardiac dysfunction was higher than among septic patients without cardiac dysfunction [7,8]. Regarding the heterogeneity of cardiovascular reserves among individual patients, tailor-based resuscitation may be preferred [9,10].

Defining how the heart interacts with arterial system using ventriculo-arterial (VA) coupling, and how the venous system interacts with the heart using venous return (VR)-related parameters [i.e., central venous pressure (CVP), mean systemic pressure (Pms), pressure gradient of venous return (Pvr), and global cardiac efficiency (Eh)] could enhance more physiologic understanding of hemodynamic changes during acute circulatory failure. Currently, these parameters are also measurable at the bedside [11, 12, 13, 17, 20]. The concept of VA coupling demonstrated that the cardiovascular system works better when the heart and the arterial system are coupled [14,15]. The dynamic interaction between the heart and systemic circulation allows the cardiovascular system to efficiently provide adequate cardiac output (CO) and arterial pressures necessary for sufficient organ perfusion [16]. VA coupling can be defined as the ratio of the arterial elastance (Ea) to the left ventricular end-systolic elastance (Ees) or Ea/Ees. Ea expresses all extracardiac forces and Ees represents the cardiac contractility [17,18]. Therefore, VA coupling is tightly linked to left ventricular ejection efficiency (LVeff), defined as the ratio of external cardiac stroke work (SW) to total cardiac work during one cardiac cycle [10]. Related studies have demonstrated that VA coupling was blunted (so-called "VA decoupling") in early phase septic shock, which mainly related to impaired left ventricular performance. Additionally, fluid resuscitation may restore an optimal VA coupling; however, these studies were performed in early phase septic shock [9,10 ,18].

To date, no physiologic study has been conducted on VA coupling and venous return (VR)-related parameters among patients with normotensive septic shock receiving both vasopressor and fluid resuscitation but still presenting hyperlactatemia. We hypothesized that in this patient phenotype, VA decoupling occurred, and a hemodynamic response to more vasopressor or more fluid resuscitation may improve VA coupling and venous return (VR)-related parameters.

KEY MESSAGES:

- We found normal VA coupling in normotensive septic shock receiving initial resuscitation and still presenting hyperlactatemia. Increasing NE dosage or fluid bolus increased most VA coupling-related parameters and VR-related parameters, but not Ea/Ees.

MATERIALS AND METHODS

Study design

This prospective experimental cohort study was conducted in the medical intensive care unit, Phramongkutklao Hospital (Bangkok, Thailand) from December 2020 to February 2021. The study was approved by the Ethics Committee Institutional Review Board of Royal Thai Army Medical Department (R206h/63). Patients who met all inclusion criteria were enrolled in this study. Inclusion criteria included 1) aged >20 years old, 2) diagnosed septic shock (defined by Sepsis-3 definition) [1], 3) persistent hyperlactatemia (blood lactate >2.0 mmol/L) although receiving initial fluid resuscitation and norepinephrine (NE), and 4) normotensive [mean arterial pressure (MAP) >65 mmHg]. Exclusion criteria included 1) known mitral or aortic valve pathology, 2) arrhythmia, 3) chest wall deformity causing poor echocardiographic window, 4) receiving high dose NE (>1 mcg/kg/min), and 5) other causes of hyperlactatemia. Previous amounts of initial fluid resuscitation and NE dosage were based on attending physician's judgement.

Interventions

At baseline, all patients were mechanically ventilated with controlled tidal volume of 8 mL/kg of predicted body weight with positive end-expiratory pressure of 5 cmH_2O. The patients already had central venous catheter and arterial catheter in place to allow continuous monitoring of CVP, MAP, and pulse contour-derived hemodynamic parameters. All hemodynamic parameters of this study were recorded at 4 time points based on timing of two interventions included 1) pre-increased NE phase (baseline-1), 2) postincreased NE phase (added 2 mcg/min from baseline dosage to reach MAP >10% from baseline, for patient safety - additional NE dosage was limited to not more than 8 mcg/min), 3) prefluid bolus phase (baseline-2 or washout period; decreased NE to baseline dosage after waiting 15 min), and 4) postfluid bolus phase (finished loading of 100 mL iso-oncotic albumin intravenously).

Hemodynamic measurements

During the four time points mentioned above, all VA coupling-related parameters (Ea, Ees, Ea/Ees, LVeff, potential energy (PE), stroke volume (SV), and SW), venous return-related parameters (CVP, Pms, Pvr, and Eh), and routine hemodynamic parameters [arterial blood pressure (ABP), heart rate, pulse pressure variation (PPV), stroke volume variation (SVV)] were recorded. To achieve VA coupling-related parameters and venous return-related parameters, transthoracic echocardiography (TTE) was performed with Phase array transducer (1-5MHz), Affiniti 30&50 Phillips ultrasound by operator. Left ventricular end-diastolic volume (LVEDV), left

ventricular end-systolic volume (LVESV) and calculated left ventricular ejection fraction (LVEF) were measured using the biplane method in the apical four-chamber view. SV, pre-ejection time, and total ejection time were obtained from aortic doppler waveform in apical five-chamber view (Figure 1A). All echocardiographic findings were validated by a cardiologist. Following TTE, derived hemodynamic parameters were calculated using standard formulae, based on pressure-volume relationship (Figure 2). Ea was calculated as the ratio of 0.9SBP and SV, end-systolic pressure-volume relationship (ESPVR) slope or Ees was calculated using the single beat method purposed by Chen [19]; VA coupling was Ea over Ees. To measure cardiac energetic index, PE was calculated from the triangle area of Ees to LVESV (Figure 2), and SW was the area inside the LV pressure volume loop by estimating from product of the left ventricular end-systolic pressure (LVESP). SV. LVeff was defined as the ratio between SW and sum of SW and PE. Mean systemic pressure was estimated from Pmsa, derived from CO, CVP, and MAP as proposed by Parkin and Leaning [12]. Pvr was the difference between Pmsa and CVP and Eh was the ratio of Pvr and Pmsa [10,12].

Statistical analysis

Primary outcome was average Ea/Ees among patients with normotensive septic shock with persistent hyperlactatemia. Secondary outcomes were differences in VA coupling-related parameters and VR-related parameters between pre- vs. post-increased NE phase, pre- vs. post-fluid bolus phase, and survivor vs. non-survivors. To analyze average VA coupling among patients with septic shock, the adequate sample size of patients calculated from a related study was 19 patients [10].

Differences were observed in hemodynamic parameters between survivors and nonsurvivors as well as differences between baseline-1 vs. post-increased NE phase, baseline-2 vs. postfluid bolus phase, and survivors vs. nonsurvivors using the Mann-Whitney U, Fisher's exact, or Wilcoxon signed rank tests as appropriate. Values were presented as median and interquartile range (IQR), or number and proportion (%). We analyzed correlations between changes in Pvr and changes in CO using linear correlation analysis. P <0.05 was considered statistically significant, And the SPSS statistical analysis program (V.23.0) was used.

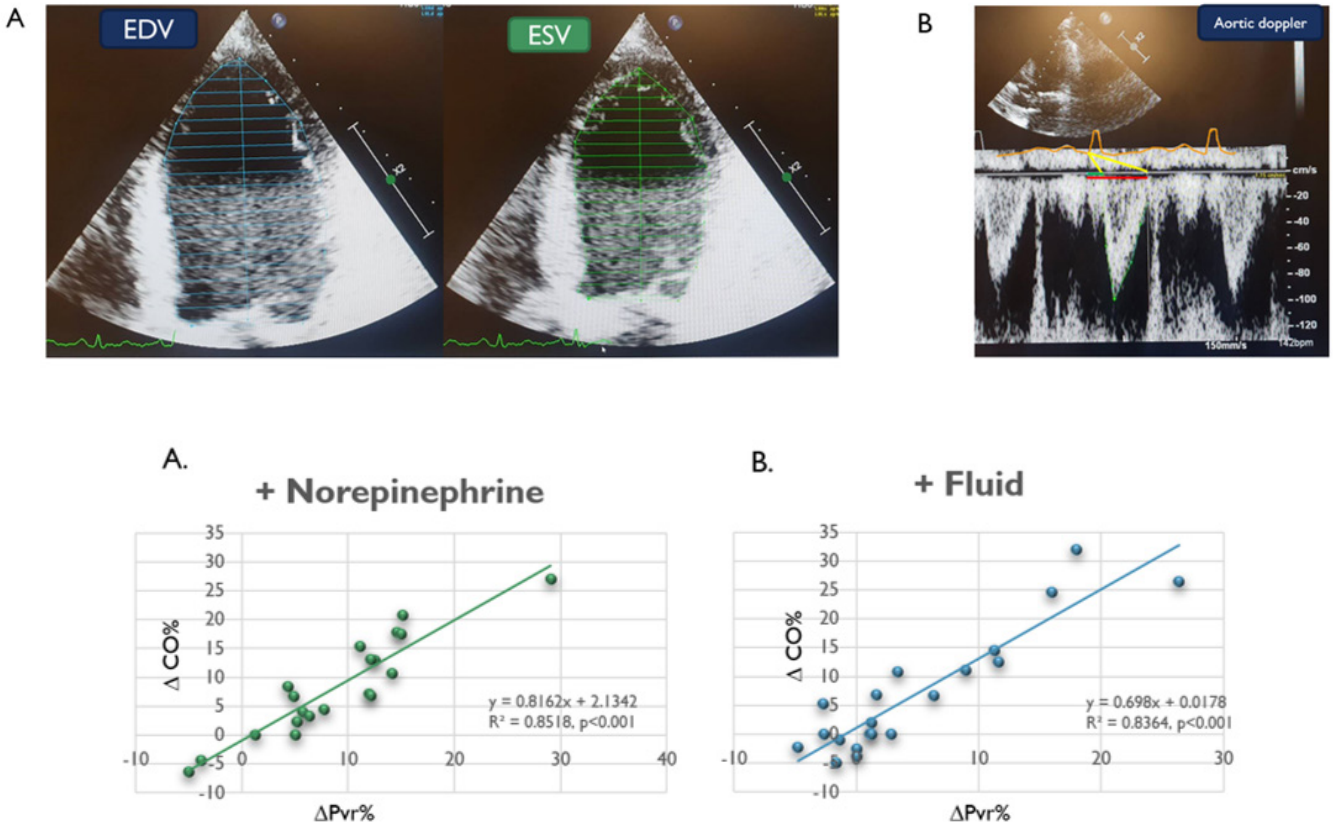

Figure 1A. (A) The biplane method in the apical four-chamber view was used to measure left ventricular end-diastolic volume (EDV), left ventricular end-systolic volume (ESV) and calculate left ventricular ejection fraction (LVEF). (B) Aortic doppler waveform in apical five-chamber view was used to calculate stroke volume (SV), pre-ejection time (green line), and total ejection time (red line).

Figure 1B. Both increased norepinephrine dosage (A) and fluid bolus (B) changes CO in proportion to changes in Pvr

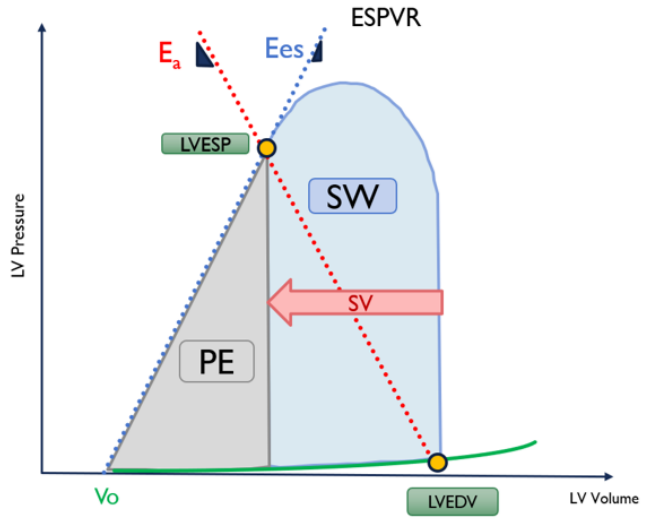

Figure 2. Left ventricular pressure–volume relation during a cardiac cycle. The slope of end-systolic pressure-volume relationship (ESPVR) (blue line) represents end-systolic elastance (Ees). The slope of arterial elastance (Ea) (red line) represents relation between stroke volume (SV) and left ventricular end-systolic pressure (LVESP). The potential energy (PE) is the triangle area of Ees to end-systolic volume. Left ventricular stroke work (SW) is the area inside the left ventricular pressure volume loop. Left ventricular ejection efficiency (LVeff) is the ratio of SW/SW+PE.

RESULTS

In all, 20 patients receiving a diagnosis of septic shock were enrolled in this study. All demographic data, laboratory variables, and ICU outcomes of all patients are described in Table 1. Median patient's age was 73.5 (62-82) years, including 10 (50%) males. Median baseline MAP was 74 (68-80) mmHg with high blood lactate (2.7 (2.4-3.6) mmol/L). Median SOFA score was 10 (9 to 12), ICU length of stay was 10 days (7 to 14), dose of NE at enrollment was 0.09 (0.055 to 0.3) and mcg/kg/min and mortality rates were 35%. Compared with nonsurvivors, survivors had significantly higher lactate at enrolment (3.3 vs. 2.5 mmol/L, p=0.015), higher lactate clearance (12 vs. 2.3%, p=0.001), and lower proportion of patients with chronic lung disease (0 vs. 43%, p=0.031).

Median Ea/Ees in normotensive septic shock patients with hyperlactatemia

We found a median Ea/Ees of 0.89 (0.61-1.16) (Table 2). Most patients (65%) in this study had Ea/Ees within normal range at baseline. The individual Ea/Ees of all patients are demonstrated in Figure 3.

Effects of increased norepinephrine dosage and fluid bolus

Compared with baseline-1, postincreased NE phase significantly had higher SBP, DBP, MAP, CVP, SV, SW, PE, Pmsa, and Pvr. Likewise, compared with baseline-2, and postfluid bolus showed significant higher SBP, DBP, MAP, CVP, SV, Ees, SW, Pmsa, and Pvr (Table 3). However, we found no difference of Ea/Ees following both interventions (Figure 3). Interestingly, we found that either increased NE dosage or fluid bolus, changes in CO were significantly correlated with changes in Pvr (R^2= 0.85, p<0.001 and R^2=0.84 p<0.001, respectively). (Figure 1B). Effects of increased NE dosage and fluid bolus on the left ventricular pressure-volume relationship diagram and venous return to cardiac output diagrams are summarized in Figure 4 and 5.

Differences in hemodynamic parameters between survivors vs nonsurvivors

Baseline VA coupling-related parameters and venous return-related parameters did not significantly differ between survivors and nonsurvivors (Table 3). among nonsurvivors, a trend was observed toward a higher Ea/Ees (1.18 vs. 0.84, p=0.075), and a trend of higher Ea (1.96 vs. 1.57 mmHg/mL, p=0.09). Survivors had a trend toward higher LVeff than nonsurvivors (0.71 vs. 0.63 %, p=0.075).

DISCUSSION

We conducted a physiologic study to demonstrate hemodynamic response following increased NE dosage and fluid bolus among patients with septic shock and presenting persistent hyperlactatemia. The mortality of patients in our study (35%) was similar to those of related studies among patients with septic shock [1,21]. In terms of VA coupling, related studies demonstrated that cardiovascular function was optimal when cardiac and arterial system were coupled, meaning that Ea/Ees was near unity or close to 1.0 [13]. Ea/Ees is widely used to determine VA coupling. The optimal Ea/Ees is of 1+0.36, while normal ranges of Ea and Ees are 2.2+0.8 mmHg/mL and 2.3+1 mmHg/mL, respectively [23,24,31]. In this study, we found that median VA coupling was within normal range [0.89 (0.61-1.16)]. Our finding contradicts related studies among patients with early phase septic shock. They demonstrated a higher proportion of VA decoupling (defined as Ea/Ees >1.36) among patients with septic shock than nonseptic shock patients. (Ea/Ees 1.81 vs.1.07, p=0.01) [24]. The possible explanation why Ea/Ees among our patients with septic shock had Ea/Ees within normal ranges may have been because our enrolled patients already received initial resuscitation until reaching acceptable MAP. Although tissue hypoperfusion existed from the evidence of hyperlactatemia among our patients, early macrocirculation, supported by adequate fluid resuscitation, and evidenced by low PPV and SVV values at baseline as well as NE receiving before enrolment may have provided an "acceptable" coupling between cardiac and arterial systems, resulting in absence of VA decoupling in our study.

NE is a first line recommended vasopressor to restore MAP in septic shock [4]. As a result of complex effects of NE on contractility, and cardiac loading condition, affecting both arterial and venous systems, we found several hemodynamic parameters changed from increased NE dosage in this study (Table 3). NE significantly increased ABP (SBP, DBP, MAP) from baseline (Figure 4). For venous return related-parameters, we found that NE increased both Pmsa and CVP (Figure 5). However, the effect of NE was more prominent on Pmsa than CVP; hence, increased NE also increased Pvr. In addition, we found changing CO also correlated with changing Pvr (Figure 6). Similar to a related study [10], presumably, increasing NE could convert unstressed volume into stressed volume and increasing VR

Table 1. Baseline characteristics of all patients compared between survivors vs. nonsurvivors.

	Total (n=20)	Survivors (n=13)	Nonsurvivors (n=7)	p-value
Age, year	73.5 (61.5-82)	69 (60-80)	80 (65-84)	0.250
BMI, kg/m^2	22.67 (19.79-23.72)	22.89 (20.81-23.78)	20.81 (19.38-22.49)	0.230
Male, n (%)	10 (50%)	7 (53.8%)	3 (42.9%)	1.000
SOFA score	10 (9-12)	10 (9-11)	12 (10-13)	0.210
NE at enrollment (mcg/kg/min)	0.10 (0.055-0.30)	0.10 (0.06-0.29)	0.09 (0.07-0.29)	0.925
Laboratory variable				
Lactate at onset of sepsis, mmol/L	4.19 (3.32-5.29)	4.07 (3.58-5)	4.53 (2.5-6.8)	0.970
Lactate at enrollment, mmol/L	2.7 (2.4-3.58)	3.3 (2.6-4)	2.5 (2.1-2.5)	0.015
Lactate clearance, %	7.05 (4.42-12.15)	12 (6.8-14.7)	2.28 (1.13-4.9)	0.001
BUN, mg/dL	46.7 (27.25-77.4)	37.4 (28-48.1)	81 (26.5-83.5)	0.088
Creatinine, mg/dL	1.91 (1.21-3.71)	2.20 (1.27-3.81)	1.59 (1.09-3.01)	0.360
Hematocrit, %	28.2 (25.1-32.75)	29.6 (25.4-31.9)	26 (20.8-34)	0.360
Hemoglobin, g/dL	8.95 (8.15-10.6)	9.40 (8.8-10.5)	8.40 (6.9-10.7)	0.150
Pre-existing diseases				
Diabetes, n (%)	3 (15%)	2 (15.4%)	1 (14.3%)	1.000
Hypertension, n (%)	16 (80%)	10 (76.9%)	6 (85.7%)	1.000
Chronic kidney disease, n (%)	10 (50%)	7 (53.8%)	3 (42.9%)	1.000
Chronic lung disease, n (%)	3 (15%)	0 (0%)	3 (42.9%)	0.030
Chronic heart disease, n (%)	5 (25%)	5 (38.5%)	0 (0%)	0.110
ICU length of stay, days	10 (7-13.5)	10 (7-13)	10 (7-18)	0.580

Mann-Whitney U test and Fisher's exact test. Data are median (interquartile range) for continuous variables, The p-values are compared between survivors and nonsurvivors.

Table 2. Conventional hemodynamic parameters, VA coupling-related, and venous return-related parameters compared between survivors vs. nonsurvivors.

	Total (n=20)	Survivors (n=13)	Nonsurvivors (n=7)	p-value
SBP, mmHg	112 (101-134)	112 (102-131)	107 (100-139)	1.000
MAP, mmHg	74 (68-80)	70 (68-77)	77 (74-83)	0.220
HR, mmHg	93 (77-103)	84 (74-100)	94 (90-140)	0.190
CVP, mmHg	12 (7.5-13)	12 (8-13)	12 (6-15)	0.810
PPV, %	5 (3.5-8)	5 (3-8)	6 (4-10)	0.450
SVV, %	7 (5-9)	7 (5-9)	8 (5-10)	0.600
LVEF, %	54.05 (44.65-66.5)	57.1 (45.6-66.3)	52.1 (35.5-74.3)	0.910
SV, mL	62 (48-80)	67.2 (52-82)	58 (35-78)	0.290
CO, L/min	5.75 (4.4-7.2)	5.9 (4.5-6.9)	4.8 (4-7.8)	0.870
VA coupling-related parameters				
Ea, mmHg/mL	1.7 (1.5-2)	1.57 (1.42-1.93)	1.96 (1.55-2.67)	0.090
Ees, mmHg/mL	2.19 (1.64-2.71)	2.31 (1.81-2.75)	1.67 (1.56-2.46)	0.360
Ea/Ees	0.89 (0.61-1.16)	0.84 (0.58-0.96)	1.18 (0.91-1.31)	0.075
SW, mmHg mL	6480.84 (4544.89-9283.91)	8206.66 (5306.46-8973.12)	6112.95 (3196.42-10229.3)	0.500
PE	2654.85 (2036.57-3724.12)	2754.49(2005.26-3807.31)	2555.22(2067.88-3106.17)	0.910
Lveff, %	0.69 (0.63-0.77)	0.71 (0.68-0.78)	0.63 (0.6-0.69)	0.075
VR related - parameters				
Pmsa, mmHg	19.6 (17.55-22.05)	18.8 (17.6-20.8)	20.2 (17.3-23.2)	0.660
Pvr, mmHg	8 (6.25-10.6)	7.8 (6.3-9.6)	8.2 (6-12.6)	0.630
Eh, %	0.44 (0.32-0.58)	0.43 (0.33-0.5)	0.49 (0.31-0.67)	0.450

Mann-Whitney U test and Fisher's exact test, data are median (interquartile range) for continuous variables

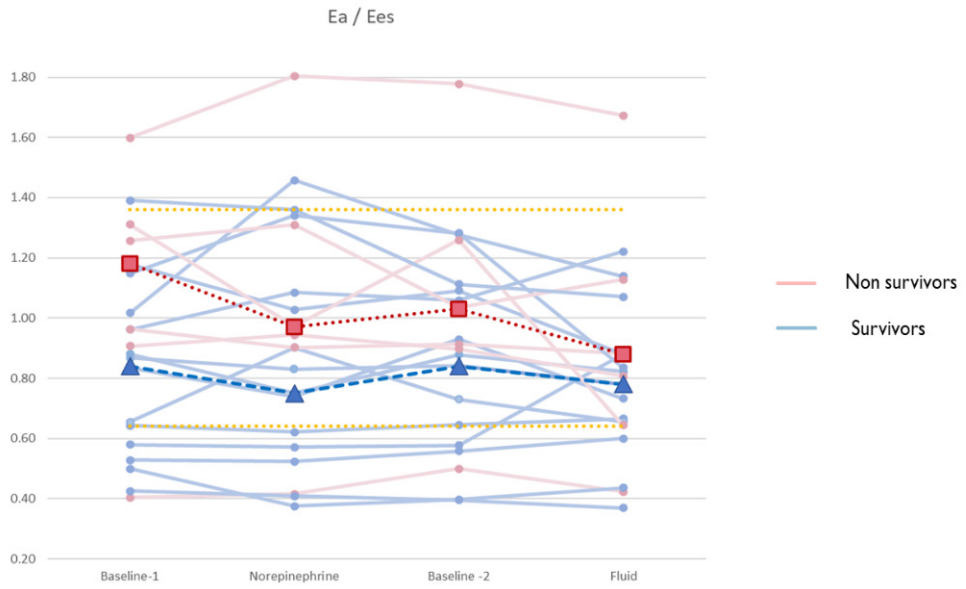

Figure 3. Individual Ea/Ees at 4 time points were demonstrated as continuous lines. Median Ea/Ees of survivors is represented in dashed blue line (0.84, 0.75, 0.84, and 0.78, respectively) and non-survivors' Ea/Ees is represented in dashed red line (1.18, 0.97, 1.03 and 0.88, respectively). Two yellow dashed lines refer to upper and lower normal range of Ea/Ees (0.64-1.36).

Table 3. Effects of increasing norepinephrine dosage and fluid bolus on hemodynamic parameters

	Baseline-1	PostNE	p-value *	Baseline-2	Postfluid	p-value **
SBP	112 (101-134)	138 (113-145)	<0.001	119 (103-136)	129 (110-149)	0.002
DBP	54 (50-59)	59 (57-63)	<0.001	54 (51-61)	59.5 (56-65)	0.003
MAP	74 (68-80)	82 (78-87)	<0.001	74 (70-82)	81 (75-85)	0.004
HR	93 (77-103)	92 (75-104)	0.530	92 (75-103)	92 (75-102)	0.93
CVP	12 (7.5-13)	12 (8.5-15)	0.038	11.5 (7.5-14)	12 (9.5-16)	0.002
PPV	5 (3.5-8)	5 (3-6.5)	0.110	5.5 (3-8.5)	5 (3-8)	0.49
SVV	7 (5-9)	6 (4-8)	0.400	7 (4-10)	5.5 (4-8)	0.34
LVEF	54 (45-67)	52 (48-70)	0.180	50 (45-66)	55 (46-69)	0.12
SV	62 (48-80)	66 (54-88)	0.001	64 (49-80)	72 (52-82)	0.011
CO	5.8 (4.4-7.2)	6.2 (4.7-8.0)	0.002	5.9 (4.4-7.6)	6.9 (4.5-8.0)	0.013
VA coupling-related parameters						
Ea	1.7 (1.5-2)	1.8 (1.51-2.04)	0.200	1.72 (1.4-2.03)	1.77 (1.57-1.98)	0.314
Ees	2.19 (1.64-2.71)	2.11 (1.49-2.95)	0.200	1.95 (1.63-2.71)	2.2 (1.82-2.91)	0.006
Ea/Ees	0.89 (0.61-1.16)	0.9 (0.6-1.2)	0.910	0.9 (0.6-1.1)	0.81 (0.65-0.98)	0.067
SW	6481 (4545-9284)	8251 (5981-11117)	<0.001	7197 (4604-9517)	9037 (5039-11452)	<0.001
PE	2656 (2037-3724)	3304 (2348-4091)	0.004	2659 (2218-3586)	2880 (2456-3808)	0.23
Lveff	0.69 (0.63-0.77)	0.69 (0.63-0.77)	0.790	0.69 (0.64-0.77)	0.71 (0.67-0.75)	0.062
VR-related parameters						
Pmsa	19.6 (17.55-22.05)	21 (19-23)	0.002	20.55 (17.75-22.15)	21.75 (19.25-24.15)	0.001
Pvr	8 (6.25-10.6)	8.6 (6.8-11.55)	0.001	8.15 (6.3-11.25)	8.25 (6.4-11.7)	0.047
Eh	0.44 (0.32-0.58)	0.45 (0.33-0.55)	0.330	0.46 (0.33-0.56)	0.46 (0.32-0.53)	0.12

Wilcoxon signed rank test, data are median (interquartile range) for continuous variables, p-values* compared between baseline-1 vs. postincreased norepinephrine (NE) dosage vs. baseline-1, p-values** compared between baseline-2 vs. post-fluid bolus

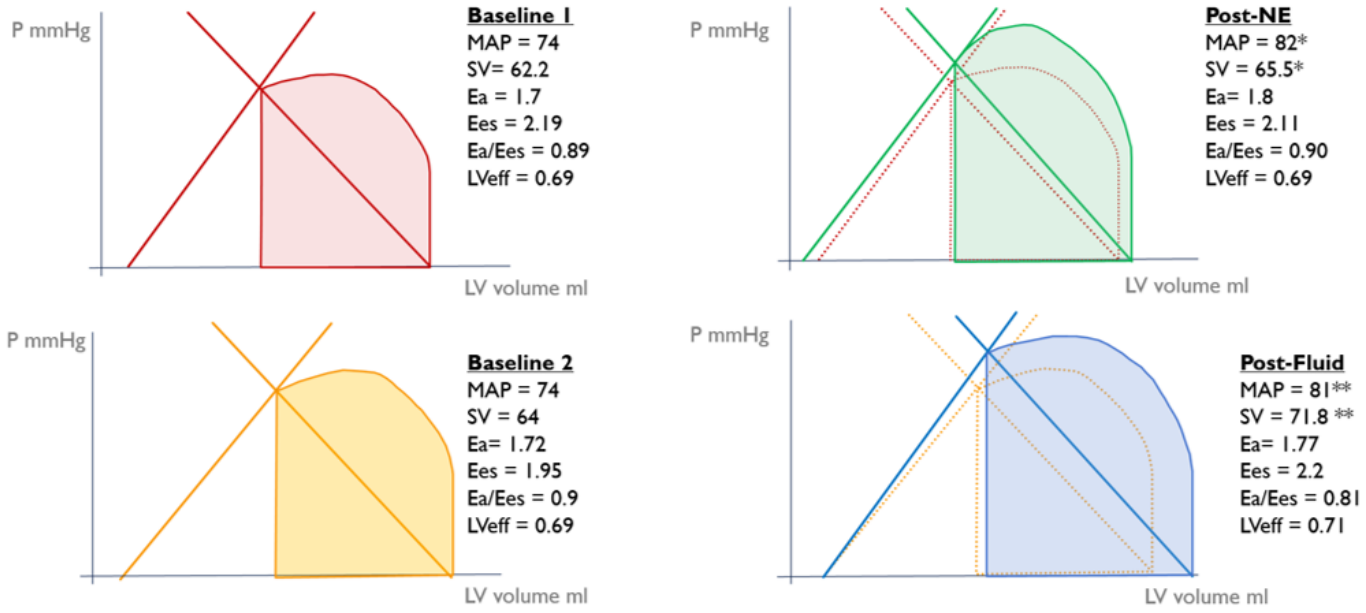

Figure 4. Hemodynamic parameters as left ventricular pressure-volume relationship diagram at baseline-1, postincreased norepinephrine (NE) dosage, baseline-2, and postfluid bolus phases, after receiving NE (NE, right upper picture), MAP rose significantly from 74 to 82 mmHg and SV increased significantly from 62.2 to 65.5 mL with no significant changes in other VA-related parameters (Ea, Ees, VAC, LVeff). Likewise, after fluid bolus (fluid, right lower picture), MAP significantly rose from 74 to 81 mmHg and SV significantly increased from 64 to 71.8 mL. Similar to received NE, no significant changes were found in VA -related parameters. *P<0.05, compared between baseline-1 vs. postincreased NE. ** P<0.05, compared between baseline-2 vs. postfluid bolus.

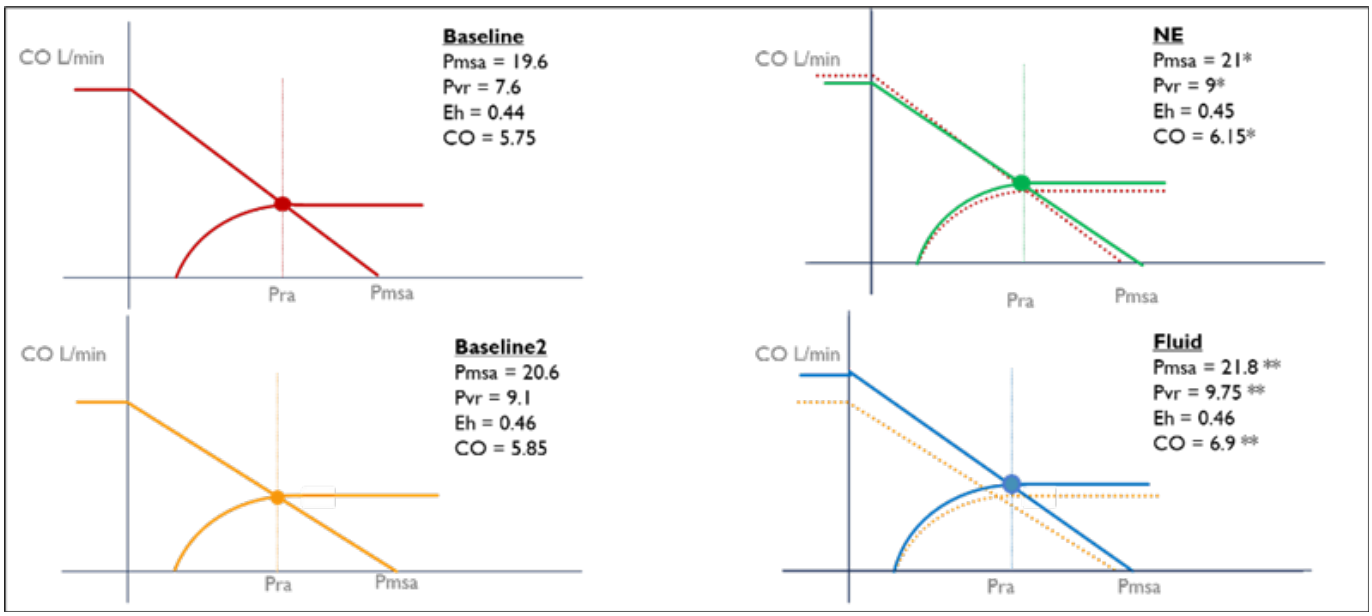

Figure 5. Venous return to cardiac output (CO) diagrams at 4 phases. After receiving NE (NE, right upper picture), Pmsa, Pvr and CO increased significantly at the same as received fluid bolus (fluid, right lower picture) * P<0.05, compared between baseline-1 and after increased norepinephrine (NE), **P<0.05, compared between baseline-2 and after fluid bolus.

and cardiac preload as mentioned in several studies [10, 25-28]. However, we found no significant difference in Ea/Ees compared between baseline-1 and postNE while one related study found that NE worsened VA coupling [10]. This may have been the result from differences in dosage of NE infusion between our study and related studies. Also, one patient with septic shock in our study indicated no response (MAP increased less than 10% from baseline) to increasing NE dosage even when the maximum limit was reached. Therefore, the effects of increased NE dosage on Ea in our study was not clearly found.

In terms of the effects of fluid bolus on VA coupling-related parameters and VR-related parameters, our study found that fluid bolus significantly increased ABP, SV, and CO. These findings resulted from changes in VR-related parameters. We demonstrated that fluid bolus increased both Pmsa and CVP but increased Pmsa more than CVP (Figure 5). Thus, increasing VR driving pressure, Pvr, allowed more venous blood return to the right atrium, so SV increased significantly even most of our patients were volume nonresponders at baseline. Moreover, we also found that fluid bolus also significantly increased Ees and had a trend to increase LVeff. Presumably, increasing MAP may improve coronary perfusion causing increased Ees and Lveff [10].

Interestingly, we found that, compared with survivors, nonsurvivors revealed a trend toward higher Ea/Ees (1.18 vs. 0.84, p=0.075) and a trend of higher Ea (1.96 vs. 1.57 mmHg/mL, p=0.09) while no difference as observed in NE-dosage required at enrollment (0.09 vs 0.1mcg/kg/min, p=0.93). A trend toward high Ea/Ees possibly resulted from trending higher Ea among nonsurvivors. As higher Ea reflected a higher degree of arterial vasoconstriction, nonsurvivors may have exhibited a higher sympathetic response to more endogenous catecholamine release or exogenous catecholamine (NE) requirement than survivors. However, regarding Ea/Ees, no statistically significant difference was found between survival vs. non-survival. This finding aligned to those of related studies in that no difference was observed in Ea/Ees when compared between survivors and nonsurvivors [10].

Limitations

Our study included patients with an adequate sample size and demonstrated physiologic alterations in the cardiovascular system based on VA coupling and VR physiology. However, our study encountered some limitations. First, we did not record hemodynamic parameters before the initial resuscitation phase. Thus, we could not compare hemodynamic parameters between before vs. after hemodynamic resuscitation. Also, we were unable to demonstrate whether VA decoupling occurred before resuscitation. However, following resuscitation, we found that most of our patients had normalized VA coupling with median Ea/Ees of 0.89. Second, the single-beat method [19] estimation of Ees did not consider the curvilinear shape of the elastance curve which could be misleading in severe cardiologic conditions. However, median Ees of our patients were within normal limit (2.19 mmHg/mL). Thus, cardiac contractility may not have been sufficiently depressed to reach curvilinearity. Third, one related study indicated a concern that NE may worsen VA coupling [10]. In this study, for patient's safety protocol, we encountered a limitation of added NE dosage at 8 mcg/min; one case added NE reaching the maximum limit. However, patient's MAP did not change from baseline and no adverse effects of NE occurred to this patient. Further, this patient may have underscored the effects of norepinephrine. Fourth, we studied these hemodynamic parameters changing over s short period of interventions. Finally, our results could not be interpreted in very early phase septic shock or non-distributive shock.

CONCLUSION

Among patients with normotensive septic shock presenting persistent hyperlactatemia, we found an average Ea/Ees of 0.89. Neither increasing NE dosage nor fluid bolus improved Ea/Ees. However, increasing NE dosage increased ABP, CVP, SV, SW, PE, Pmsa, and Pvr, while fluid bolus increased ABP, CVP, SV, Ees, SW, Pmsa, and Pvr. No difference was observed in Ea/Ees between survivors and nonsurvivors in our study. Further large study is needed to validate our findings.

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AUTHORS' CONTRIBUTIONS

Study concept and design: Dujrath Somboonviboon, Petch Wacharasint. Acquisition of data: Dujrath Somboonviboon, Petch Wacharasint, Waraphon Tiyanon. Analysis and interpretation of data: Dujrath Somboonviboon, Petch Wacharasint, Waraphon Tiyanon. Drafting of the manuscript: Dujrath Somboonviboon, Petch Wacharasint. Critical revision of the manuscript for important intellectual content: Dujrath Somboonviboon, Petch Wacharasint. Statistical analysis: Dujrath Somboonviboon, Petch Wacharasint, Dollapa Panpanich. Administrative, technical, or material support: Dujrath Somboonviboon, Petch Wacharasint. Supervision: Petch Wacharasint.

SUPPLEMENTARY MATERIALS

none

ABBREVIATIONS

ABP, Arterial blood pressure; CO, Cardiac output; CVP, Central venous pressure; DBP, Diastolic blood pressure; Ea, Arterial elastance; Ees, Left Ventricular end-systolic elastance; Eh, Global cardiac efficiency; ESPVR, End-systolic pressure volume relationship; LVeff, Left ventricular ejection efficiency; LVEDP, Left ventricular end-diastolic pressure; LVEF, Left ventricular ejection fraction; LVESP, Left ventricular end-systolic pressure; LVEDV, Left ventricular end-diastolic volume; LVESV, Left ventricular end-systolic volume; MAP, Mean arterial pressure; NE, Norepinephrine; PE, Potential energy; Pms, Mean systemic pressure; Pmsa, Mean systemic pressure analogue; PPV, Pulse pressure variation; Pra, Right atrial pressure; Pvr, Venous return pressure; SBP, Systolic blood pressure; SSC, Sepsis Surviving Campaign; SV, Stroke volume; SVV, Stroke volume variation; SW, Stroke work; TTE, Transthoracic echocardiography; VA, Ventriculo-arterial; VR, Venous return.

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