Physiologic Cardiovascular Studies in Resuscitated Normotensive Septic Shock with Persistent Hyperlactatemia.

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Research

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Abstract

**Background:** To study effects of increasing vasopressor dosage and fluid resuscitation on ventriculoarterial (VA) coupling and venous return (VR)-related parameters in resuscitated normotensive septic shock patients with persistent hyperlactatemia.

**Methods:** We performed a prospective experimental study in patients with septic shock who was admitted to medical intensive care unit and still had hyperlactatemia even received initial resuscitation to maintain mean arterial pressure (MAP) >65 mmHg. All patients received incremental dose of norepinephrine (NE) to increased MAP, then NE was titrated to baseline dosage and waited for 15 mins, then fluid bolus was given. VA coupling-related parameters [arterial elastance (Ea), left ventricular end-systolic elastance (Ees), left ventricular stroke work (SW), potential energy (PE), stroke volume (SV), and Ea/Ees], and VR-related parameters [central venous pressure (CVP), mean systemic pressure analogue (Pmsa), venous return pressure (Pvr)] were measured at 4 time points including pre-increased NE phase, post-increased NE phase, pre-fluid bolus phase, and post-fluid bolus phase. Primary outcome was average of Ea/Ees. Secondary outcomes were differences in VA coupling-related parameters and VR-related parameters between pre- vs. post- interventions.

**Results:** All 20 patients were normotensive [MAP 74 (66-80) mmHg] with elevated blood lactate [2.7 (2.4-3.6) mmol/L] at enrollment. Average Ea/Ees was 0.89 (0.61-1.16). Compared to pre-increased NE phase, post-increased NE phase had significantly higher MAP, CVP, SV, SW, PE, Pmsa, and Pvr. Likewise, compared to pre-fluid bolus phase, post-fluid bolus raised MAP, CVP, SV, Ees, SW, Pmsa, and Pvr significantly. No difference in Ea/Ees compared between before- vs. after- received both interventions.

**Conclusions:** In resuscitated normotensive septic shock patients with persistent hyperlactatemia, we found an average Ea/Ees of 0.89. Increasing NE dosage or fluid bolus increased most of VA coupling-related parameters and VR-related parameters, but not Ea/Ees. Further large study is warranted to validate these findings.

**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 in which particularly profound circulatory, cellular and metabolic abnormalities [1]. Both syndromes need urgent awareness and treatment. Despite a substantial number of researches have increased the speed of recognition and treatment over past 30 years, sepsis remains the most common cause of death in critically-ill patients worldwide [2, 3]. In the early phase of septic shock, a lot of inflammatory cytokines were released causing arterial vasodilatation. However, hemodynamic response of patients with septic shock may be manifested 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 initiate of
appropriate antimicrobial therapy, restoration of tissue perfusion with fluid bolus, and vasopressor for maintain tissue perfusion [2, 4]. However, even early initial resuscitation, sepsis-induced cardiomyopathy still occurred [5, 6]. Previous studies demonstrated that mortality of septic patients with cardiac dysfunction was higher than septic patients without cardiac dysfunction [7, 8]. Regards to the heterogeneity of cardiovascular reserve in individual patient, 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 [central venous pressure (CVP), mean systemic pressure (Pms), pressure gradient of venous return (Pvr), and global cardiac efficiency (Eh)] enhance more physiologic understanding of hemodynamic changes during acute circulatory failure. Currently, these parameters are also measurable at the bedside [11–13, 17, 20]. Concept of VA coupling was demonstrated that cardiovascular system works better when the heart and the arterial system are coupled [14, 15]. The dynamic interaction between heart and systemic circulation allows the cardiovascular system to be efficient in providing 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 tightly linked to the left ventricular ejection efficiency (LVeff), defined as the ratio of external cardiac stroke work (SW) to total cardiac work during one cardiac cycle [10]. Previous studies demonstrated that VA coupling was blunted (so-called “VA decoupling”) in early phase of septic shock, which mainly related to impaired left ventricular performance and fluid resuscitation may restored an optimal VA coupling; however, these studies were performed in early phase of septic shock [9, 10, 18].

To date, there is no physiologic study on VA coupling and venous return (VR)-related parameters in normotensive septic shock patients who received both vasopressor and fluid resuscitation but still had hyperlactatemia. We hypothesized that in this patient phenotype, VA decoupling occurred, and hemodynamic response to more vasopressor or more fluid resuscitation may improves VA coupling and venous return (VR)-related parameters.

Materials And Methods

Study design

This prospective experimental cohort study was conducted in the medical intensive care unit, Phramongkutklao Hospital (Bangkok, Thailand) during December 2020 – 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 of inclusion criteria were enrolled in this study. Inclusion criteria including aged ≥ 20 years old, diagnosed septic shock (defined by Sepsis-3 definition) [1], persistent hyperlactatemia (blood lactate ≥ 2.0 mmol/L) although received initial fluid resuscitation and norepinephrine (NE), and normotensive (mean arterial pressure, MAP ≥ 65 mmHg). Exclusion criteria
including known mitral or aortic valve pathology, arrhythmia, chest wall deformity causes poor echocardiographic window, and received high-dose of NE (> 1 mcg/kg/min). Previous amount of initial fluid resuscitation and NE dosage based on attending physician's judgement.

**Interventions**

At baseline, all patients were controlled mechanically ventilated with tidal volume of 8 mL/kg of predicted body weight with positive end-expiratory pressure of 5 cmH₂O. 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 which were 1. pre-increased NE phase (baseline-1), 2. post-increased 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. pre-fluid bolus phase (baseline-2 or washout period; decreased NE to baseline dosage and waited for 15 mins), and 4. post-fluid bolus phase (finished loading of 100 mL iso-oncotic albumin intravenously).

**Hemodynamic measurements**

During 4 time points mentioned above, all VA coupling-related parameters (Ea, Ees, Ea/Ees, LVeфф, potential energy (PE), stroke volume (SV), and SW), venous return-related parameters (CVP, Pms, Pvr, and Eh), and routine hemodynamic parameters [systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, 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 was performed with phase array transducer (1–5 MHz), Affiniti 30, Phillips ultrasound™. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and calculated left ventricular ejection fraction (LVEF) were measured using 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 (Fig. 1). All echocardiographic findings were validated by cardiologist. Following transthoracic echocardiography, derived hemodynamic parameters were calculated using standard formula, based on pressure-volume relationship (Fig. 2). Ea was calculated as the ratio of 0.9SBP and SV, end-systolic pressure-volume relationship (ESPVR) slope or Ees was calculated by using single beat method proposed 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 (Fig. 2), and SW was the area inside LV pressure volume loop by estimated from product of left ventricular end-systolic pressure (LVESP) and SV. LVeфф defined as ratio between SW and sum of SW and PE. Mean systemic pressure was estimated from Pmsa which derived from CO, CVP, and MAP as purposed by Parkin and Leaning [12]. Pvr was the different between Pmsa and CVP. Eh was the ratio of Pvr and Pmsa [10, 12].

**Statistical analysis**

Primary outcome was average Ea/Ees in normotensive septic shock patients 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.
To analyze average VA coupling in patients with septic shock, adequate sample size of patients calculated from previous study was 19 patients [10]. Difference in hemodynamic parameters between survivors and non-survivors as well as difference between baseline-1 vs. post- increased NE phase, baseline-2 vs. post-fluid bolus phase, and survivors vs. non-survivors using Mann-Whitney U test, Fisher’s exact test, or Wilcoxon signed rank test as appropriate. Values were presented as median and interquartile range (IQR), or number and proportion (%). We analyzed correlation between changes in Pvr and changes in CO using linear correlation analysis. P < 0.05 was considered statistically significant. SPSS statistical analysis program (v.23.0) was used.

Results

There were 20 patients who were diagnosed septic shock and were enrolled in this study. All demographic data, laboratory variables, and intensive care unit length of stay of all patients were described in Table 1. Average patient’s age was 73.5 (62–82) years, and there were 10 (50%) males. Average baseline MAP was 74 (68–80) mmHg with high blood lactate (2.7 (2.4–3.6) mmol/L). Average SOFA score was 10 (9–12), intensive care unit length of stay was 10 days (7–14), dose of NE at enrollment was 0.09 (0.055-0.3) mcg/kg/min, and mortality rate was 35%. Compared to non-survivors, 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).

Table 1. Baseline characteristics of all patients and compared between survivors vs. non-survivors.
|                                | Total (n=20) | Survivors (n=13) | Non-Survivors (n=7) | p-value* |
|--------------------------------|--------------|------------------|---------------------|----------|
| **Age, year**                  | 73.5 (61.5-82) | 69 (60-80)       | 80 (65-84)          | 0.25     |
| **BMI, kg/m²**                 | 22.67 (19.79-23.72) | 22.89 (20.81-23.78) | 20.81 (19.38-22.49) | 0.23     |
| **Male, n (%)**                | 10 (50%)     | 7 (53.8%)        | 3 (42.9%)           | 1.0      |
| **SOFA score**                 | 10 (9-12)    | 10 (9-11)        | 12 (10-13)          | 0.21     |
| **NE at enrollment (mcg/kg/min)** | 0.095 (0.055-0.30) | 0.1 (0.06-0.29) | 0.09 (0.07-0.29) | 0.925    |
| **Laboratory variables**       |              |                  |                     |          |
| Lactate at onset of sepsis, mmol/L | 4.19 (3.32-5.29) | 4.07 (3.58-5) | 4.53 (2.5-6.8) | 0.97     |
| 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) | 29.6 (25.4-31.9) | 26 (20.8-34) | 0.36     |
| Hematocrit, %                 | 28.2 (25.1-32.75) | 9.4 (8.8-10.5) | 8.4 (6.9-10.7) | 0.15     |
| Hemoglobin, g/dL              | 8.95 (8.15-10.6) |                  |                     |          |
| **Pre-existing diseases**      |              |                  |                     |          |
| Diabetes, n (%)               | 3 (15%)      | 2 (15.4%)        | 1 (14.3%)           | 1.0      |
| Hypertension, n (%)           | 16 (80%)     | 10 (76.9%)       | 6 (85.7%)           | 1.0      |
| Chronic kidney disease, n (%) | 10 (50%)     | 7 (53.8%)        | 3 (42.9%)           | 1.0      |
| Chronic lung disease, n (%)   | 3 (15%)      | 0 (0%)           | 3 (42.9%)           | 0.03     |
| Chronic heart disease, n (%)  | 5 (25%)      | 5 (38.5%)        | 0 (0%)              | 0.11     |
| ICU length of stay, days      | 10 (7-13.5)  | 10 (7-13)        | 10 (7-18)           | 0.58     |

BMI, body mass index; BUN, blood urea nitrogen; ICU, intensive care unit; NE, norepinephrine; SOFA, sequential organ failure assessment. *P values were calculated with the use of Mann-Whitney U test and Fisher's exact test, and compared between survivors and non-survivors. Data are median (interquartile range) for continuous variables.
Average Ea/Ees in resuscitated normotensive septic shock patients with persistent hyperlactatemia

We found an average Ea/Ees of 0.89 (0.61–1.16) (Table 2) and individual Ea/Ees of all patients were shown in Fig. 3.

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

|                                      | Total (n=20)   | Survivors (n=13) | Non-survivors (n=7) | p-value* |
|--------------------------------------|----------------|------------------|---------------------|----------|
| SBP, mmHg                            | 112 (101-134)  | 112 (102-131)    | 107 (100-139)       | 1.0      |
| MAP, mmHg                            | 74 (68-80)     | 70 (68-77)       | 77 (74-83)          | 0.22     |
| HR, /min                             | 93 (77-103)    | 84 (74-100)      | 94 (90-140)         | 0.19     |
| CVP, mmHg                            | 12 (7.5-13)    | 12 (8-13)        | 12 (6-15)           | 0.81     |
| PPV, %                               | 5 (3.5-8)      | 5 (3-8)          | 6 (4-10)            | 0.45     |
| SVV, %                               | 7 (5-9)        | 7 (5-9)          | 8 (5-10)            | 0.60     |
| LVEF, %                              | 54.05 (44.65-66.5) | 57.1 (45.6-66.3) | 52.1 (35.5-74.3)    | 0.91     |
| SV, mL                               | 62 (48-80)     | 67.2 (52-82)     | 58 (35-78)          | 0.29     |
| CO, L/min                            | 5.75 (4.4-7.2) | 5.9 (4.5-6.9)    | 4.8 (4-7.8)         | 0.87     |
| **VA coupling-related parameters**   |                |                  |                     |          |
| Ea, mmHg/mL                          | 1.7 (1.5-2)    | 1.57 (1.42-1.93) | 1.96 (1.55-2.67)    | 0.09     |
| Ees, mmHg/mL                         | 2.19 (1.64-2.71)| 2.31 (1.81-2.75) | 1.67 (1.56-2.46)    | 0.36     |
| 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) | 0.50 |
| PE                                   | 2654.85 (2036.57-3724.12) | 2754.49(2005.26-3807.31) | 2555.22(2067.88-3106.17) | 0.91 |
| Lveff, %                             | 0.69 (0.63-0.77) | 0.71 (0.68-0.78) | 0.63 (0.6-0.69)     |          |
| **VR-related parameters**            |                |                  |                     |          |
| Pmsa, mmHg                           | 19.6 (17.55-22.05) | 18.8 (17.6-20.8) | 20.2 (17.3-23.2)    | 0.66     |
| Pvr, mmHg                            | 8 (6.25-10.6)  | 7.8 (6.3-9.6)    | 8.2 (6-12.6)        | 0.63     |
| Eh, %                                | 0.44 (0.32-0.58) | 0.43 (0.33-0.5)  | 0.49 (0.31-0.67)    | 0.45     |
CO, cardiac output; CVP, central venous pressure; Ea, arterial elastance; Ees, left-ventricular end-systolic elastance; Eh, global cardiac efficiency; HR, heart rate; LVEF, left-ventricular ejection fraction; Lveff, left-ventricular ejection efficiency; MAP, mean arterial pressure; PE, potential energy; Pmsa, mean systemic pressure analogue; PPV, pulse pressure variation; Pvr, venous return pressure; SBP, systolic blood pressure; SV, stroke volume; SVV, stroke volume variation; SW, stroke work; VA, ventriculoarterial; VR, venous return. *P-values compared between survivors vs. non-survivors, and were calculated with the use of Mann-Whitney U test and Fisher’s exact test. Data are median (interquartile range) for continuous variables.

**Table 3.** Effects of increasing norepinephrine dosage and fluid bolus on hemodynamic parameters.
|               | Baseline-1 | Post-NE | p-value* | Baseline-2 | Post-Fluid | p-value** |
|---------------|------------|---------|----------|------------|------------|----------|
| SBP, mmHg     | 112 (101-134) | 138 (113-145) | <0.001   | 119 (103-136) | 129 (110-149) | 0.002    |
| DBP, mmHg     | 54 (50-59) | 59 (57-63) | <0.001   | 54 (51-61) | 59.5 (56-65) | 0.003    |
| MAP, mmHg     | 74 (68-80) | 82 (78-87) | <0.001   | 74 (70-82) | 81 (75-85) | 0.004    |
| HR, /min      | 93 (77-103) | 92 (75-104) | 0.53     | 92 (75-103) | 92 (75-102) | 0.93     |
| CVP, mmHg     | 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)  | 0.11     | 5.5 (3-8.5) | 5 (3-8)    | 0.49     |
| SVV, %        | 7 (5-9)      | 6 (4-8)    | 0.40     | 7 (4-10)    | 5.5 (4-8)  | 0.34     |
| LVEF, %       | 54 (45-67)   | 52 (48-70) | 0.18     | 50 (45-66)  | 55 (46-69) | 0.12     |
| SV, mL        | 62 (48-80)   | 66 (54-88) | 0.001    | 64 (49-80)  | 72 (52-82) | 0.011    |
| CO, L/min     | 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, mmHg/mL   | 1.7 (1.5-2)  | 1.8 (1.51-2.04) | 0.19     | 1.72 (1.4-2.03) | 1.77 (1.57-1.98) | 0.314    |
| Ees, mmHg/mL  | 2.19 (1.64-2.71) | 2.11 (1.49-2.95) | 0.20     | 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)  | 0.91     | 0.9 (0.6-1.1)  | 0.81 (0.65-0.98) | 0.067    |
| SW, mmHg mL   | 6481 (4545-9284) | 8251 (5981-11117) | <0.001  | 7197 (4604-9517) | 9037 (5039-11452) | <0.001    |
| PE            | 2656 (2037-3724) | 3304 (2348-4091) | 0.79     | 2659 (2218-3586) | 2880 (2456-3808) | 0.62     |
| Lveff, %      | 0.69 (0.63-0.77) | 0.69 (0.63-0.77) | 0.69     | 0.69 (0.64-0.77) | 0.71 (0.67-0.75) | 0.62     |
| **VR-related parameters** |
| Pmsa, mmHg    | 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, mmHg     | 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) | 0.12     |
| Eh, %         | 0.45 (0.33-0.55) | 0.45 (0.33-0.55) | 0.33     | 0.45 (0.33-0.55) | 0.45 (0.33-0.55) | 0.33     |
CO, cardiac output; CVP, central venous pressure; Ea, arterial elastance; Ees, left-ventricular end-systolic elastance; Eh, global cardiac efficiency; HR, heart rate; LVEF, left-ventricular ejection fraction; Lveff, left-ventricular ejection efficiency; MAP, mean arterial pressure; NE, norepinephrine; PE, potential energy; Pmsa, mean systemic pressure analogue; PPV, pulse pressure variation; Pvr, venous return pressure; SBP, systolic blood pressure; SV, stroke volume; SVV, stroke volume variation; SW, stroke work; VA, ventriculoarterial; VR, venous return. P-values were calculated with the use of Wilcoxon signed rank test. Data are median (interquartile range) for continuous variables, *p-values compared between baseline-1 vs. post-increased NE dosage. **P-values compared between baseline-2 vs. post-fluid bolus.

**Effects of increased norepinephrine (NE) dosage and fluid bolus**

Compared to baseline-1, post-increased NE phase significantly had higher SBP, DBP, MAP, CVP, SV, SW, PE, Pmsa, and Pvr. Likewise, compared to baseline-2, post-fluid bolus had 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 (Fig. 3). Interestingly, we found that either increased NE dosage or fluid bolus, changes in CO was significantly correlated with changes in Pvr ($R^2 = 0.85, p < 0.001$ and $R^2 = 0.84 p < 0.001$ respectively) (Supplemental Fig. 1). Effects of increased NE dosage and fluid bolus on left ventricular pressure-volume relationship diagram and venous return to cardiac output diagrams were summarized in Fig. 4 and Fig. 5.

**Differences in hemodynamic parameters between survivors vs non-survivors**

Baseline VA coupling-related parameters and venous return-related parameters were not significantly difference between survivors and non-survivors (Table 2). In non-survivors, there was a trend 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 non-survivors (0.71 vs. 0.63 %, p = 0.075).

**Discussion**

We demonstrated physiologic study to demonstrate hemodynamic response following increased NE dosage and fluid bolus in resuscitated normotensive septic shock patients with persistent hyperlactatemia. The mortality of patients in our study (35%) closed to previous studies [1, 21]. Regards
to VA coupling, previously studies demonstrated that cardiovascular function is optimal when cardiac and arterial system are coupled, meaning that $\frac{E_a}{E_{es}}$ is near the unity or close to 1.0 [13]. $\frac{E_a}{E_{es}}$ is widely used as determinant of VA coupling, it was found that an optimal $\frac{E_a}{E_{es}}$ is of $1 \pm 0.36$, while normal range of $E_a$ and $E_{es}$ are $2.2 \pm 0.8$ mmHg/mL and $2.3 \pm 1$ mmHg/mL respectively [23, 24, 31]. In this study, we found that average VA coupling was within normal range [$0.89 (0.61–1.16)$]. Our finding contradicts to previous studies in early phase of septic shock patients, they demonstrated more proportion of VA decoupling (defined as $\frac{E_a}{E_{es}} > 1.36$) in septic shock patient than non-septic shock patients. ($\frac{E_a}{E_{es}} 1.81$ vs. 1.07, $p = 0.01$) [24]. The possible explanation why $\frac{E_a}{E_{es}}$ in our septic shock patients had $\frac{E_a}{E_{es}}$ within normal ranges maybe because of our enrolled patients already received initial resuscitation until reaching acceptable MAP. Although tissue hypoperfusion existed from the evidence of hyperlactatemia in our patients, early macrocirculation support by adequate fluid resuscitation, evidence by low PPV and SVV values at baseline as well as NE receiving before enrolment may provide “acceptable” couple between cardiac and arterial system, and resulted in absence of VA decoupling in our study.

NE is a first-line recommended vasopressor for restoration of MAP in septic shock [4]. As a result of complex effects of NE on contractility, cardiac loading condition, and affecting both arterial and venous systems, in this study we found several hemodynamic parameters changed from increased NE dosage (Table 3). NE not only significantly increase arterial blood pressure (ABP) including SBP, DBP, and MAP from baseline (Fig. 4) but also increased venous return related-parameters such as Pmsa and CVP (Fig. 5). However, effect of NE is more prominent on Pmsa than CVP; hence increased NE also increased $P_{vr}$. In addition, we also found that changing in CO correlated with changing in $P_{vr}$ (Supplemental Fig. 1). Similar to previous study [10], presumably, increasing NE could convert unstressed volume into stressed volume and causes increasing of VR and cardiac preload as previously mentioned in several studies [10, 25–28]. However, we found no significant difference in $E_a/E_{es}$ compared between baseline-1 and post-NE while previous study found that NE worsen VA coupling [10]. This maybe result from difference dosage of NE infusion between our study and previous studies. Also, one septic shock patient in our study had no response (MAP increased less than 10% from baseline) to increasing NE dosage even a maximum limit was reached. So, the effects of increased NE dosage on $E_a$ in our study was not clearly found.

In terms of the effects of fluid bolus on VA coupling-related parameters and VR-related parameters, in our study we 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 more Pmsa than CVP (Fig. 5). Increasing $P_{vr}$ allow more venous blood return to the right atrium, so SV was increased significantly even most of our patients were volume non-responder at the baseline. Moreover, we also found that fluid bolus also significantly increased $E_{es}$ and had a trend to increase $L_{veff}$. Presumably, increasing MAP may improve coronary perfusion causing increased $E_{es}$ and $L_{veff}$ [10].

Interestingly, we found that, compared to survivors, non-survivors had a trend toward a higher $\frac{E_a}{E_{es}}$ ($1.18$ vs. 0.84, $p = 0.075$) and a trend of higher $E_a$ ($1.96$ vs. 1.57 mmHg/mL, $p = 0.09$) while there was no
difference in NE-dosage requiring at enrollment (0.09 vs 0.1mcg/kg/min, p = 0.93). A trend toward high Ea/Ees possibly result from trending higher Ea in non-survivors. As higher Ea reflect a higher degree of arterial vasoconstriction, non-survivors may exhibit a higher sympathetic response to more endogenous catecholamine release or exogenous catecholamine (NE) requirement than survivors. However, regards to Ea/Ees, there was no statistically significant difference between survival vs. non-survival, this finding aligned to previous studies that there was no difference in Ea/Ees when compared between survivors and non-survivors [10].

Although our study included the patients with adequate sample size and demonstrated physiologic alterations in cardiovascular system based on VA coupling and VR physiology. This study had some limitations. Firstly, we did not record hemodynamic parameters before initial resuscitation phase. Thus, we cannot compare hemodynamic parameters between before- vs. after- hemodynamic resuscitation. We also unable to demonstrate whether VA decoupling occurred before resuscitation. However, following resuscitation, we found that most of our patients had normalized VA coupling with average Ea/Ees of 0.89. Secondly, the single-beat method [19] estimation of Ees had been does not take into consideration the curvilinear shape of elastance curve which could be misleading in severe cardiologic condition. However, average Ees of our patients were within normal limit (2.19 mmHg/mL). So, cardiac contractility may not be depressed enough to reach curvilinearity. Thirdly, previous study concerns that NE may worsen VA coupling [10]. In our study, for patient’s safety protocol, we had a limitation of added NE dosage at 8 mcg/min. There is one case which added NE reaching the maximum limit. However, patient’s MAP did not change from the baseline and there was no adverse effect of NE occurred to this patient. Included this patient may causes underscore the effect of norepinephrine. Fourthly, we just studied these hemodynamic parameters changing in short period of interventions. Finally, our results cannot be interpreted in very early phase of septic shock or non-distributive shock.

Conclusions

In normotensive septic shock patients with persistent hyperlactatemia, we found average Ea/Ees of 0.89. Neither increasing NE dosage nor fluid bolus can 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. There was no difference in Ea/Ees between survivors and non-survivors in our study. Further large study is needed to validate our findings.

Declarations

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AUTHORS’ CONTRIBUTIONS
DS, WT and PW designed the study. DS and PW managed data and its quality. DS and PW performed the statistical analysis. DS, WT and PW participated in the data analysis and helped to draft the manuscript. All authors read the manuscript carefully and approved the final version.

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**DATA AVAILABILITY**

The datasets used for the analysis in the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee Institutional Review Board of Royal Thai Army Medical Department (R206h/63).

**Consent for publication**

All the text, figures and tables in this study are original. The manuscript has been read and approved for submission and publication by all authors.

**Competing interests**

The authors declare that there is no conflict of interest.

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Figures

**Figure 1**

(A) Biplane method in the apical four chamber view for measuring left ventricular end-diastolic volume (EDV), left ventricular end-systolic volume (ESV) and calculating left ventricular ejection fraction (LVEF). (B) Aortic doppler waveform in apical five chamber view for calculating stroke volume (SV), pre-ejection time (green solid line), and total ejection time (red line).
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 left ventricular pressure volume loop. Left ventricular ejection efficiency (LVeff) is the ratio of SW/SW+PE.
Figure 3

Individual arterial elastance/left ventricular end-systolic elastance (Ea/Ees) at 4 time points were demonstrated as continuous lines. Median Ea/Ees of survivors represented in dashed blue lines (0.84, 0.75, 0.84, and 0.78, respectively) and non-survivors’ Ea/Ees represented in dashed red line (1.18, 0.97, 1.03 and 0.88, respectively).

Figure 4
Hemodynamic parameters as left ventricular pressure-volume relationship diagram at baseline-1, post-increased norepinephrine (NE) dosage, baseline-2, and post-fluid bolus phases. *P<0.05, compared between baseline-1 vs. post-increased NE. ** P<0.05, compared between baseline-2 vs. post-fluid bolus.

**Figure 5**

Venous return to cardiac output (CO) diagrams at 4 phases. * P<0.05, compared between baseline-1 and after increased norepinephrine (NE). **P<0.05, compared between baseline-2 and after fluid bolus.

**Supplementary Files**

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