Effects of excess fluid administration and dehydration treatment on venous return in canine model of septic shock

Wei Du, Jianhua Sun, Huan Chen

Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Dongcheng District, Beijing 100730, China.

To the Editor: Current guidelines recommend resuscitation with ≥30 mL/kg of crystalloid fluid immediately upon recognition of septic shock patients.[1] However, compliance with sepsis bundles requiring fluid administration to pre-specified goals has failed to improve mortality when compared with non-protocolized resuscitation.[2] An inappropriate fluid administration dosage, whether insufficient or excessive, will increase the risk of harm. To our knowledge, few studies have been performed to evaluate the hemodynamic status during standard fluid resuscitation, fluid overload, and dehydration treatment in sepsis. Additionally, little is known about the relationship between fluid administration and altered hemodynamic states, especially changes in venous return, in sepsis. The usefulness of the mean systemic filling pressure (Pmsf) in guiding hemodynamic therapy has been investigated in recent studies. The mean systemic filling pressure (Pmsf) is determined by both vascular filling and vascular tone and the difference between Pmsf and central venous pressure (CVP) represents the driving pressure for the return of blood to the heart and thus for cardiac output (CO).

In the present study, we achieved a negative balance by administering bolus infusions of furosemide. Objective of the present study is to examine the hemodynamic changes especially in venous return that occurred with fluid administration, including standard fluid resuscitation, fluid overload, and step-by-step dehydration treatment can improve hemodynamics, in a canine model of sepsis.

This study involved 16 adult mongrel dogs (age: 1–2 years; weight: 30.8 ± 0.3 kg). The animals were fasted for 12 h before the start of the experiment and had free access to water. The study was carried out according to the Guidelines for the Care and Use of Laboratory Animals. All experiments were approved by the Experimental Animal Department of Peking Union Medical College Hospital (Beijing, China) Care and Use Committee (XHDW-2019-002).

All animals were anesthetized and analgesic was titrated to maintain adequate surgical anesthesia. Ventilation was accomplished using the constant-pressure mode of the 840 Ventilator system (Nellcor Puritan Bennett Ireland, Dublin, Ireland). The initial parameters were set at a tidal volume of 8 mL/kg without any spontaneous breath, positive end-expiratory pressure of 5 cmH$_2$O, and fraction of inspired oxygen of 28%.

Hemodynamic variables were measured at baseline. The 16 animals were randomly divided into two groups ($n = 8$ in each group) according to random number table: (1) after induction of acute endotoxemia and three 30-mL/kg volume expansions and (2) after dehydration by three 10-mL/kg bolus injections of furosemide. No vasopressor drug support was used for the overall procedure. Baseline was defined as the time point at which the hemodynamics had been stable for at least 30 min after completion of anesthetic preparation. Endotoxemia was induced with a 2-h infusion of a total dose of 5.3 µg/kg of *Escherichia coli* endotoxin, serotype 055:B5 (Sigma, St. Louis, MO, USA) dissolved in 6 mL of saline. The initial infusion rate was 5 µg·kg^{-1}·h^{-1} for 5 min followed by 2.5 µg·kg^{-1}·h^{-1}. The control group received a 5% glucose solution at 5 mL/h.[3] The endotoxemia state was defined as a 40 mmHg decrease in the mean arterial pressure (MAP) compared with the baseline state, and then we collected the variables in the endotoxemia state. The animals underwent fluid resuscitation with 30 mL/kg of compound sodium chloride injection given >1 h, and all variables were recorded; this was termed the fluid resuscitation (FR)-30 mL/kg state. The animals then received another two 30-mL/kg fluid resuscitation treatments within 1 h (termed the FR-60 mL/kg and FR-90 mL/kg states, respectively). Next, all animals received 20 mg of intravenous furosemide, and when the urine output reached 10 mL/kg, we used a urine collector to measure urine volume every hour, and all variables were recorded; this was considered to be a state of negative balance (NB-10 mL/kg state).

Correspondence to: Wei Du, Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China
E-Mail: pink_dallas@126.com

This protocol was repeated until the urine output reached 20 mL/kg (termed the NB-20 mL/kg state) and 30 mL/kg (termed the NB-30 mL/kg state). Figure 1A shows a flowchart of the study protocol.

Hemodynamic measurements were performed with the PiCCOplus® device (Pulsion Medical Systems, Munich, Germany). The heart rate, systolic blood pressure, diastolic blood pressure, MAP, and CVP were continuously monitored and recorded. At each measurement time point, two 15-mL bolus injections of 4°C normal saline were administered.

We constructed venous return curves and arterial blood flow curves by measuring the steady-state arterial pressure, CVP, and CO during the final 2 s for a set of four 8-s

inspiratory hold maneuvers at inspiratory pressures of 5, 15, 25, and 35 cmH$_2$O.[4]

We used tissue microdialysis of the muscle to check for pathological tissue hypoperfusion. Microdialysis samples were collected and analyzed for lactate (lactate$_{muscle}$) and pyruvate (pyruvate$_{muscle}$) using a bedside analyzer (CMA 600 Microdialysis Analyzer; CMA Microdialysis AB). The L/P ratio was defined as lactate$_{muscle}$/pyruvate$_{muscle}$ × 1000.

Statistical analyses were performed using SPSS 21.0 (IBM, Armonk, NY, USA). All quantitative data had a normal distribution and are shown as the mean and standard deviation (SD). Comparisons of data among the two groups were performed using the paired samples t test. For each animal measurement, linear regressions for the four
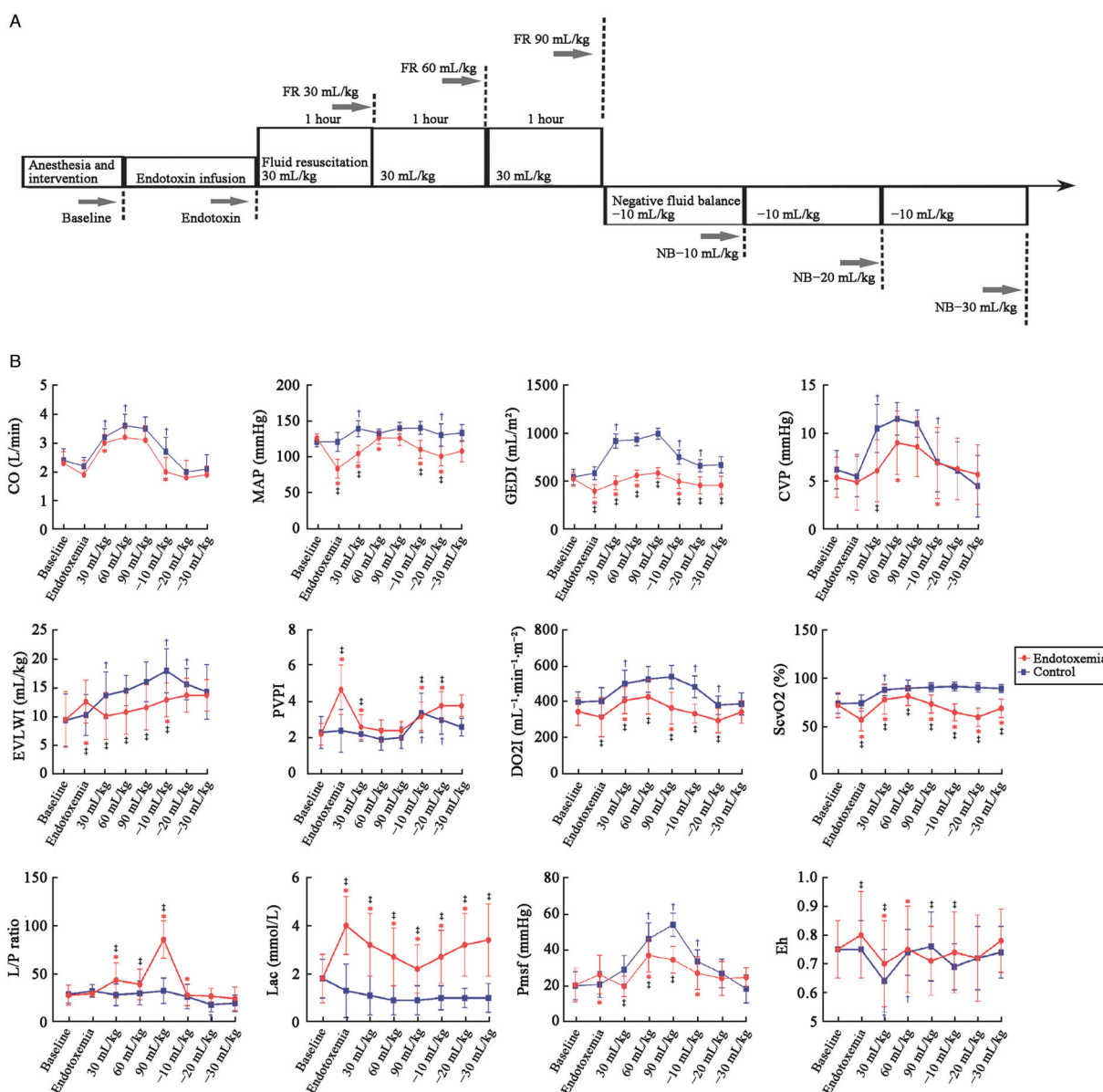

Figure 1: (A) Flowchart of study protocol. (B) Hemodynamic variables in each group; tissue perfusion variables in each group; and Pmsf and Eh in each group. $^*P < 0.05$ *vs.* previous state in endotoxemia group; $^†P < 0.05$ *vs.* previous state in control group; and $^‡P < 0.05$ endotoxemia group *vs.* control group. CO: Cardiac output; CVP: Central venous pressure; DO2I: Oxygen supply index; Eh: Cardiac efficiency; EVLWI: Extravascular lung water index; FR: Fluid resuscitation; GEDI: Global lobal end-diastolic volume index; Lac: Lactic acid; L/P ratio: Lactatemuscle/pyruvatemuscle ×1000; MAP: Mean arterial pressure; NB: Negative balance; Pmsf: Mean systemic filling pressure; ScvO2: Central venous oxygen saturation.

pairs of CVP and CO, Pa and CO were fitted using the least-squares method. The strength of the correlation between variables was measured with Pearson's rank coefficient. Data are presented as the mean ± SD unless otherwise stated. Differences with a P value <0.05 were considered statistically significant.

In the endotoxemia group, CO was increased only in the FR-30 mL/kg state ($P = 0.006$). The Pmsf was higher in FR-60 mL/kg than FR-30 mL/kg state ($P = 0.025$). Dogs in the endotoxemia group showed a lower CO ($P = 0.019$), higher extravascular lung water index (EVLWI) ($P = 0.040$), and pulmonary vascular permeability index (PVPI) ($P = 0.007$) in the NB-10 mL/kg than FR-90 mL/kg state. In the univariate analysis, we found a significant difference in Pmsf according to CO, PVPI, lactate, and stroke volume variation.

Other results and trends are shown in the [Figure 1B and Supplementary Tables, http://links.lww.com/CM9/B386].

We found that CO does not increase when fluid therapy was from 60 to 90 mL/kg, consider that is because the fluid resuscitation entering a plateau on the Frank-Starling curve. Unexpectedly, however, both the control group and the endotoxemia group showed a significant decrease in CO with tissue perfusion deterioration when given a small dose of dehydration after excessive hypervolemic resuscitation. Some physiological experiments have shown that reducing the circulating volume can increase the CO; this is called the diastolic ventricular interaction phenomenon.[5] If the right ventricular overfilling reduced, the left ventricular CO will increase. Few reports have described treatment through dehydration with volumetric overload in sepsis. In the present study, however, the sepsis model had no right ventricular changes and may not have benefited from improving the right ventricular diastolic function. Thus, we hypothesized that dehydration after fluid overload can improve hemodynamics by involving right ventricular dysfunction or chronic capacity overload. However, the result of our study is not to suggest the clinician not to dehydrate in a canine model of sepsis with volumetric overload. The clinical significance of our study is that it shows that clinicians should be extremely careful to avoid volume overload during fluid treatment because the expense of dehydration is a decrease in CO and deterioration of tissue perfusion.

Two results of our study are particularly interesting. First, in the endotoxemia group, the EVLWI increased with fluid resuscitation from 30 to 90 mL/kg, but it then unexpectedly continued to increase after treatment with dehydration. Second, in all states from fluid resuscitation to dehydration, the EVLWI was almost consistently higher in the control group than endotoxemia group. The EVLWI in the endotoxemia group continued to increase from fluid resuscitation to the negative balance state, and the highest hydrostatic pressures for both CVP and Pmsf appeared at FR-60 mL/kg. This suggests that even when the circulating hydrostatic pressure decreases after the alveolocapillary barrier is broken, an increase in the EVLWI cannot be avoided. Additionally, in clinical practice, if the alveolocapillary barrier is damaged and has not yet been repaired, the circulating hydrostatic pressure must be strictly monitored and maintained at an acceptable low level. We also found that the EVLWI was higher in the control group than endotoxemia group, while the hydrostatic pressure was higher in the control group than endotoxemia group with infusion of the same amount of fluid.

The Pmsf was lower in the endotoxemia group than control group in each period of fluid therapy. Septic vasoplegia leads to an increase in unstressed volume, decreasing the Pmsf because many previously non-perfused vascular beds receive blood flow. This may indicate that the EVLWI is more significantly affected by an increase in hydrostatic pressure than by destruction of the alveolocapillary barrier in sepsis, but a series of quantitative studies will be required for confirmation.

We found a negative correlation between the PVPI and Pmsf, which could mean that if the PVPI increases, substantial capillary leakage has occurred and high hydrostatic pressure cannot occur in the circulation. We also found that the Pmsf was negatively correlated with the lactic acid concentration. This suggests that if an increased PVPI is found, the Pmsf as an indicator of hydrostatic pressure should be monitored more frequently during fluid treatment.

If volume overload occurs during fluid resuscitation for septic shock, Pmsf and EVLWI will be increase, after the treatment by dehydration may cause a decreased CO, increased EVLWI, and tissue perfusion deterioration. The clinical significance is that in fluid management for sepsis, prevention of fluid overload is far more important than treatment of fluid overload.

Funding

Conflicts of interest

None.

References

1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304–377. doi: 10.1007/s00134-017-4683-6.
2. Rhee C, Jones TM, Hamad Y, Pande A, Varon J, O'Brien C, et al. Prevalence, underlying causes, and preventability of sepsis-associated mortality in US acute care hospitals. JAMA Netw Open 2019;2:e187571. doi: 10.1001/jamanetworkopen.2018.7571.
3. Belenkie I, Sas R, Mitchell J, Smith ER, Tyberg JV. Opening the pericardium during pulmonary artery constriction improves cardiac function. J Appl Physiol 2004;96:917–922. doi: 10.1152/japplphysiol.00722.2003.
4. Du W, Liu D, Long Y, Wang X. The (-blocker esmolol restores the vascular waterfall phenomenon after acute endotoxemia. Crit Care Med 2017;45:e1247–e1253. doi: 10.1097/CCM.0000000000002721.
5. Williams L, Frenneaux M. Diastolic ventricular interaction: from physiology to clinical practice. Nat Clin Pract Cardiovasc Med 2006;3:368–376. doi: 10.1038/ncpcardio0584.