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Effect of acute endotoxemia on analog estimates of mean systemic pressure☆,☆☆

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Abstract Dynamic estimates of mean systemic pressure based on a Guytonian analog model (Pmsa) appear accurate under baseline conditions but may not remain so during septic shock because blood volume distribution and resistances between arterial and venous beds may change. Thus, we examined the effect of acute endotoxemia on the ability of Pmsa, estimated from steady-state cardiac output, right atrial pressure, and mean arterial pressure, to reflect our previously validated instantaneous venous return measure of mean systemic pressure (Pmsi), derived from beat-to-beat measures of right ventricular stroke volume and right atrial pressure during positive pressure ventilation. We studied 6 splenectomized pentobarbital-anesthetized close chested dogs. Right ventricular stroke volume was measured by a pulmonary arterial electromagnetic flow probe. Instantaneous venous return measure of mean systemic pressure and Pmsa were calculated during volume loading and removal (±100-mL bolus increments ×5) both before (control) and 30 minutes after endotoxin infusion (endo). Cardiac output increased (2628 ± 905 vs 3560 ± 539 mL/min; $P < .05$) and mean arterial pressure decreased (107 ± 16 vs 56 ± 12 mm Hg; $P < .01$) during endo. Changes in Pmsi and Pmsa correlated during both control and endo ($r^2 = 0.7$) with minimal bias by Bland-Altman analysis (mean difference ± 95% confidence interval, 0.47 ± 5.04 mm Hg). We conclude that changes in Pmsa accurately tracts Pmsi under both control and endo.

1. Introduction

The accurate assessment of cardiovascular state in the critically ill is difficult because easily measured hemodynamic variables, such as blood pressure and cardiac output (CO), can coexist with different levels of ventricular pump function, vasomotor tone, and effective circulating blood volume. Although fluid resuscitation therapy is important in the management of unstable patients, excessive fluid resuscitation can be harmful in acute lung injury [1], head injury [2], and postoperative patients [3]. Thus, a measure of effective volume status and its change in response to therapy is useful to avoid volume overload because even volume-overloaded patients may remain volume responsive.

Mean systemic pressure (Pms) is a direct measure of the effective circulating blood volume, being dependent on

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absolute blood volume, systemic vascular compliance, and unstressed vascular volume, all of which may change rapidly in the critically ill patient. Operationally, Pms is the pressure anywhere in the circulation during circulatory arrest and is the upstream pressure driving venous return [4]. We have previously shown that Pms can be measured in ventilator-dependent animals during positive pressure breathing plotting right ventricular stroke volume (SV_{RV}) to right atrial pressure (Pra) extrapolating to zero SV_{RV} [5] and in patients using inspiratory hold maneuvers defining Pra/CO data pairs extrapolating to zero CO [6]. This calculated Pms parameter accurately follows changes in intravascular volume in dogs under baseline and endotoxic conditions [5,7] and in postoperative cardiac surgery patients [6]. Unfortunately, beat-to-beat measures of SV_{RV} require accurate measures of instantaneous pulmonary blood flow, and inspiratory hold technique maneuvers require several minutes to complete the multiple steps in a sedated and ventilated patient. Thus, these techniques are not readily applicable to frequent sequential measures in critically ill patients.

Other more simple methods have been proposed to estimate Pms at the bedside. Anderson [8] hypothesized that the circulation of the arm behaves similar to total systemic circulation during steady-state conditions with venous flow behaving as if its upstream pressure is Pms. Accordingly, transient stop-flow forearm arterial and venous equilibrium pressure was referred to as arm equilibrium pressure (Parm). This technique has the advantage of being simpler than the inspiratory hold technique but still can be measured only intermittently. Similarly, Parkin and Leaning [9] proposed to estimate effective circulatory volume based on an electrical analog simplification of Guytonian circulatory physiology estimating mean circulatory pressure (Pmsa) from directly measured Pra, mean arterial pressure (MAP), and CO. We recently compared the measures of Pms using inspiratory hold, Parm and Pmsa, to each other in 16 postoperative surgical patients [10]. We saw that inspiratory hold–derived Pms and Parm were similar but that Pmsa displayed a systematic bias, which could be corrected for. Importantly, Pmsa changes faithfully tracked Pms changes in response to fluid challenges independent of this bias. Because Pmsa can be calculated continuously if CO, MAP, and Pra are continuously monitored, it offers the potential to have a continuous online assessment of effective circulatory blood volume, cardiac performance, and vasomotor tone, the 3 primary determinants of cardiovascular state.

We hypothesized that Pmsa would accurately track instantaneous venous return measure of mean systemic pressure (Pmsi) under baseline conditions but may become imprecise following the induction of endotoxic shock because of the recently documented changes in peripheral vascular compliance during the induction of acute endotoxic shock [11]. Thus, we compared the ability of Pmsa to track Pmsi using our previously acquired and validated data from an intact canine model during fluid volume and removal before and after the endotoxin of acute endotoxemia.

2. Methods

We performed a retrospective analysis of the high-quality hemodynamic data from a subset of 6 mongrel dogs used in a previous publication from our group [7]. Those data sets allowed the calculation of Pmsi and Pmsa during each volume loading/removal step and before and during acute endotoxemia. The details of the surgical procedure and data collection have been previously described and validated by us [5,7]. Briefly, after approval by our Institutional Animal Care and Use Committee, 6 mongrel dogs were anesthetized with intravenous pentobarbital sodium (30 mL/kg) and intubated with a 9.0-mm ID cuffed endotracheal tube equipped with a distal port to measure airway pressure. Intermittent positive pressure ventilation was accomplished by a constant volume (10 mL/kg) ventilator (Harvard Apparatus, Cambridge, MA) with enriched inspired O_2. Following a midline sternotomy, a calibrated electromagnetic flow probe (Carolina Medical, East Bend, NC) was placed around the main pulmonary artery to measure SV_{RV}. Fluid-filled arterial, left atrial, and pulmonary artery catheters and a pleural air-filled balloon catheter were inserted allowing continuous measures of all vascular pressures both absolute and relative to pleural pressure (transmural pressure). The pericardium and chest were then closed in multiple layers. Following a 30-minute recovery period during which time there were no episodes of cardiovascular instability, arrhythmias, or excessive blood loss through the bilateral chest tubes (ie, <50 mL/h), the protocol was started.

2.1. Protocol

The protocol consisted of noting the effects of intermittent positive pressure ventilation (tidal volume, 10 mL/kg) on dynamic changes in SV_{RV} and Pra values across conditions as well as end-expiratory steady-state MAP, CO, and Pra values 5 minutes after each volume challenge or removal. Intravascular volume (0.9 N NaCl) was loaded in 100-mL increments up to a total administration of 500 mL and then removed as whole blood in 100-mL decrements. This maneuver was performed during the hemodynamically stable postoperative state (control) and after induction of a stable endotoxic state (endo). Acute endotoxemia was induced by an infusion of *Escherichia coli* lipopolysaccharide (endotoxin) (1 mg/kg) (single lot, 055:B5; Sigma Laboratories, St. Louis, MO) over a 5-minute period through the left atrial catheter. Fluid resuscitation with dextran (6% wt/vol) in 50-mL boluses was performed as necessary if end-expiratory SV_{RV} decreased to less than 50% control or MAP decreased to less than 50 mm Hg. Postendotoxin fluid requirements during this acute resuscitation interval varied widely across animals. All animals were stable following this resuscitation before starting the endo volume challenges.