

Case Series: A Description of the Pleth Variability Index in Patients with Septic Shock

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Abstract

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Pulse variability index (PVI) is a new functional hemodynamic measurement value that is noninvasive and has been shown to predict fluid responsiveness in critically ill patients. Few studies have examined the use of PVI in patients with severe sepsis or septic shock. This prospective case series described the pattern of PVI and continuous hemoglobin measurements during the initial resuscitation phase of newly diagnosed septic shock. PVI and PI were described in four patients with severe sepsis and/or septic shock (three men, age 52 ± 7 ; and one female, age 73). Therapies varied for each patient, including tidal volume, positive end expiratory pressure, vasopressor dose, and fluid boluses. Three patients received high dose norepinephrine. In these three patients norepinephrine influenced the PI, causing the PVI to increase but not because the patient was a fluid responder. In the patient not on high dose vasopressors the PVI increase did indicate fluid responsiveness. Three patients had a tidal volume less than 8 ml/kg; thus, the PVI may not adequately reflect if they will respond as these patients may not demonstrate as large a PVI due to the small changes in the intrathoracic pressure. This case

series suggests that PVI does not assist in identifying fluid response status in patients receiving vasopressor therapy and tidal volumes less than 8 ml/kg. There were not enough data to evaluate agreement in SpHb and lab hemoglobin. One patient showed perfect agreement with laboratory Hgb and the other patient had a clinically significant difference. Continued studies with larger sample sizes are needed in populations of severe sepsis and septic shock to determine the utility of this technology to guide fluid resuscitation. The PVI and PI may be useful to determine hypoperfusion in septic shock patients, but further studies are needed.

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DEDICATION

To my parents Janet and Kenny

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CHAPTER I: BACKGROUND

Approximately 750,000 individuals in North America develop severe sepsis each year. For those patients admitted to the intensive care unit, mortality continues to be as high as 60% ("Surviving Sepsis Campaign, "). Septic shock is defined as hypotension and lactic acidosis, or other indications of hypoperfusion, persisting after initial intravenous fluid resuscitation. Studies have shown that survival is significantly improved the more rapidly perfusion is restored and the lactate level is normalized (Kumar et al., 2004; Marik, Monnet, & Teboul, 2011; Osman et al., 2007). The initial treatment for a patient identified as having septic shock currently is a minimum of 20 ml/kg intravenous crystalloid infusion used for intravascular volume expansion. This volume of fluid is a minimum guideline suggested by the Surviving Sepsis Campaign. Currently there is no evidence based practice guideline that provides clinicians with the maximum amount of intravenous crystalloid or colloid to be infused; therefore, a quantitative value is needed by bedside practitioners guide practice and decisions about when to stop intravenous fluid resuscitation and begin vasopressor therapy.

Static indicators of preload status and the ability to respond to a fluid bolus with a clinically significant increase in stroke volume, such as central venous pressure (CVP), pulmonary arterial occlusion pressures (PaOP), and pulmonary artery end-diastolic pressure (PAEDP) have been shown to be inferior to functional hemodynamic parameters such as systolic pressure variation and pulse pressure variation (PPV)(Kumar et al., 2004). In studies that evaluated the efficacy of these static indicators to predict fluid responsiveness (i.e., a clinically significant increase in stroke volume [$> 10-15\%$] in response to a fluid bolus) approximately 50% of patients were fluid responders (Marik, Monnet, and Teboul, 2011), suggesting that the remaining patients were at increased risk for fluid volume overload. In contrast to static

indicators, functional hemodynamic indicators reflect respiratory changes in stroke volume and stroke volume derived parameters such as pulse pressure variation (PPV) and stroke volume variation (SVV). During inspiration right ventricular output is decreased (due to decreased venous return), followed by a decrease in left ventricular output, which is reflected as a variation in the arterial waveform. Variation in the arterial waveform is greatest in a mechanically ventilated patient is on the steep portion of the ventricular function curve, suggesting that if the patient is given a fluid bolus they will respond with a clinically significant increase in stroke volume and cardiac output. Alternately, when the patient is on the flat portion of the ventricular function curve, possibly suggesting hypervolemia, less variation is observed in the arterial waveform. A limitation of these functional hemodynamic indicators (SPV, PPV) is that they require the placement of an invasive arterial line.

Rivers et al. (2001) showed that patient outcomes were significantly improved with the use of early goal directed therapy (EGDT). A level one trauma center in the Pacific Northwest recently established an EGDT protocol for patients with severe sepsis or septic shock. The fluid resuscitation component of this protocol is guided by measures of lactate, CVP and central venous oxygen saturation (ScVO₂); the latter two measurements require the placement of a central venous catheter. The placement of a central venous catheter may optimize outcomes of these patients by providing the clinician with static hemodynamic variables such as CVP and continuous values such as ScVO₂, which aid in the identification of the end-point for intravenous fluid resuscitation. However, numerous articles have cited the poor relationship between CVP and blood volume as well as the inability of CVP to predict a patients response to an intravenous fluid challenge (Marik, Baram, and Vahid, 2008). Additionally, not all patients

admitted with septic shock have an arterial or central venous catheter to obtain real-time measurements of blood pressure, static hemodynamic measurements or functional hemodynamic parameters.

New proprietary technology (Masimo Rainbow 7, Masimo Corporation, Irvine, CA) has been developed to non-invasively obtain a functional hemodynamic measurement, specifically the ventilator-induced change in amplitude of a pulse oximeter waveform, known as the pleth variability index (PVI). The PVI is obtained noninvasively via a pulse oximeter probe on the patient's finger, whereas other dynamic methods (such as PPV, SPV, and stroke volume variation (SVV)) require the placement of an invasive arterial line. The PVI is derived via a mathematical equation utilizing the perfusion index (PI). The PI is a measurement obtained from a pulse oximeter, describing the difference in pulsatile and non-pulsatile blood flow at the monitoring site (typically the finger). The Masimo Rainbow 7 monitor was initially used in patients undergoing cardiac surgery (Cannesson, Delannoy, et al., 2008; Haas et al., 2012) and in the perioperative setting (Cannesson, Desebbe, et al., 2008; Cannesson, Sliker, et al., 2008; Forget, Lois, & de Kock, 2010; Hood & Wilson, 2011), but few studies have been published for patients diagnosed with severe sepsis or septic shock (Feissel et al., 2007).

A study published in 2009 described 25 septic shock patients and attempted to determine threshold values for PVI for fluid responders and nonresponders. Fluid challenges were given to patients with a PPV of > 15% (indicating the patient was likely to be a fluid responder) or a passive leg raise (PLR) maneuver was performed for patients whose PPV was <15% (indicating that they would not be fluid responders and might be harmed by the administration of additional fluids). A PVI threshold of 20% was found to differentiate fluid responders from

nonresponders(Feissel et al., 2009). In addition to PVI, the Rainbow 7 monitor also displays perfusion index (PI) and non-invasive hemoglobin (SpHb) values. This case series was designed to explore the potential to use the noninvasive PVI parameter to guide fluid resuscitation in the care of patients with septic shock.

Purpose

A prospective descriptive case series was undertaken to describe the changes in the PVI and continuous hemoglobin during the initial fluid resuscitation phase of the early goal directed septic shock protocol. Specific aims for studying PVI and continuous hemoglobin were to: 1) Describe the pattern of a non-invasive hemodynamic parameter (PVI) during the initial resuscitation period of severe sepsis or septic shock; 2) Determine the agreement, precision and correlation of continuous Hgb obtained from the Masimo Rainbow 7 (SpHb) with laboratory values during the study period.

CHAPTER II: Literature Review

Pleth Variability Index

The PVI is a functional hemodynamic indicator that is obtained noninvasively via a pulse oximeter probe placed on the patient's finger; The PVI is derived via a mathematical equation utilizing the perfusion index (PI). The PI is a measurement obtained from a pulse oximeter, describing the difference in pulsatile and non-pulsatile blood flow at the monitoring site (typically the finger). The PI is expressed as a ratio of the pulsatile pulse oximeter signal (AC) to the nonpulsatile signal (DC); therefore the equation is stated as $PI = AC/DC$. Limitations of the PVI to predict fluid responsiveness is dependent on the PI. Biais et al. (2011) described the influence of norepinephrine (NE) (a potent peripheral vasoconstrictor) on the ability of PVI to predict fluid responsiveness. In a study of 67 mechanically ventilated ICU patients, those who were receiving NE had a weak correlation when compared to PPV ($r^2 = 0.04$; $p > 0.05$). In contrast, patients who did not receive NE had a stronger correlation to ΔPP ($r^2 = 0.52$; $p < 0.001$) (Biais et al., 2011).

Pulse variability index has been most commonly measured intraoperatively to predict fluid responsiveness. A patient is generally considered a fluid responder if in response to a fluid bolus their cardiac index or stroke volume increases greater than 15%. A non-responder fails to demonstrate this response (i.e., increase in cardiac index or stroke volume $<15\%$). The operating room provides a controlled setting to evaluate the changes in PI and PVI as the patients are mechanically ventilated without spontaneous respiration. Studies suggest that while in the operating room under controlled circumstances, continuous monitoring of the PVI can distinguish between responders and nonresponders. Cannesson et al. (2005) demonstrated fluid

responsiveness with variations in the pulse oximetry plethysmographic (POP) waveform (Cannesson, Besnard, Durand, Bohé, & Jacques, 2005). Cannesson et al. (2008) compared PPV in cardiac surgery patients. After undergoing general anesthesia (tidal volume = 8-10 ml/kg/PEEP 0-2 cm H₂O) the patients received 500ml hetastarch 6% over 10 minutes. Following the bolus, changes in hemodynamic variables were recorded. Cardiac index (CI) increased from 2.0 ± 0.9 L/min/m² to 2.5 ± 1.2 L/min/m² and the indicators for fluid responsiveness decreased as would be expected: PPV ($14 \pm 7\%$ to $7 \pm 4\%$) and PVI ($14 \pm 7\%$ to $9 \pm 3\%$). A significant difference ($p < 0.01$) was found when comparing responders (R) and nonresponders (NR) after intravenous fluid boluses were administered. The following values represent thresholds for each respective category of responders and nonresponders: PPV (R $18 \pm 5\%$ /NR $7 \pm 4\%$, $p < 0.01$) and PVI (R $18 \pm 6\%$ /NR $8 \pm 4\%$, $p < 0.01$). Fluid responders were identified in patients receiving a tidal volume > 8 ml/kg as a PVI $> 13\%$ (Forget et al., 2010).

A study was conducted to determine if the PVI could be used to predict fluid response status in patients with septic shock (Feissel et al., 2009). In a study of 25 patients diagnosed with septic shock. Patients received either a fluid bolus or underwent passive leg raising and changes in aortic blood flow were used to evaluate their response to the fluid challenge. A PPV $> 15\%$ was established *a priori* as an indication of fluid responsiveness. A PVI of $> 20\%$ accurately classified responders from nonresponders. A PPV $> 15\%$ has a sensitivity of 84% and a specificity of 90% and a PVI of 20% was 100% specific and sensitive with respect to fluid responsiveness (Feissel et al., 2009). These studies describe the ability of the PVI to predict fluid responsiveness at a single time point in patients with severe sepsis and septic shock, but the

changes in PVI that occur during early goal directed therapy for septic shock, and its usefulness for potentially monitoring and guiding fluid resuscitation have not yet been described.

Noninvasive Hemoglobin (SpHb)

In addition to standard pulse oximetry, PVI and PI the Masimo Rainbow 7 measures and displays noninvasive continuous hemoglobin (SpHb). Patients in severe septic shock are at high risk for developing coagulopathies due to an activated Protein C deficiency and the subsequent development of a consumptive coagulopathy, such as disseminated intravascular coagulation. Patients who are treated with EGDT receive a minimum of 20-30 ml/kg of IV fluids, and are at risk for hemodilution and, blood transfusion recommendations are included in the EGDT guidelines if a patient remains hypoperfused and has a low hematocrit. No studies have reported the accuracy of SpHb compared to standard laboratory measurements of Hgb and Hct in this population.

The Masimo Rainbow 7 measures continuous hemoglobin (SpHb), which allows for the calculation of oxygen content ($\text{Hgb} \times 1.34 \times \text{SaO}_2$). The reported accuracy of the SpHb is 8-17 g/dl \pm 1 g/dL with a 0.1 g/dL resolution (Masimo Radical 7 Product Manual). Agreement and correlation of the noninvasive SpHb with laboratory Hgb has been demonstrated in surgical and trauma populations (Causey et al., 2011; Frasca et al., 2011). In 30 surgical patients and 18 healthy volunteers, Hgb was monitored using the Radical-7 compared to the total Hgb reported by a Radiometer ABL-735 co-oximeter (Radiometer America, Westlake, OH). The healthy subjects had one unit of blood removed, which was replaced with 39 ml/kg saline. Data were collected during surgery or the hemodilution protocol for the healthy subjects. Total hemoglobin ranged from 4.4 to 15.8 g/dl (mean 10.7 ± 2.2 g/dl). Based on 802 data points the bias was 0.03

g/dl and precision of 1.13 g/dl, %A_{RMS} 1.12, $r=0.882$ (Macknet, Kimball-Jones, Applegate, Martin, & Allard, 2007).

PVI has been shown to be useful in the operating room under controlled conditions to predict fluid responsiveness. Feissel et al. (2009) described the accuracy of PVI as an indicator of fluid responsiveness in septic shock patients similar to patients represented in this case series. In this case series, PVI and PI were described and SpHb was compared to laboratory Hgb values, which were measured as part of the standard of care of these critically ill patients.

CHAPTER III: Methodology

Design

A case series design was used to document changes in the PVI, PI, and noninvasive Hgb in patients with septic shock while they received rapid resuscitation with intravenous fluids. The PVI and PI were assessed utilizing the Radical 7, with a noninvasive probe placed on the ring finger of the non-dominant hand or the hand adjacent to where the hemoglobin values were drawn. After placement of the Masimo probe, an opaque shield covered the probe and finger to shield ambient light from interfering with the pulse oximeter. The opaque shield was supplied by Masimo Corp for purposes of this study. The goal of measuring the PVI was to determine the PVI before, during, and after rapid intravenous fluid administration. This study is the first to describe the PVI during resuscitation of patients with septic shock; thus, initiates a foundation for future research. Data were collected using a structured data collection form (see Appendices) as well as transferring real-time data to a laptop computer using proprietary software obtained from Masimo Corporation. The independent variables for this observational case series study were the intravenous fluid boluses and vasopressor agents (or changes in their respective doses). The dependent variables were PVI, SpHb, heart rate (HR), systolic blood pressure (SBP) and mean arterial pressure (MAP).

Sample

Descriptive variables collected were: diagnosis, suspected infectious source, height, weight, age, and gender. Patients who were admitted with the diagnosis of severe sepsis or septic shock, and met “code sepsis” criteria as defined by the level one trauma center’s “code sepsis” protocol were enrolled in this study. Nonprobability purposive sampling was used to identify

subjects who meet the specific criteria of septic shock, and were mechanically ventilated. This level one trauma center and safety net hospital serves the geographic region of: Washington, Wyoming, Alaska, Montana, and Idaho. The medical center serves a large number of high acuity patients who have been diagnosed with septic shock. Therefore, the patients in this case series were representative of the target population, as these methods would be utilized only on the highest acuity mechanically ventilated patients identified with characteristics consistent with severe sepsis or septic shock.

Eligible subjects were identified in the Emergency Department (ED) of the trauma center. The eligibility criteria for initiation of the sepsis bundle orders included inclusion of at least two of the four SIRS criteria and a suspicion of infection. The SIRS criteria are: 1) Temperature >38.0 C or <36.0 C; 2) Heart Rate >90 beats/min; 3) Respiratory rate >20 breaths/min, PaCO₂ <32 , or intubation for respiratory failure; 4) WBC count $>12,000/\text{mm}^3$, $<4000/\text{mm}^3$ or $>10\%$ immature (band) form. If a “code sepsis” was initiated by the ED, then a page was sent to a specified team of clinicians to immediately care for this respective patient. Members of this research team were included among the clinicians who receive this page. Subjects were transferred to the trauma center after being treated for septic shock and their septic condition had been resolved as evidenced by not meeting any of the aforementioned SIRS criteria were not included in the study. However, if a patient presented after being transferred from another medical facility and/or while they were admitted to the trauma center and met septic shock criteria they were included, and data were gathered during their respective resuscitation period.

Exclusion criteria were based on an existing research protocol designed by Dr. Elizabeth Bridges at the University of Washington School of Nursing. These criteria were age less than 18, pregnancy, cardiac arrhythmias (atrial fibrillation/flutter, frequent atrial or ventricular ectopy such that three ventilator sequences are not interrupted by ectopy), spontaneous ventilation (triggering ventilator), open chest, cor pulmonale, adjustment of ventilator parameters, vasoactive medications, or presence of an intraaortic balloon pump.

During the data collection period for this study, four patients who met inclusion criteria were identified and enrolled. Table 1 summarizes patient characteristics, diagnosis, and their outcomes.

Table 1. Patient characteristics and outcomes

	Age	Gender	Height (cm)	Weight (kg)	Dubois BSA (m ²)	Admit Diagnosis	Suspected Source of Infection	Outcome
Patient 1	45	M	182	92	2.13	Septic Shock	Lungs	Expired
Patient 2	59	M	178	53	1.66	DKA/Septic Shock	Lungs	To SNF
Patient 3	73	F	173	79	1.93	Septic Shock	UTI/Lungs	To SNF
*Patient 4	51	M	160	59	1.61	Septic Shock	Lungs	Inpatient

*At the time of this paper, this patient remains in critical condition in the ICU. Skilled Nursing Facility (SNF), Diabetic Ketoacidosis (DKA), Urinary Tract Infection (UTI)

Measures

A data collection form developed by the PI, was used to record study variables listed on the data collection sheet, in addition to the information obtained from the Masimo Rainbow 7 pulse oximeter. The Masimo Set Rainbow 7 is a FDA approved device that provides noninvasive

measures of PVI and continuous hemoglobin (SpHb). The pulse oximeter probe (Rev E) was connected to the Masimo Radical 7 monitor (Masimo SET, Masimo Corp.) with PVI software (version 7.0.3.3) and hemoglobin software (7.6.2.1). Sensitivity and specificity with respect to identifying those patients who are responders and nonresponders to infusion of IV fluid boluses are reported in the literature (Cannesson, Desebbe, et al., 2008; Cannesson, Sliker, et al., 2008; Feissel et al., 2007). The reported accuracy of the SpHb is 8-17 g/dl \pm 1 g/dl resolution (Masimo Radical 7 Product Manual). The validity and reliability of the noninvasive SpHb has been demonstrated in several studies (Causey et al., 2011; Frasca et al., 2011; Macknet, Kimball-Jones, Applegate, Martin, & Allard, 2007; Macknet, Allard, Applegate, & Rook, 2010).

Procedures

The Principal Investigator obtained approval from the thesis chair and committee. The committee members evaluated the data collection tool and procedures to ensure clarity, and accuracy regarding the original IRB study completed by Dr. Bridges, Associate Professor and Clinical Nurse Researcher at the University Of Washington School Of Nursing. After obtaining approval from the thesis committee a modification form (version 3.91) was completed and reviewed by committee member Dr. Bridges; thereafter submitted to the University of Washington Human Subjects Division for approval. The original study which received minimal risk review and approval was granted a waiver of consent by the IRB on September 26, 2007. While awaiting IRB approval, this proposed research study was presented to the Nursing Research Committee at the level one trauma center and received approval. After obtaining approval from the University of Washington IRB and the Nursing Research Committee the PI provided documentation of confidentiality training (HIPAA) and submitted this statement. Post-

hoc consent was obtained for each individual patient, by either themselves (n=1) or their prescribed legal representative (n=3).

Training was obtained from committee member Dr. Elizabeth Bridges and a clinical specialist from Masimo Corporation. Training received from Dr. Elizabeth Bridges consisted of adherence to the original study protocol from which this study was derived from; thus, ensuring intrarater reliability for the data collected from this study. Massimo Corp. provided training specific to the Masimo Rainbow 7 pulse oximeter, which has the ability to measure PVI and continuous hemoglobin. The PI is employed by the trauma center as a Registered Nurse and did not need additional training of ORCA (the electronic medical records system) to extract patient specific data listed on the data collection form. The PI obtained a pager and was added to the “code sepsis” group page, to facilitate patient enrollment in the study.

During the data collection phase, chart data were accessed from each subject from a computer workstation within the nursing unit which the patient resided. Patient information was protected at all times and only de-identified data were recorded on the tool. Data collected from the Masimo Rainbow 7 pulse oximeter were downloaded to a dedicated laptop computer. This computer, along with the codes that link the de-identified data with the subject’s records were kept in a locked file and secure area of the trauma center.

Analysis

As described in Table 1, descriptive data on four patients were collected. All data collected from the Masimo pulse oximeter is presented as a 5 minute continuous average. Raw data were cleaned prior to obtaining the 5 minute average. Missing data were identified as a “zero” when downloaded. These ‘zeros’ were not included in the average, and are shown

graphically as gaps in the continuous linear representation in Figures 1 through 4. Changes in hemodynamic measures induced by fluid boluses are displayed on the individual graphs, as well as lactate and CVP measurements recorded during the study period.

Each case presented below includes background information, inclusion criteria met respective of each case, duration of data collection, an explanation of interventions, and rationale for the trends reported on each respective figure. If hemoglobin data were collected that is also discussed in terms of agreement between the SpHb and laboratory Hgb. Patient characteristics, diagnosis, and outcomes are displayed on Table 1.

Ethics

The PI accessed subjects' records using an electronic medical records system named, ORCA at the trauma center. This study was a prospective case series with minimal risks to subjects, a waiver of consent was requested. University of Washington granted approval of this study, with the condition that post hoc consent be obtained to analyze the data. This consent process was adhered to.

Risks to the participants were minimal. If confidential data were lost or made public the subjects could experience a loss of privacy. The PI took all steps outlined in the procedures section to ensure confidentiality of the data at all times. The adult subjects of this study did not directly benefit from this study, because his or her medical care was not altered as a result of the data collected. However, data gathered will describe changes in PVI in this specific septic shock population. Knowledge derived from the analysis of this study will be utilized as a basis for future studies designed to guide fluid resuscitation of septic shock patients and potentially lead to

improved outcomes by minimizing complications that arise from administration of excess intravenous fluids.

CHAPTER IV: Findings and Discussion

Patient 1

A 45 year old Ethiopian male, admitted to the Emergency Department (ED) by ambulance complaining of “not feeling well for several days.” The ED records revealed a HR>SBP(134 beats per minute>129 mmHG) and a respiratory rate of 22-28 breaths per minute. Laboratory data revealed a leukocytosis (WBC 14.9 thousand/microL), and 90% neutrophils. A chest radiograph revealed a left lower lobe consolidation consistent with pneumonia or aspiration. He received four different antibiotics, 3100 ml of intravenous lactated ringers solution and was admitted to the acute care floor. Upon admission to the acute care floor, the patient was found to be hypotensive (78/52 mm Hg) with increased work of breathing. After 6 hours in acute care he was transferred to the ICU. The patient was in the ICU from November 15 to November 26, 2011 before meeting inclusion criteria for this study.

On November 26, 2011 this patient met inclusion criteria for this study. Criteria met were: 1) known or suspected infection, 2) white blood cell count (WBC) of 29,000/microL, 3) respiratory rate of 22 breaths per minute, 4) mechanically ventilated, and 5) sinus tachycardia.

Data were collected for approximately 76 minutes. Figure 1 represents data collected during this respective period at 5 minute average intervals. Before data collection this patient received 6700 ml of intravenous fluids (IV), at the time that data collection was started the patient was receiving norepinephrine (NE) at 35 mcg/min and vasopressin at 0.04 u/min. There was no titration of vasopressors or IV fluid boluses during the study period. Ventilator support remained constant, with a tidal volume (Vt) of 6 ml/kg and positive end-expiratory pressure (PEEP) of 10 cm H₂O. The Masimo pulse oximeter probe was placed on the patient’s right middle finger; in addition a functional right radial arterial line was present. The arterial line was

assessed for accuracy by the rapid flush test and was also referenced at the phlebostatic axis.

Each time the patient was repositioned or an intervention was performed using the arterial line, this process was repeated by the data collector to ensure accuracy of data collected from this source.

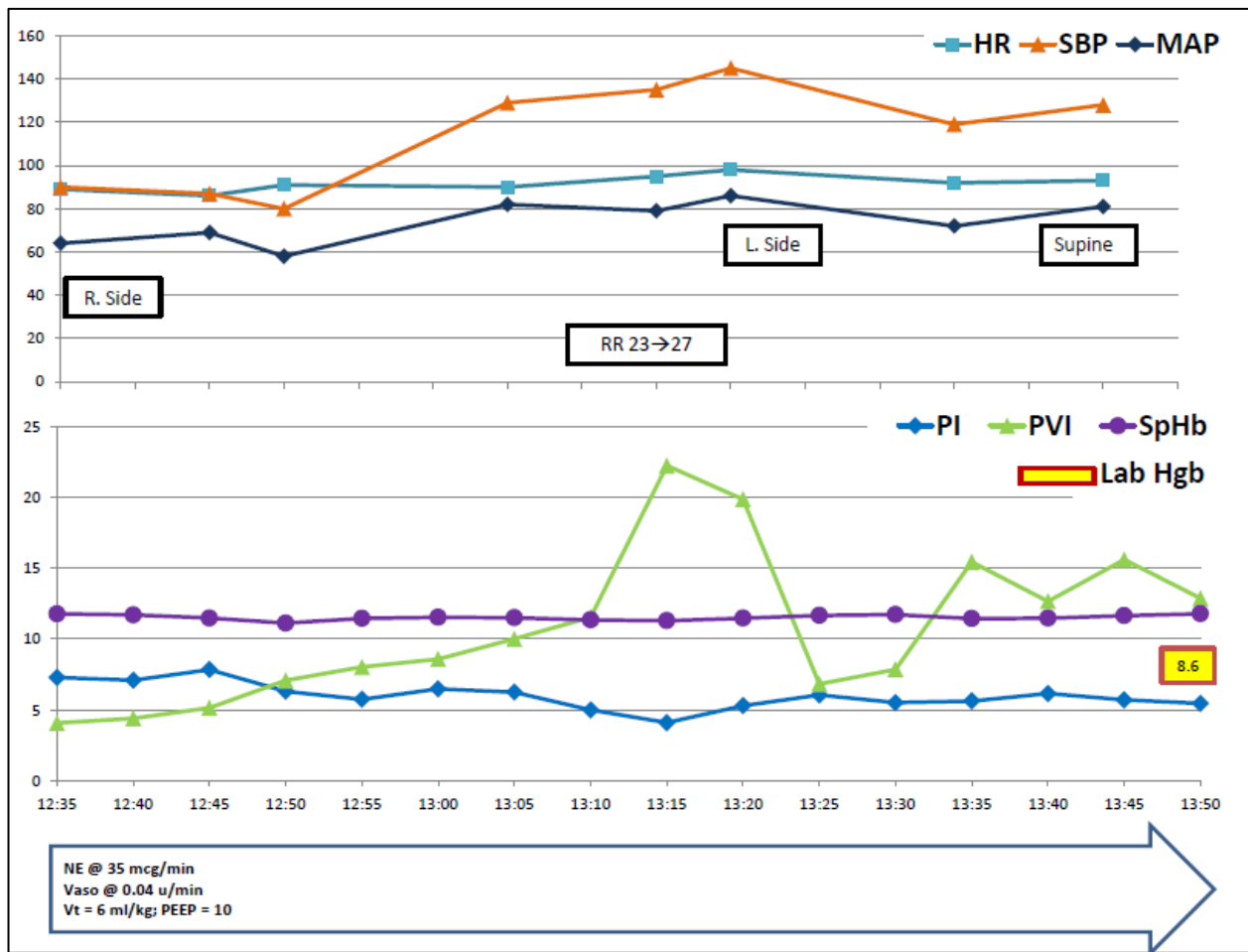


Figure 1.45 year old male suffering from septic shock.

At 1245 the patients HR>SBP (shock index)suggested intravascular volume depletion. The SBP and PVI increased as the PI began to trend downward, perhaps suggesting worsening perfusion and not fluid responsiveness. About 1315 the patient began having some spontaneous respirations, which could have caused a spurious increase in the PVI. When a patient is showing

signs of volume depletion, the SBP typically trends downward, and the patient becomes tachycardic. In this case the SBP was maintained likely due to vasoconstriction from the extremely high doses of NE. The PVI and PI are inversely proportional despite adequate systolic and mean arterial blood pressure. The inverse relationship of the PVI and PI are expected due to the mathematical derivation of PVI ($(PI_{max}-PI_{min}/PI_{max}) \times 100$).

SpHb was also collected during this case. A lab value of 8.6 g/dl was reported, and compared to its respective SpHb. There was a 3.1 g/dl difference between the noninvasive SpHb and the clinical laboratory value. This discrepancy in SpHb to Hgb may be explained by a sampling error from the bedside nurse. If the nurse obtaining the specimen from the arterial line did not waste an adequate volume of blood prior to obtaining the sample, then the specimen sent for analysis would be diluted thus under representing the actual value. The low PI could also be indicative of low pulsatile blood flow in the finger, thus creating an environment for local hemoconcentration. This hypothetical hemoconcentration would explain a higher SpHb when compared to the Hgb from the clinical laboratory.

Patient 2

A 59 year old African American male arrived to the ED with hyperglycemia (blood glucose =850 mg/dL). Past medical history revealed Type 2 Insulin-Dependent Diabetes and an old traumatic brain injury. Due to transportation difficulties he stopped taking his insulin three weeks prior to admission. The patient was admitted to the ICU with a diagnosis of diabetic ketoacidosis and pneumonia. He developed septic shock as a result of his pneumonia, requiring intubation and mechanical ventilation; thus, meeting inclusion criteria for this study. The Masimo probe with an opaque shield covering the probe was placed on the right ring finger.

A left radial arterial line was in place for blood pressure and pulse pressure variation. An Edwards Preceptcatheter (Edwards LifeSciences, Irvine, CA) was placed in the internal jugular vein. The ScVO₂ and CVP readings were obtained from this catheter and recorded as part of the standard of care.

Data collection began immediately following endotracheal intubation for respiratory failure, and continued for approximately 2 hours. Neuromuscular blocking agent rocuronium and the sedative etomidate were given for intubation at the beginning of this study. No spontaneous breaths were noted while data were collected. Ventilator settings included a tidal volume of 8 ml/kg and 5 cm H₂O of PEEP; these ventilator settings remained unchanged during data collection. Figure 2 graphically displays data in five minute average intervals.

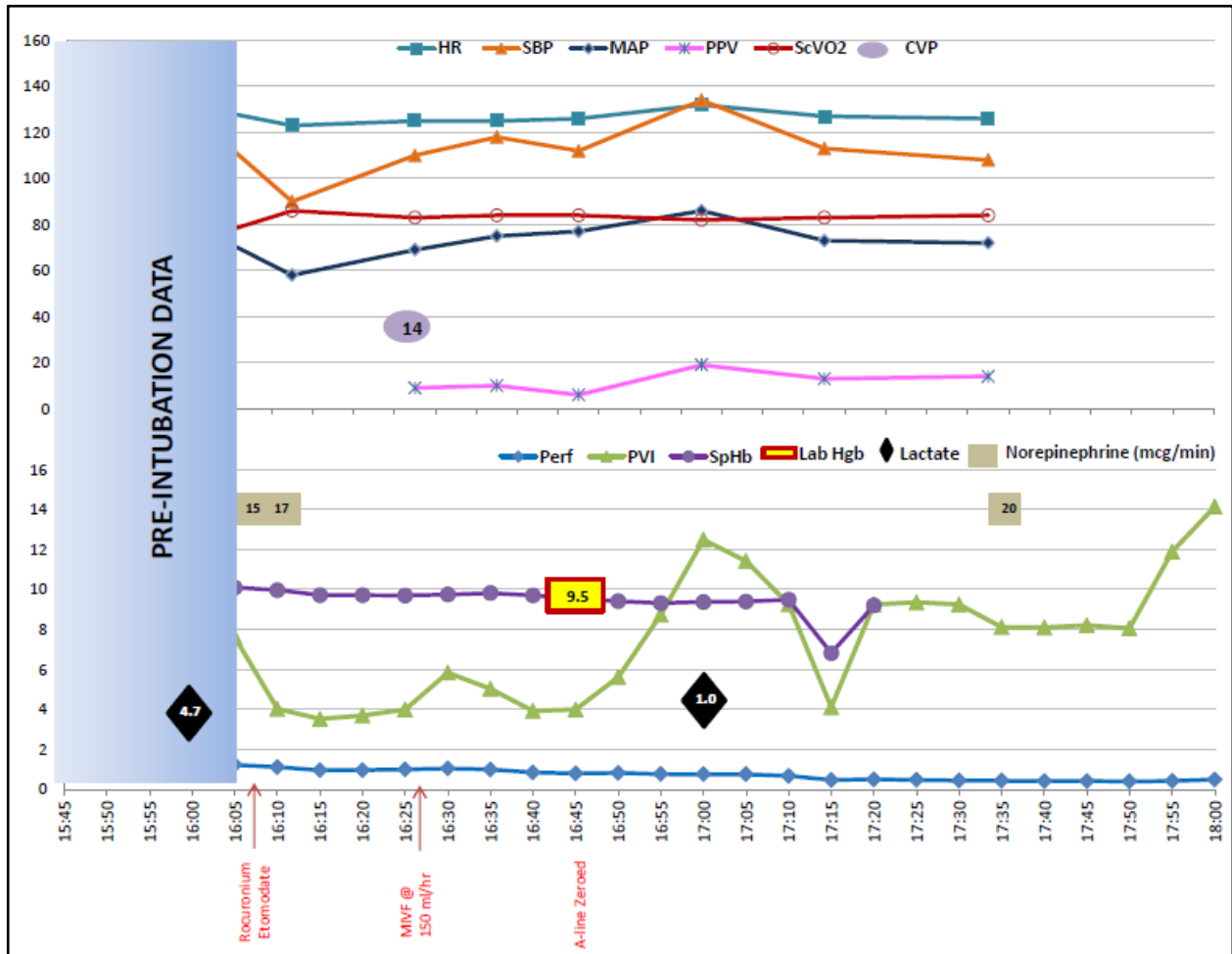


Figure 2. 59 year old male diagnosis DKA, septic shock, and pneumonia

A CVP reading was taken at 1625 indicating an adequate pressure (CVP = 14 mmHg). A CVP reading >10 mm Hg (for intubated patients, CVP goal >8 mm Hg for non-intubated patients) meets the goal of adequate fluid resuscitation per the Surviving Sepsis guidelines. At 1645 hour the PVI began to trend upward, while at 1630 the PI and ScVO₂ began trending down. This change in PI and ScVO₂ were noticed 15 minutes before the change in PVI, suggesting inadequate tissue perfusion and a change in fluid response status. As the ScVO₂, PI and PVI were changing the CVP remained unchanged at 14 mm Hg. Throughout this study, a continuous infusion of normal saline at 150 ml/hr was infusing, and the lactate decreased from 4.7mmol/L to

1.0mmol/L over 60 minutes. Pulse pressure variation was also recorded from the arterial line and peaked at the same time point as the PVI (1700hours), suggesting that the changes in PVI are an accurate reflection of the patients fluid response status. There was excellent agreement with SpHb and the clinical lab Hgb (data).

Patient 3

A 73 year old Caucasian female arrived to the ED by ambulance. She resided in a skilled nursing facility (SNF), and was admitted for septic shock. The presumed source for her sepsis was urosepsis and community acquired pneumonia. The patient's past medical history was significant for a cerebral vascular accident with residual left sided hemiparesis, type-two diabetes, and coronary artery disease. Presenting symptoms to the ED were tachypnea (40 breaths per minute), fever (38.2°C), sinus tachycardia (HR = 160 beats per minute), and leukocytosis (WBC 31,000/microL). According to the Surviving Sepsis guidelines, the aforementioned presenting symptoms met criteria for early goal directed therapy. In addition, the patient required intubation for respiratory failure. Criterion met for inclusion in this study consisted of all presenting symptoms mentioned; in addition the patient was unresponsive to intravenous fluid bolus, and required mechanical ventilation, signs of organ failure.

Data collection began immediately following intubation and initiation of mechanical ventilation in the ED, and lasted approximately 60 minutes. Ventilator support remained constant, with a tidal volume (Vt) of 6 ml/kg and positive end-expiratory pressure (PEEP) of 5 cm H₂O. Data collection was ended when the patient was transferred from the ED to the ICU. The patient received 1850 ml of IV fluids prior to data collection. An oscillometric blood pressure cuff was in place on her left upper extremity. The Masimo probe was placed on her

right index finger. The patient had severe contractions to her bilateral upper extremities and fingers; therefore the Masimo probe was unable to be placed on the ring finger of her non-dominant hand.

Figure 3 contains a five minute continuous average of data collected during the care of this critically-ill patient while in the ED. Also, IV fluid boluses are shown, the time of which the boluses were given are represented with arrows. The patient did not require any vasopressor therapy, although she did require an additional 2200 ml of IV fluids to improve perfusion and maintain blood pressure. As a result of very low perfusion throughout this study, SpHb was unable to be measured by the Masimo monitor.

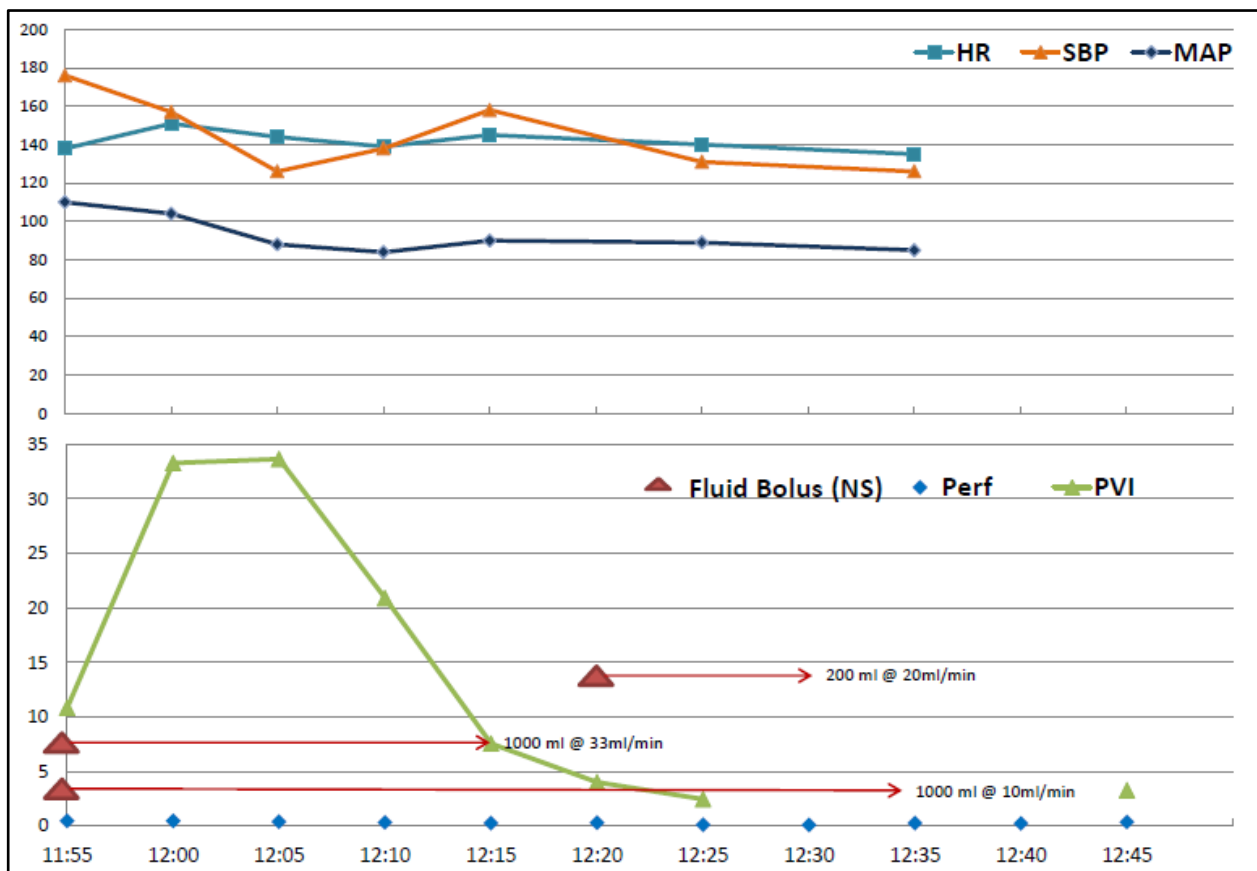


Figure 3. 73 year old female admitted with urosepsis and pneumonia.

There were dramatic changes in PVI over the course of data collection. IV fluid boluses were rapidly infusing at a rate of 33 ml/min and 10 ml/min when data collection began. Due to the small size of the IV catheter and lack of central IV access, more rapid infusion was not possible. As mentioned throughout this study the perfusion index (PI) was low, and unable to represent as a continuous line in Figure 3; although these data are continuous they are displayed as individual data points for clarity. The PI at 1200 hours is 0.45 and reached an average low at 1225 hours of 0.08, and was 0.21 at the conclusion of this study. At 1225 hours there was dropout of the PVI signal, which most likely was related to a low PI. At 1245 the PI reached 0.36 and the PVI signal was restored.

The initial PVI value obtained was 10%. It is unlikely within five minutes the PVI increased by 24%. One explanation is that the data represented in the graphs is a continuous five minute average. It is likely there were extreme differences in the PVI during this time period, since the patient was transitioning from spontaneous breathing to mechanical ventilation. In a patient who is spontaneously breathing the PVI variability would be greater, than when they are mechanically ventilated. The trend in PVI was consistent with the HR, SBP and MAP. At 1145, when the HR was lower, SBP and MAP were higher; the PVI was 10% suggesting the patient is not fluid responsive. At 1200 the HR increased, SBP and MAP trended downward and the PVI began to increase suggesting fluid responsiveness if the patient was given IV fluids. IV fluids were infusing at the time when the PVI was highest and over time the PVI trended downward along with HR; SBP and MAP increased. As the PVI trended down a third fluid bolus was started. Although the PVI is accurately displaying a trend suggestive of fluid responsiveness, the measure of perfusion (PI) on a distal extremity is suggestive of poor perfusion. The low values

of PI could also be explained by severe contractures in her fingers, and inability to detect adequate blood flow which may not be descriptive of the patients' actual perfusion. As a measure of perfusion prior to data collection the serum lactate level was 2.3 mmol/L, and later peaked after data collection at 5.6 mmol/L despite adequate fluid resuscitation. These lactate values are in agreement with a decreasing PI, suggestive of poor perfusion.

Patient 4

A 51 year old Vietnamese male arrived by ambulance and was admitted to the ED with a decreased level of consciousness, hypotension, and hypoxic respiratory failure due to H1N1 virus. Immediately after arrival to the ED the patient was intubated. Prior to data collection 2500 ml of IV fluids were given. The oscillometric cuff was located on the left upper extremity, and the Masimo probe was placed on the patient's left middle finger and covered with an opaque shield. Figure 4 graphically represents the data collected over approximately 140 minutes reported in 5 minute average intervals, during which the patient was aggressively resuscitated in the ED, and continued to the intensive care unit (ICU).

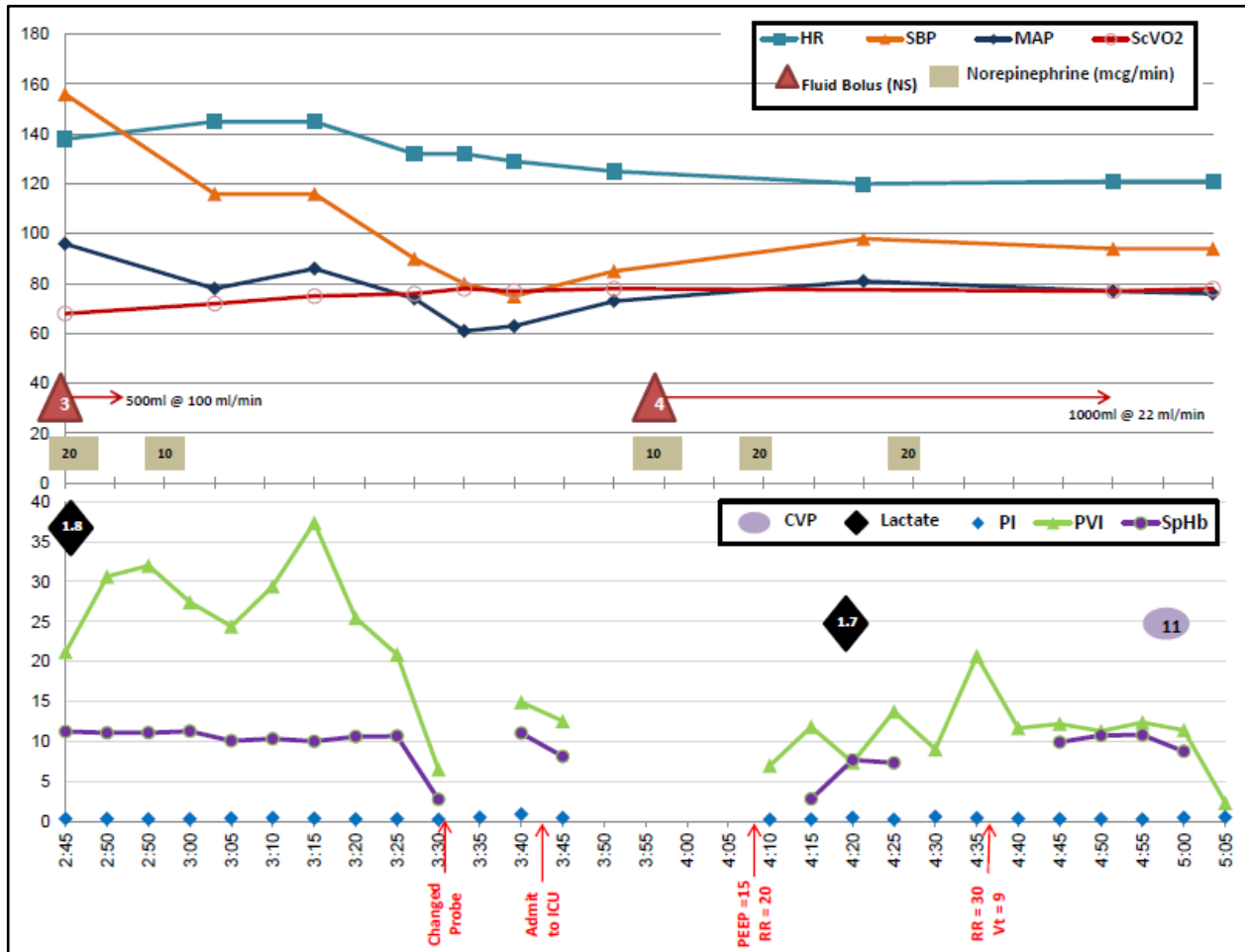


Figure 4.51 year old male in septic shock.

Data collection began at 1445 and is represented as a continuous 5 minute average. At the time that data collection was initiated, the patient was receiving a third intravenous fluid bolus of normal saline and was also started on a norepinephrine (NE) infusion at 20 mcg/min. The NE dose was titrated by the bedside nurse throughout this study to maintain an adequate clinical blood pressure.

There were gaps in data collection representing signal drop-out. From 1542 to 1610 the patient was transferred to the ICU. During this period, data collection was interrupted. Data collection was restarted upon arrival to the ICU. The transfer time is noted in Figure 4 and

displayed graphically as a gap in data. The PI was collected as a continuous variable, but displayed in Figure 4 as individual data points for clarity due to the extremely low values.

No laboratory values of hemoglobin (Hgb) were obtained during the study time period. An Edwards Precept catheter (Edwards LifeSciences, Irvine, CA) was placed in the internal jugular vein. The ScVO₂ and CVP readings were obtained from this catheter and recorded as part of the standard of care. Other care interventions are also displayed such as IV fluid boluses, changes in ventilator settings, titration of NE, and laboratory lactate values.

The PVI was initially high (>13% suggesting fluid responsiveness), the patient was receiving an IV fluid bolus and NE was infusing. The initial PVI of 20% is suggestive of fluid responsiveness and over the next 30 minutes after admission the PVI continued to trend upward and peaked at approximately 37%. During these 30 minutes the fluid bolus ended, and NE dose was decreased by 50%, both of which could contribute to the increase in the PVI. The MAP and SBP continued to trend downward from 155 mm Hg to 70 mm Hg, despite additional IV fluids. The ScVO₂ trend indicates worsening shunt, as a result of peripheral vasoconstriction. When the MAP and SBP were lowest (1535), the PVI, PI and SpHb signals were lost. The PVI and SpHb signals were restored 10 minutes later as the MAP and SBP increased without any additional interventions. At 1530 when the signal was lost the average PI were 0.26, and the PI increased to 0.91 when the signal was restored at 1540. When the signal was lost, the Masimo probe was changed to ensure signal was not lost as a result of equipment failure, but due to the patient's change in clinical condition.

Variability in the PVI was greatest when NE was lowest. The trends in PVI and PI collected for this patient accurately describe the patients changing clinical condition. When the

PVI was high, the patient's blood pressure trended down, suggesting fluid responsiveness. Of note, the PI began its downward trend before a subsequent rise in PVI independent of any clinical interventions. The SpHb remained constant throughout the study period, although the rate of signal drop-out was greatest for this parameter.

Discussion

The aims of this study were 1) to describe the pattern of PVI in a real-time critical care environment, and 2) to determine agreement of SpHb with clinical laboratory values obtained as part of the standard of care. In this small series, the PVI and PI in patients with severe sepsis and septic shock did not demonstrate promise for predicting fluid responsiveness.

All patients in this case series, with the exception of Patient 3, received a continuous infusion of norepinephrine. With respect to the patient's receiving NE, as the PI decreased the PVI would subsequently increase, regardless of the patient's blood pressure measurements. In all cases the downward trend of the PI was seen earlier than an increase in PVI, suggesting a more sensitive measure of the patient's worsening perfusion or the effects of vasoconstriction as a result of increasing doses of vasopressors. This potential effect of norepinephrine on PI and PVI was described by Biais et al. (2011). Biais et al. (2011) and colleagues described the relationship between PVI and PPV for patients receiving NE and not receiving NE. A poor correlation was found with patients receiving NE ($r^2=0.04$, $P>0.05$) in contrast to patients who were not receiving NE ($r^2 = 0.52$, $p < 0.001$), which is consistent with the findings of this case series for those patients who were receiving NE.

PVI is derived from the difference in the PI divided by the $PI_{max}((PI_{max} - P_{min})/PI_{max})$. The inverse relationship between the PVI and PI are described in this equation.

Clinically it would be expected that as NE is increased and perfusion decreased (as indicated by a decrease in PI) the PVI would increase. The change in PVI in this situation is likely due to the effects of NE on peripheral circulation and the PI rather than as an indicator that the patient is a fluid responder. This effect on perfusion and PI is dose dependent, and theoretically at higher doses more there is increased vasoconstriction in the periphery (site of the Masimo probe). By decreasing pulsatile flow at the monitoring site, one would expect the PI to decrease as a result of less pulsatile blood flow. Clinically, the spurious increase in PVI due to the mathematical relationship to the PI could have adverse consequences for a patient if the provider chose to give more IV fluids based on the elevated PVI.

Other factors that likely affect the accuracy of PVI as an indicator of fluid response status in this patient population are low tidal volumes (<8 ml/kg) and use of high levels of PEEP during mechanical ventilation. Studies have shown a poor sensitivity for the PVI to predict fluid responsiveness with a low tidal volume (Lansdorp et al., 2012). Based on PPV studies with tidal volumes less than 8 ml/kg one would hypothesize that the PVI threshold for fluid responsiveness is lower than it would be for patients receiving >8 ml/kg in tidal volumes. Recently Lansdorp et al. (2012) described an optimal predictive value (AUC = 0.95) for predicting fluid responsiveness utilizing PPV in patients ventilated with >7 ml/kg; and poor predictive value (AUC = 0.51) in patients whose tidal volumes was less than 7 ml/kg (Lansdorp et al., 2012). Patients in this case series received between 6-8 ml/kg. The limitations described are important to the application of this technology for this patient population, where the standard of care may include low tidal volume ventilation, and vasopressor therapy. In this case series the PVI did not appear to accurately reflect changes in the patients' fluid response status. Rather, because there

is a mathematical relationship between the PI and PVI, changes in perfusion may cause an increase in PVI that does not reflect fluid response status. In this case the use of PVI to guide fluid resuscitation cannot be recommended.

The final aim of this study was to describe the agreement between laboratory hemoglobin values with noninvasive continuous hemoglobin data from the Masimo Rainbow 7 monitor. However, only two laboratory Hgb values were recorded. In Patient 1 there was a clinically significant difference between SpHb and Hgb (11.7 g/dl and 8.6 g/dl respectively) of 3.1g/dl; whereas in Patient 2, there was precise agreement between the two values. Reasons for discrepancies between these values could be related to sampling errors, a state of low perfusion or a combination both. Another possible explanation may be that when the PI is extremely low, and there is significant vasoconstriction at the monitoring site, blood could become pooled creating a hemoconcentrated state; thus, causing the SpHb to falsely read higher than a patient's actual Hgb.

Most of the published studies involving PVI and PI were conducted in the operating room. This is one of the first studies to collect these parameters during real-time resuscitation efforts for septic shock. Although this case series cannot be generalized to a broader population, successful efforts in collecting these data suggests that this technology can be used at the bedside of a critically ill patient and potentially guide IV fluid administration non-invasively. The results suggest further investigation is needed in regard to the PI as it appears to be a much more sensitive and early indicator of a patient's worsening condition than any of the other variables collected in this study.

Conclusion

The PVI was not found to be an accurate indicator of fluid responsiveness in this case series of critically ill patients with septic shock. Continued research with larger sample sizes are needed to analyze the utility of this technology, verify the trends identified in this case series, and guide clinical decisions for fluid resuscitation in patients with severe sepsis and septic shock.

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Appendix A - Study Protocol

Pulse Variability Index during Fluid Resuscitation of Septic Shock

VERIFY patient inclusion/exclusion

- Inclusion
 - Age \geq 18
 - Mechanically ventilated with no (few) spontaneous breaths (need 3 uninterrupted ventilatory cycles)
 - Regular cardiac rhythm (no atrial fibrillation/flutter, frequent ectopy)
 - Hemodynamically stable (MAP or HR variability $<10\%$ over 1 minute)
 - No change in ventilator parameters, vasoactive medications during bolus measurement period
- Exclusion
 - Age $<$ 18
 - Pregnant
 - Marked arrhythmia (atrial fibrillation/flutter or frequent ectopy)
 - Spontaneous ventilation during data collection period
 - Open chest
 - Cor pulmonale
 - IABP
 - Active pacemaker
 - Change in ventilatory parameters or vasoactive medications during each bolus measurement period.

SET UP

- Confirm with patients nurse OK to enroll patient (no study data will be shared with any care provider)
- Apply the Masimo pulse oximeter probe to the ring finger on the non-dominant hand/ or hand adjacent to where the Hgb will be drawn and start continuous data collection with Masimo pulse oximeter.
- Note any fingernail abnormalities prior to placement of probe (note on demographic data collection tool)
- Ensure Masimo pulse oximeter data collection probe is covered to prevent interference from ambient light.
- If A-line is in use for patient care: Zero transducer with laser a level to phlebostatic axis (4th ICS mid-axillary line), ensure adequate dynamic response (goal <2.5 small boxes between oscillations with record strip running at 25mm/sec), confirm adequate fluid in pressure bag, ensure 300mmHg in pressure bag.
- Record/Measure HOB angle
- Complete demographic data sheet

DATA COLLECTION PROCEDURE

- PreBolus Measurements
 - Obtain vital signs per PVI Data collection Tool v1.0
 - Obtain vent settings
- Bolus Information
 - Start stopwatch as RN starts IV fluid bolus
 - Record duration of IV fluid bolus
 - Record total volume of IV fluid bolus
 - Calculate rate of IV fluid bolus administration
- Post-Bolus Information
 - Begin timing with stopwatch when bolus is completed
 - At 270 seconds record vital signs per PVI data collection Tool v1.0
- Repeat this procedure for each IV fluid bolus administered
- Continuous Hgb & Lactate
 - Abstract Hgb from EMR (electronic medical record) and time sample was obtained
 - Abstract lactate value and time sample was obtained from EMR

CONCLUSION OF DATA COLLECTION

- Ensure all equipment utilized for data collection is removed from patient
- Notify subjects RN that data collection is complete
- Disinfect monitor per institution protocol
- Return all data collection materials to a locked file cabinet in the clinical education department at HMC

Appendix C - Demographic Data Collection Form

SUBJECT # _____

DEMOGRAPHIC DATA COLLECTION TOOL

Age _____ Gender (circle one): M F

Ht(cm) _____ Wt(kg) _____ BSA _____

Admission Diagnosis: _____

Suspected or Known Source of Infection: _____

SIRS Criteria Met (circle all that apply)

Temperature >38° or <36°	Respiratory Rate >20 breaths/min PaCO2 <32, or intubated for respiratory failure
Heart Rate >90 beats/min	WBC count >12,000/mm ³ , <4000/mm ³ or >10% immature (band) form

BLOOD PRODUCTS given prior to data collection: YES NO

Type of Blood products given _____

Quantity of Blood Products administered (ml) _____

Total IV Crystalloids Received Prior to Data Collection (ml) _____

HOB Elevation _____

Oscillometric Cuff Location _____

Masimo Pleth Probe Location _____

A-Line Location (if applicable) _____

Finger Nail Abnormalities: _____

Appendix D - Hemoglobin Data Collection Form

**Continuous Hemoglobin
Data Collection Tool**

SUBJECT # _____

DATE	TIME (Masimo Monitor)	Lab Specimen Source (CIRCLE ONE)	TIME (lab specimen taken from subject; obtain from Masimo monitor)	Lab Value (g/dl)	Hgb (Masimo monitor @ time of lab draw)
		ARTERIAL			
		VENOUS			
		ARTERIAL			
		VENOUS			
		ARTERIAL			
		VENOUS			
		ARTERIAL			
		VENOUS			
		ARTERIAL			
		VENOUS			

NOTES:

Appendix E - Consent Form

UNIVERSITY OF WASHINGTON CONSENT FORM

Systolic /Pulse Pressure Variation in Post-Operative Cardiac Surgery and Liver Transplant Patients

Principle Investigator:

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Associate Investigators:

Todd D. Ray, RN BSN. University of Washington Doctor of Nursing Practice Student. Pager: 206-450-6360

JoAnne D. Whitney, PhD RN, Professor, Biobehavioral Nursing and Health Sciences and Clinical Research Scientist, Harborview Medical Center. Phone: 206-685-2264

Nicole Kupchik, RN, MSN. Clinical Nurse Specialist – Harborview Medical Center. Adjunct Faculty, University of Washington School of Nursing. Phone: 206-744-8404

Researchers' statement

If you are reading this consent form as someone's legally authorized representative, please note that the terms "you" and "your" throughout refer to the research participant.

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in this study or not. Please read this form carefully. You may ask questions about why we are performing this study, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about this study or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called "informed consent." We will give you a copy of this form for your records.

The information collected for this study needs to be gathered within a particular timeframe. In the circumstance that a legal authorized representative is not immediately available, the Human Subjects Division at the University of Washington has granted this study team permission to collect data. To utilize this data in a meaningful manner we must obtain permission from a legal authorized representative of the patient. If you decline participation in this study, any data that has been collected will be destroyed and not used for further analysis.

PURPOSE OF THE STUDY

A serious infection (sepsis or septic shock) may cause your blood pressure to drop. As a part of the treatment of septic shock we give intravenous fluids. Intravenous fluids refer to the fluid infused into a vein. It is important for us to be able to predict if an intravenous fluid bolus will increase the amount of blood pumped by your heart and your blood pressure. There are new ways to predict if a patient will respond to a fluid bolus, but many of these require sticking a catheter into your artery. We also draw blood to measure the amount of hemoglobin. Hemoglobin is a molecule in the blood which carries oxygen throughout the body. A new method allows us to continuously get this same information from a

Appendix E Continued

special pulse oximeter placed on your finger. The measurements are called the pleth variability index (PVI) and continuous hemoglobin (SpHb). There is limited information on the use of this noninvasive device in patients being treated for severe sepsis or septic shock.

The purpose of this study is to describe the changes in the PVI during the treatment of patients with severe sepsis and septic shock. We will also describe the changes in the SpHb and compare it to the blood hemoglobin levels drawn as a routine part of your care.

STUDY PROCEDURES

Before asking you to be part of this study, we collected information from a device that was put on your finger. We also looked at your medical records to find out about your age, ethnicity, medical history, and to confirm that you had a suspected infection to see if you qualified to be in the study. We were not able to ask you for permission to do this because of your illness. If you agree to continue to participate in the study, we will keep the information that we recorded.

These are the specific procedures that were performed.

1. The study team was notified of a patient who was critically ill as a result of a potential infection.
2. Once your eligibility was determined, the Masimo probe was placed on your finger and covered with a black shield to protect it from light.
3. The monitor continuously collected data, and every 15 minutes we also recorded your heart rate, blood pressure, and information from the machine that was helping you to breathe.
4. If a fluid bolus was given, we recorded your heart rate, and blood pressure before and after each bolus. We also record any medications used to maintain your blood pressure.
5. Hemoglobin values obtained as part of the routine care were also copied from your electronic medical record.
6. The study lasted no longer than 6 hours.
7. The information we gathered from the Masimo monitor was not used as part of your care. All of the treatment you received were a routine part of your care and were not done because you were in a research study.
8. At the end of the study the pulse oximeter probe was carefully removed.
9. The data collected were transferred to a password protected computer.
10. Your information was assigned a study number and a separate file was kept to link your name to the study number. We will use this information only to identify your data once you decide whether or not to be in this study.

RISKS, STRESS, OR DISCOMFORT

The finger probe contains medical adhesive. There is a chance of minor skin irritation from this adhesive.

ALTERNATIVES TO TAKING PART IN THIS STUDY

An alternative to taking part in this study is to not have the information recorded be included in the study. If you choose to not participate we will destroy all information collected.

Appendix E Continued

BENEFITS OF THE STUDY

This study did not directly benefit you. The results of this study may help us to determine if this noninvasive monitoring is useful in guiding treatment of other critically ill patients with severe sepsis or septic shock.

SOURCE OF FUNDING

Masimo Corporation loaned us the monitor and provided the finger probes used in this study. The study team did not receive any financial support from Masimo.

OTHER INFORMATION

You may refuse to participate and you are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled.

All of the information you provide will be confidential.

Government or university staff sometimes reviews studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm. Any link that is made to connect your loved ones name with the data collected will be destroyed at the conclusion of this study or by July 1, 2012, whichever time comes first.

A copy of the consent form will be placed in your loved one's medical record.

COMPENSATION FOR INJURY

If you think you have an injury or illness related to this study, contact the study staff (listed above) right away. The study staff will treat you or refer you for treatment.

The UW will pay up to \$10,000 to reimburse for treatment of injury or illness resulting from the study.

Printed name of study staff obtaining consent	Signature	Date
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Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, I can ask one of the researchers listed above. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098. I give permission to the researchers to use my medical records as described in this consent form. I will receive a copy of this consent form.

Appendix E Continued

Printed name of subject Signature of subject Date

When subject is not able to provide informed consent

Printed name of representative Signature of representative Date

Relationship of representative to subject

Copies to: Researcher
 Subject