



Detecting central-venous oxygen desaturation without a central-venous catheter: Utility of the difference between invasively and noninvasively measured blood pressure ☆☆☆☆☆



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ABSTRACT

Objective: The objective was to determine whether central-venous oxygen saturation ($ScvO_2 < 70\%$) can be detected from the difference between invasively and noninvasively measured systolic blood pressure (BP) (ie, ΔBP defined as arterial BP minus noninvasive BP).

Methods: This is a cross-sectional study at a single medical and surgical intensive care unit in Japan. All hypotensive patients admitted to intensive care unit were eligible. Arterial BP was measured via a radial-artery catheter, and non-invasive BP on the same side was measured via a brachial cuff. $ScvO_2$ was measured by gas analysis of blood sampled from a central-venous catheter (CVC). We calculate the area under the curve for ΔBP as an indicator of $ScvO_2 < 70\%$.

Results: Usable data were obtained from the records of 111 patients. The median and interquartile range of ΔBP and $ScvO_2$ were -4 mm Hg ($-11, 6$) and 67% ($60.9, 73.9$), respectively. The area under the curve of ΔBP as an indicator of $ScvO_2 < 70\%$ was 0.81 (95% confidence interval [CI], $0.73-0.89$). With a cutoff ΔBP of 0 , sensitivity was 65.7% (95% CI, $53.1-76.8$), specificity was 97.7% (95% CI, $88.0-99.8$), and positive predictive value was 97.8 (95% CI, $88.2-99.9$).

Conclusions: ΔBP can indicate whether $ScvO_2$ is lower than 70% . When that difference is greater than 0 , $ScvO_2$ is very likely to be lower than 70% .

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1. Introduction

In recent large randomized trials of treatments of sepsis, therapy guided by measured values of central-venous oxygen saturation ($ScvO_2$) did not reduce all-cause mortality [1–4]. However, in the treatment of critically ill patients, $ScvO_2$ is still used as a prognostic marker, with values less than 70% indicating a poor prognosis, and it is also used to guide fluid therapy [5,6–8]. In recent randomized controlled trials, $ScvO_2$ -guided fluid therapy reduced perioperative complications.

$ScvO_2$ reflects the balance between oxygen delivery and consumption and is used as a surrogate marker of cardiac output [9,10]. It is widely considered to be important for evaluating hemodynamic stability [5].

However, measuring $ScvO_2$ requires a central-venous catheter either for repeated blood sampling or for continuous monitoring via a costly device. In addition to its unavoidable costs, central-venous catheterization carries risks of complications that, although infrequent, can be fatal [11,12]. Less invasive and costly methods of obtaining variables about oxygen delivery are needed [13]. Here we present a study of one such less invasive method.

Compared with central-venous catheterization, blood-pressure monitoring is safer, relatively inexpensive, and more commonly used in managing hemodynamically unstable patients. Two frequently used methods are to monitor blood pressure via an arterial catheter (invasively measured arterial blood pressure [ABP]) [14] and oscillometric noninvasive measurement (NIBP) [15]. Discrepancies between ABP at radial and NIBP at brachial have been found in patients with septic shock and in those who are hypotensive and under general anesthesia [16–23]. Although there are no previous published study which reports the relationship between this discrepancy and $ScvO_2$, we presented at the 44th Critical Care Congress (Phoenix, AZ) that, in patients with hypotension, the discrepancy between systolic ABP at

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radial and systolic NIBP at brachial was negatively associated with ScvO₂; correlation coefficient was 0.67 (95% confidence interval [CI], 0.38–0.84). If that association between ScvO₂ and the ABPs – NIBPs difference is strong, then the latter index, which can be obtained simply and inexpensively, can be used instead of ScvO₂. We evaluated the ABPs – NIBPs difference as an indicator of central-venous oxygen desaturation (ScvO₂ < 70%) in patients with hypotension.

2. Materials and methods

2.1. Design and setting

We retrospectively reviewed the medical records of adults with hypotension who were admitted to the intensive care unit (ICU) of Sakai City Medical Center (a tertiary center in Osaka, Japan), which has 8 beds and any medical patients and surgical patients except cardiac surgical patients are admitted to, between July 2013 and June 2015. This study was approved by the Institutional Review Boards at Sakai City Medical Center and Kyoto University.

2.2. Participants

We examined the records of all patients who were 18 years old or older and were admitted to the ICU at Sakai City Medical Center during the study period. We defined *hypotension* as ABPs < 90 mm Hg, and we analyzed data from all adults who were in hypotension at the time of ICU admission and whose ABP, NIBP, and ScvO₂ were simultaneously recorded.

2.3. Measurements

Arterial blood pressure was measured using a 20-gauge short Teflon catheter in a radial artery. The catheter was connected to a pressure transducer via 30 cm of noncompliant extension tubing with a continuous-flush device. The pressure transducer system was connected to a bedside monitor (IntelliVue MX800, Phillips, Andover, Massachusetts, USA) to display the arterial waveform and systolic, diastolic, and mean arterial pressures. The transducer was zeroed to atmospheric pressure and referenced to the midaxillary line with the patient in the supine position. On the same side as the radial-artery catheter, noninvasively measured brachial blood pressure (NIBP) was measured by oscillometry with a brachial cuff. The size of the cuff was chosen according to recent guidelines [24]. Both ABP and NIBP were displayed on a bedside monitor (IntelliVue MX800, Phillips) and were recorded simultaneously.

Central-venous oxygen saturation was measured by analysis of blood sampled from a central-venous catheter. As a usual practice, the central-venous catheter (CVC) tip was positioned in superior vena cava. To ensure the optimal placement of the CVC tip, each physician who performed CVC insertion confirmed that the position of the CVC tip was positioned above the tracheal carina level by chest radiograph [25–27]. The blood samples were analyzed with a GEM Premier 3000 blood gas/electrolyte analyzer. Blood pressure and ScvO₂ were measured at the same times. The data analyzed here were blood pressure and ScvO₂ value at the first time when ScvO₂ was measured after admission to the ICU. Blood pressure and ScvO₂ data were collected during periods of hemodynamic stability to avoid wide fluctuations in blood pressure. We use “ΔBP” to refer to the difference between ABPs and NIBPs (ie, ABPs minus NIBPs).

We also recorded each patient's age, sex, cause of admission, heart rate, blood pressure (systolic, diastolic, and mean, from both invasive and noninvasive measurements), use of mechanical ventilation, Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score, hemoglobin level, arterial blood oxygen saturation, and lactate level.

2.4. Statistical analysis

Continuous variables normally distributed are presented as means and SDs and compared by the *t* test. Continuous variables which are not distributed normally are presented as median, first quartile, and third quartile and compared by Mann-Whitney *U* test. Shapiro-Wilk test was performed to test for the data normality. Categorical variables are shown as absolute numbers with percentages. We calculated sensitivities, specificities, and the area under the receiver operating characteristic (ROC) curve for ΔBP as an indicator of ScvO₂ < 70%. Using the same analyses, we also examined ΔBP as an indicator of a more severe level of oxygen desaturation: ScvO₂ < 65%. To determine the optimal cutoff point for ΔBP, we used the Youden index, maximum

Table 1

Information on all adults admitted to the Intensive Care Unit with hypotension (ABPs < 90 mm Hg) between July 2013 and June 2015

	Included in this study (with ScvO ₂ data) n = 111	Not included in this study (without ScvO ₂ data) n = 64	P value
Age in years	72 (57–81)	67 (57–78)	.25 [†]
Percent who were male	59.5	59.3	>.99 [‡]
Body mass index (SD)	22.1 (3.9)	21.5 (3.9)	.36 [§]
Comorbidity			
Diabetes	29.7	17.2	.07 [‡]
Hypertension	44.1	29.7	.07 [‡]
Dyslipidemia	17.1	12.5	.52 [‡]
Cause of ICU admission			
Percent surgical	5.4	68.8	<.0001 [‡]
Percent infection	61.3	70.3	.25 [‡]
Pneumonia	28/68	7/45	
Urinary	11/68	0	
Hepatic and GI	6/68	1/45	
Peritonitis	3/68	29/45	
Others	9/68	1/45	
Unknown	11/68	7/45	
Percent cardiac	18.0	4.7	.01 [‡]
Heart failure	10/20	2/3	
Arrhythmia	4/20	1/3	
ACS	2/20	0	
Others	4/20	0	
Percent GI bleeding	4.5	7.8	.5 [‡]
Percent others	16.2	17.2	>.99 [‡]
ABPs, mm Hg	82 (75–87)	83 (79–88)	.20 [†]
ABPd, mm Hg	46 (40–53)	48 (42–54)	.29 [†]
ABPm, mm Hg	59 (52.3–62.7)	60 (55–64)	.13 [†]
NIBPs, mm Hg	83 (75–92)	90 (80–95)	.007 [†]
NIBPd, mm Hg	50 (43–55)	50 (45–59)	.23 [†]
NIBPm, mm Hg	61 (56–67)	64 (57–71)	.04 [†]
ΔBP, mm Hg	–4 (–11 to 6)	–8 (–12 to –1)	.06 [†]
HR, beat/min	99 (85–110)	96 (81–113)	.61 [†]
% ScvO ₂	67.0 (60.9–73.9)	–	–
Hemoglobin, g/dL	10.8 (9.3–12.4)	10.6 (9.1–12.3)	.31 [†]
% SaO ₂	96.4 (94.6–98.0)	98.0 (96.4–98.7)	<.0001 [†]
Lactate, mmol/L	2.1 (1.2–4.1)	1.7 (0.9–2.6)	.01 [†]
Dosage of vasoactive and inotrope agents			
Norepinephrine (μg/kg/min)	0.09 (0.05–0.18)	0.07 (0–0.19)	.06 [†]
Dopamine (μg/kg/min)*	0 (0–10.8)	0 (0–5.1)	.21 [†]
Vasopressin (IU/min)*	0 (0–0.04)	0 (0–0.05)	.12 [†]
Dobutamine (μg/kg/min)*	0 (0–14.2)	0 (0–6.4)	.05 [†]
Milrine (μg/kg/min)*	0 (0–0.53)	0 (0–0.30)	.0005 [†]
APACHE II score	26 (20–32)	17 (13–25)	<.0001 [†]
SOFA score	11 (9–14)	7 (5–11)	<.0001 [†]
% on ventilator	77.5	76.6	>.99 [‡]

GI indicates gastrointestinal; ACS: acute coronary syndrome; ABPs: systolic invasive blood pressure; ABPd: diastolic invasive blood pressure; ABPm: mean invasive blood pressure; NIBPs: systolic noninvasive blood pressure; NIBPd: diastolic noninvasive blood pressure; NIBPm: mean noninvasive blood pressure; HR, heart rate; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

* These data are presented as median, minimum, and maximum values because first and third quartile values are zero.

[†] Mann-Whitney *U* test.

[‡] χ^2 test.

[§] *t* test.

Table 2
Information on all patients included in this study

	Patients with ScvO ₂ ≥ 70 n = 44	Patients with ScvO ₂ < 70 n = 67	P value
Age in years	60 (50–77.5)	75 (63–83)	.003 [†]
Percent who were male	61.4	58.2	.74 [‡]
Body mass index (SD)	22.4 (4.2)	21.8 (3.7)	.43 [§]
Comorbidity			
Diabetes	22.7	34.3	.19 [‡]
Hypertension	38.6	47.8	.34 [‡]
Dyslipidemia	13.6	19.4	.43 [‡]
Cause of ICU admission			
Percent surgical	2.3	7.46	.24 [‡]
Percent infection	77.3	50.8	.005 [‡]
Pneumonia	14/44	14/67	
Urinary	7/44	4/67	
Hepatic and GI	3/44	6/67	
Peritonitis	1/44	2/67	
Others	11/44	38/67	
Unknown	8/44	3/67	
Percent cardiac	6.8	25.4	.01 [‡]
Heart failure	1/3	9/17	
Arrhythmia	0/3	4/17	
ACS	1/3	1/17	
Others	1/3	3/17	
Percent GI bleeding	2.3	6.0	.36 [‡]
Percent Others	13.6	17.8	.80 [‡]
ABPs, mm Hg	79.5 (74.5–86.5)	84 (76–87)	.09 [†]
ABPd, mm Hg	45 (39–53)	47 (40–53)	.41 [†]
ABPm, mm Hg	57.8 (50.8–61.5)	59.7 (53–63.3)	.25 [†]
NIBPs, mm Hg	89 (84–95.5)	79 (73–85)	<.0001 [†]
NIBPd, mm Hg	51.5 (44–56)	50 (43–54)	.47 [†]
NIBPm, mm Hg	64.2 (58–68.2)	58.7 (55–64.7)	.01 [†]
ΔBP, mm Hg	−9 (−14 to −5)	4 (−7 to 9)	<.0001 [†]
HR, beat/min	104 (91–124.5)	94 (80–107)	.003 [†]
Hemoglobin, g/dL	11.4 (9.2–13.0)	10.6 (9.3–12.2)	.23 [†]
% SaO ₂	96.5 (94.7–98)	96.3 (94.5–98)	.82 [†]
Lactate, mmol/L	2.4 (1.2–4.4)	2 (1.3–4.1)	.71 [†]
Dosage of vasoactive and inotropic agents			
Norepinephrine (γ)	0.10 (0.06–0.19)	0.09 (0.05–0.17)	.28 [†]
Dopamine* (γ)	0 (0–10.1)	0 (0–10.8)	.48 [†]
Vasopressin* (IU/min)	0 (0–0.03)	0 (0–0.04)	.09 [†]
Dobutamine* (γ)	0 (0–13.9)	0 (0–14.2)	.85 [†]
Milrine* (γ)	0 (0–0.50)	0 (0–0.53)	.02 [†]
APACHE II score	28 (21.5–32.5)	26 (20–31)	.36 [†]
SOFA score	13 (10–16)	11 (8–13)	.01 [†]
% on ventilator	75.0	79.1	.61 [‡]

* These data are presented as median, minimum, and maximum values because first and third quartile values are zero.

[†] Mann-Whitney U test.

[‡] χ^2 test.

[§] t test.

{sensitivity + specificity − 1}, in which the maximum value means optimal cutoff point [28]. Because there were no previous data to determine the sample size, sample size calculation was not performed, and all eligible patients' data during the study period were analyzed. For all analyses, we used STATA version 13 (STATA, College Station, TX). For all comparisons, 2-tailed *P* values < .05 were considered statistically significant.

3. Results

During the study period, 175 patients with hypotension were admitted to the ICU, and ScvO₂ data were available for 111 of them. Table 1 shows the baseline characteristics of those 111 patients. The 64 patients for whom ScvO₂ data were not available were less severely ill, and a greater proportion of them were surgical patients. Among the 111 patients in this study, the median and interquartile range (IQR) of ABPs were 82 mm Hg (75–87), the median and IQR of NIBPs were 83 mm Hg (75–92), the median and IQR of ΔBP were −4 mm Hg (−11 to 6), and the median and IQR of ScvO₂ were 67.0% (60.9–73.9) (Table 1).

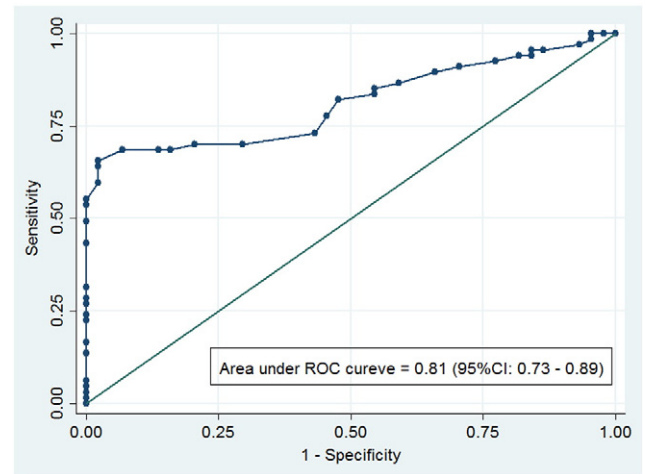


Fig. 1. Receiver operating characteristic curve of ΔBP as an indicator of ScvO₂ < 70%.

Central-venous oxygen saturation was less than 70% in 67 (60%) of the 111 patients. Among the patients with ScvO₂ less than 70%, the median and IQR of ΔBP were 4 mm Hg (−7 to 9), and among the patients with ScvO₂ more than 70%, the median and IQR of ΔBP were −9 mm Hg (−14 to −5) (Table 2). According to the type of shock, the median and IQR of ΔBP were −7 mm Hg (−13 to −1) among patients with sepsis, 7 mm Hg (4–10) among patients with cardiogenic shock, and 5 mm Hg (−1 to 7) among patients with hypovolemic shock (Supplementary Fig. 1). Fig. 1 shows the ROC curve for ΔBP as an indicator of ScvO₂ < 70%. The area under the curve was 0.81 (95% CI, 0.73–0.89). Table 3 shows sensitivity, specificity, positive predictive value, and negative predictive value for ΔBP as an indicator of ScvO₂ less than 70% at various cutoff values of ΔBP. With a cutoff ΔBP of 0 mm Hg where Youden index was maximized (0.63), sensitivity was 65.7% (95% CI, 53.1–76.8), specificity was 97.7% (95% CI, 88.0–99.8), the positive predictive value was 97.8 (95% CI, 88.2–99.9), and the negative predictive value was 65.2 (95% CI, 52.4–76.5).

Central-venous oxygen saturation was less than 65% in 44 (40%) of the 111 patients. As an indicator of more severe desaturation (ScvO₂ < 65%), a ΔBP cutoff of 0 mm Hg was also excellent: sensitivity = 93.0%, specificity = 94.0%, and Youden index = 0.87 (Fig. 2 and Table 4).

4. Discussion

In patients with hypotension, a difference of 0 mm Hg or higher between systolic blood pressure measured invasively at radial and systolic blood pressure measured noninvasively at brachial was a very highly specific indicator of ScvO₂ (<70%). Also, as an indicator of severe desaturation (ScvO₂ < 65%), a difference of 0 mm Hg or higher between invasively and noninvasively measured systolic blood pressure was extremely sensitive and specific.

We are aware of no previous study of the relationship between ΔBP and ScvO₂. Considering that ScvO₂ is usually normal or high in patients with septic shock and it is usually low in patients with hemorrhagic shock, previous results regarding differences between ABP and NIBP are consistent with our findings that ΔBP is negative (ie, NIBPs > ABPs) when ScvO₂ is greater than 70% and that ΔBP is positive (ie, NIBPs < ABPs) when ScvO₂ is less than 70% [21,23,29].

Although the physiological mechanism underlying this phenomenon is unclear, we speculate that vascular resistance of the radial artery could cause this phenomenon. Rich et al [30] reported that the gradient between aortic pressure and radial pressure changed as vascular resistance of the radial artery changed during cardiac surgery. When vascular resistance increased, radial pressure increased and exceeded aortic pressure, and the opposite occurred when vascular resistance

Table 3

Sensitivity, specificity, positive predictive value, and negative predictive value at 9 cutoff points of Δ BP as an indicator of $\text{ScvO}_2 < 70\%$

Cutoff point of Δ BP	Sensitivity	Specificity	Positive predictive value	Negative predictive value
–20	95.5 (87.5–99.1)	15.9 (6.6–30.1)	63.4 (53.2–72.7)	70 (34.8–93.3)
–15	94 (85.4–98.3)	18.2 (8.2–32.7)	63.6 (53.4–73.1)	66.7 (34.9–90.1)
–10	85.1 (74.3–92.6)	45.5 (30.4–61.2)	70.4 (59.2–80)	66.7 (47.2–82.7)
–5	70.1 (57.7–80.7)	70.5 (54.8–83.2)	78.3 (65.8–87.9)	60.8 (46.1–74.2)
0	65.7 (53.1–76.8)	97.7 (88–99.9)	97.8 (88.2–99.9)	65.2 (52.4–76.5)
5	49.3 (36.8–61.8)	100 (92–100)	100 (89.4–100)	56.4 (44.7–67.6)
10	23.9 (14.3–35.9)	100 (92–100)	100 (79.4–100)	46.3 (36–56.8)
15	4.5 (0.93–12.5)	100 (92–100)	100 (29.2–100)	40.7 (31.4–50.6)
20	1.5 (0.04–8.0)	100 (92–100)	100 (2.5–100)	40 (30.8–49.8)

decreased. When systemic vascular resistance decreases, as it does in septic shock, radial artery pressure could decrease. Conversely, when systemic vascular resistance increases, as it does in cardiogenic shock or hemorrhagic shock, then radial artery pressure could increase. Hatib et al [31] reported that systolic arterial pressure increased from aorta to radial at normal hemodynamic and that this arterial pressure gradient was lost in animal models of endotoxic shock. They explained that this phenomenon was due to a differential effect of acute endotoxemia on the central- and peripheral-derived vascular compliance.

5. Limitations

This study has several limitations. First, because we relied on chart review, we cannot be sure about the validity and reliability of the blood pressure measurements. However, blood pressures were measured at the end of expiration during the period of hemodynamic stability to avoid wide fluctuations in blood pressure, as is our usual practice, and we believe that changes in systolic arterial pressure over those several seconds were within $\pm$ or $\pm$ 3 to 5 mm Hg. As Table 2 shows, specificities and negative predictive values were very high at Δ BP of 0 mm Hg and higher, and these values would not have been affected by measurement error of arterial pressure within 3 to 5 mm Hg. Second, as the nature of the cross-sectional study, we could not evaluate the longitudinal variation of ScvO_2 . The ScvO_2 levels may vary from minute to minute; however, all participants were admitted to the ICU after initial resuscitation was performed, and we guess that the ScvO_2 would not be so unstable. Third, the sample size was small and the 95% CIs are large. Still, the area under the ROC curve is large enough that Δ BP should be clinically useful. To overcome both of those limitations, a larger, prospective study would be helpful.

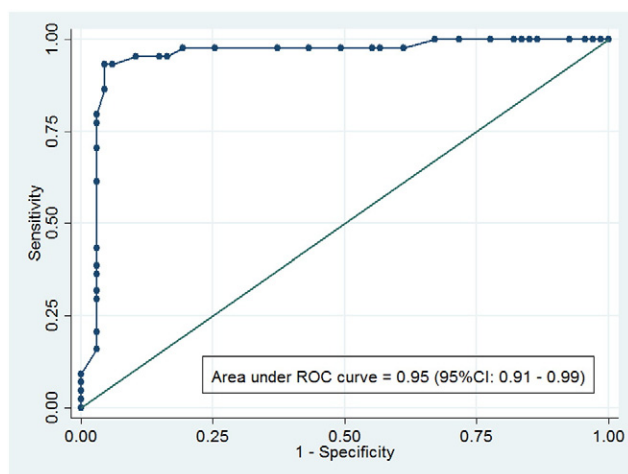


Fig. 2. Receiver operating characteristic curve of Δ BP as an indicator of $\text{ScvO}_2 < 65\%$.

Table 4

Sensitivity, specificity, positive predictive value, and negative predictive value at 9 cutoff points of Δ BP as an indicator of $\text{ScvO}_2 < 65\%$

Cutoff point of Δ BP	Sensitivity	Specificity	Positive predictive value	Negative predictive value
–20	100 (92.0–100)	14.9 (7.4–25.7)	43.6 (33.7–53.8)	100 (69.2–100)
–15	100 (92.0–100)	17.9 (9.6–29.2)	44.4 (34.5–54.8)	100 (73.5–100)
–10	97.7 (88.0–99.9)	43.3 (31.2–56.0)	53.1 (41.7–64.3)	96.7 (82.8–100)
–5	97.7 (88.0–99.9)	74.6 (62.5–84.5)	71.7 (58.6–82.5)	98.0 (89.6–100)
0	93.2 (81.3–98.6)	94.0 (85.4–98.3)	91.1 (78.8–97.5)	95.5 (87.3–99.1)
5	70.5 (54.8–83.2)	97.0 (89.6–99.6)	93.9 (79.8–99.3)	83.3 (73.2–90.8)
10	31.8 (18.6–47.6)	97.0 (89.6–99.6)	87.5 (61.7–98.4)	68.4 (58.1–77.6)
15	6.8 (1.4–18.7)	100 (94.6–100)	100 (29.2–100)	62 (52.2–71.2)
20	2.3 (0.06–12.0)	100 (94.6–100)	100 (2.5–100)	60.9 (51.1–70.1)

Fourth, data from some patients with shock were not included because there were no measurements of ScvO_2 . Those patients were less severely ill than the others, which could affect the results' generalizability. However, we believe that generalizability to patients who are not severely ill is not particularly important, as the primary utility of ScvO_2 , and thus of Δ BP, is in the management of patients such as the 111 severely ill patients whose data we did analyze.

6. Implications for future research and clinical practice

Although ScvO_2 has been studied as a prognostic marker and a resuscitation goal in patients with shock [1,32,33], therapy targeting ScvO_2 values of 70% or greater did not reduce all-cause mortality among sepsis patients in recent large randomized clinical trials [2–4]. However, Mikor et al [5] reported that ScvO_2 -assisted fluid therapy reduced postoperative complications, and several studies reported that ScvO_2 could be a prognostic marker for surgical or trauma patients [5–8]. Therefore, Δ BP could be used as a prognostic marker or a goal for resuscitation among surgical or trauma patients. Furthermore, ScvO_2 has also been studied as a surrogate marker of cardiac output [9,10]. Maintaining sufficient cardiac output is important when pure vasopressors are used [34]. Δ BP could be a surrogate marker of cardiac output when vasopressors or inotropic agents are used. Outcomes in patients with shock can be improved when advanced hemodynamic monitoring such as monitoring of cardiac output, stroke volume, stroke volume variation, and pulse pressure variation is used to guide therapy, but these indices are not monitored routinely, and arterial pressure monitoring remains the most commonly used tool, being applied in more than 80% of cases in Europe and in the United States [35]. One of the reasons may be that accurate measurement of cardiac output, stroke volume variation, and pulse pressure variation requires advanced and costly instrumentation. In contrast, Δ BP can be measured easily and relatively cheaply. Although further clinical studies of Δ BP are certainly needed, it could well become widely used in the management of critically ill patients.

7. Conclusions

The difference between invasively and noninvasively measured systolic blood pressure can indicate whether ScvO_2 is lower than 70%. When that difference is greater than 0, ScvO_2 is very likely to be lower than 70%.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jcrc.2016.02.022>.

Contributors

J. Kumasawa conceived the study, collected the data, undertook primary analyses, and drafted the manuscript. A. Ohara conceived the study, undertook and supervised data analysis, and contributed to the manuscript. H. Kohata, K. Aoyagi, and S. Fukuma advised on data

analysis and presentation and contributed to the manuscript. S. Fukuhara supervised the study design, data analysis, interpretation of results, and refined the manuscript.

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