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INFLUENCE OF ARTERIAL DISSOLVED OXYGEN LEVEL ON VENOUS OXYGEN SATURATION: DON'T FORGET THE PAO_2!

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ABSTRACT—Dissolved oxygen (i.e., unbound to hemoglobin) is often neglected as a determinant of central venous oxygen saturation ($ScvO_2$) in review articles and textbooks. These statements may lead to potential misinterpretation of $SCvO_2$ value across FiO_2 changes. In this study, we aimed to explore the influence of PaO_2 and FiO_2 on $ScvO_2$ in ventilated critically ill patients. This was a prospective observational study in two surgical intensive care units. Mechanically ventilated and sedated patients with cardiac output and $ScvO_2$ monitoring and $PaO_2/FiO_2 > 200$ with inspiratory oxygen (FiO_2) ≤ 0.5 were enrolled (cohort [$ScvO_2$]). A second cohort of brain-injured patients with jugular venous oxygen saturation monitoring was studied to assess the application of the results to regional circulation (cohort [$SjvO_2$]). Central venous oxygen saturation was measured at baseline FiO_2 and at $FiO_2 = 1$. We finally estimated the participation of the dissolved oxygen ($Pa_{dissolv}O_2$) to the $ScvO_2$ variations. Twenty patients formed the cohort $ScvO_2$ and eight formed the cohort $SjvO_2$. Central venous oxygen saturation rose from 71% (69%–76%) to 84% (78%–88%) after increasing FiO_2, whereas PaO_2 rose from 100 (85–124) mmHg to 387 (360–449) mmHg. The rise of $ScvO_2$ was mostly ascribable to the dissolved oxygen. The increase of $ScvO_2$ was not explained by changes in cardiac output or hemoglobin levels. Jugular venous oxygen saturation rose from 71% (58%–78%) to 83% (78%–89%) after increasing FiO_2. Arterial dissolved oxygen level can significantly influence the $ScvO_2$ value. Therefore, PaO_2 should not be overlooked while considering the $ScvO_2$ value as a therapeutic goal. Interpretation of $ScvO_2$ variations in response to a therapeutic challenge (i.e., fluid challenge, inotropic drug initiation) should be performed at constant FiO_2.

KEYWORDS—Oxygen saturation, oxygen pressure, hemoglobin, cardiac output, shock, resuscitation

INTRODUCTION

One major goal of critically ill patient's management is to ensure appropriate oxygen supply to the organs to avoid organ dysfunction (1). An adequate tissue oxygenation is obtained when the tissue oxygen consumption (VO_2) is covered by sufficient oxygen delivery (DO_2) associated with a normal range of oxygen (O_2) extraction (2). Central venous oxygen saturation ($ScvO_2$) measurement is considered a guide for hemodynamic optimization in circulatory failure conditions (3). Cardiac output (CO), plasma hemoglobin (Hb) concentration, arterial Hb oxygen saturation, and oxygen consumption are the most important factors influencing $ScvO_2$. In textbooks and reviews, dissolved oxygen (i.e., unbound to Hb) is often neglected as a part of DO_2 and consequently as a determinant of $ScvO_2$. This is mostly caused by the very low oxygen solubility coefficient (i.e., 0.003). However, this statement may lead to a potential misinterpretation of $ScvO_2$ values across FiO_2 changes inducing large changes in PaO_2. With this study, we aimed to study the influence of PaO_2 and FiO_2 on $ScvO_2$ in ventilated critically ill patients. We hypothesized that dissolved oxygen ($Pa_{dissolv}O_2$) can significantly contribute to $ScvO_2$ values when PaO_2 increases.

MATERIALS AND METHODS

The study population

This study was approved by our local ethics committee (Comité d'Évaluation de l'Éthique des projets de Recherche Biomédicale), and written informed consent was waived because of the noninterventional design of the study. Patients were eligible for inclusion if their blood arterial pressure was invasively monitored, if they were under sedation (with midazolam and fentanyl) with a Ramsay score of 5 to 6, mechanically ventilated with a $PaO_2/FiO_2 > 200$ with $FiO_2 \leq 0.5$, and with hemodynamic stability (i.e., no need for fluid loading or change of vasopressor infusion rate over the last 6 h). Patients had to have a central venous line and to be monitored for CO with a transoesophageal Doppler (Deltex Medical, Chicester, UK). A second cohort of brain-injured patients with jugular vein oxygen saturation ($SjvO_2$) monitoring was also included (cohort $SjvO_2$) to assess whether the concept holds true when applied to regional circulation (4).

Measurements

As a standard of care in our unit, once daily, all patients monitored with $ScvO_2$ had both arterial and venous blood gas analyses at the FiO_2 that ensure a SaO_2 greater than 95% (baseline FiO_2) and PaO_2 approximately 100 mmHg and at $FiO_2 = 1$ to assess pulmonary shunting. The blood gas analysis was performed 15 min after changing the FiO_2. Blood gases for analyses performed at both FiO_2 were collected when patients were resting without any external stimulation. No changes in vasopressor infusion rate, fluid bolus, or other therapeutic intervention between the two measurements were required for data analysis. The following parameters were measured in cohort A: hemodynamic parameters (CO, blood arterial pressure) and blood gas analysis using a Rapidlab 1265 Series automat (Siemens, Camberley, UK) including arterial oxygen pressure (PaO_2), venous oxygen pressure (PvO_2), measured Hb arterial oxygen saturation (SaO_2), Hb venous oxygen saturation measured on blood gas analysis ($ScvO_2$) and Hb concentration. A chest x-ray confirmed the adequate position at entrance of the right atrium of the tip of the central venous catheter. In cohort B ($SjvO_2$), cerebral oxygenation monitoring was performed using a retrograde internal jugular catheter. The correct placement of the catheter tip in the jugular bulb was confirmed with x-ray.

Calculation of oxygenation parameters

Formulae used for calculated oxygenation parameters are presented in Table 1. Formula 5 in Table 1 was used for predicting $ScvO_2$ variation (Delta $ScvO_2$) after change in FiO_2 (≈0.4 vs. 1), considering oxygen consumption

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TABLE 1. **Calculation of oxygenation parameters***

Variable	Abbreviation	Equation	Unit
(1) O_2 delivery	DO_2	$CO \times CaO_2$	mL O_2/min
(2) Arterial O_2 content	CaO_2	$(1.34 \times Hb \times SaO_2) + (0.003 \times PaO_2)$	mL O_2/mL
(3) Dissolved arterial O_2 content	$Ca_{dissolv}O_2$	$0.003 \times PaO_2$	mL O_2/mL
(4) Venous O_2 content	CvO_2	$(1.34 \times Hb \times SvO_2) + (0.003 \times PvO_2)$	mL O_2/mL
(5) Predicted variation of $ScvO_2$	Delta $ScvO_2$	$Hb \times 1.34 \times [SaO_{2(100\%)} - SaO_{2(40\%)}] + 0.003 \times [PaO_{2(100\%)} - PaO_{2(40\%)}] - [PvO_{2(100\%)} - PvO_{2(40\%)}]/(Hb \times 1.34 \times 100)$	%
(6) Estimated variation of dissolved oxygen to the $ScvO_2$	Delta $dScvO_2$	$(\text{Delta } ScvO_2) - (\{Hb \times 1.34 \times [SaO_{2(100\%)} - SaO_{2(40\%)}]\}/(Hb \times 1.34) \times 100)$	%

*Delta $ScvO_2$, difference (%) of $ScvO_2$ between two measurements; Hb, blood hemoglobin concentration (g/dL); $SaO_{2(40\%)}$, arterial oxygen saturation (%) at FiO_2 0.4; $SaO_{2(100\%)}$, arterial oxygen saturation (%) at FiO_2 1; $PaO_{2(40\%)}$, arterial oxygen pressure at FiO_2 = 0.4; $PaO_{2(100\%)}$, arterial oxygen pressure at FiO_2 = 1; $PvO_{2(40\%)}$, venous oxygen pressure at FiO_2 = 0.4; $PvO_{2(100\%)}$, venous oxygen pressure at FiO_2 = 1; CO, cardiac output.

was stable between the two measurements. Impact of dissolved oxygen content ($Ca_{dissolv}O_2$) on $ScvO_2$ (Delta $dScvO_2$) was evaluated by subtracting the $ScvO_2$ at FiO_2 approximately 0.4 and 1 (Table 1). All were paired measures.

Statistical analysis

Values are reported as median (25–75 percentiles). Paired Wilcoxon test analysis was used for intragroup comparisons for $ScvO_2$ and $SjvO_2$ between FiO_2 at approximately 0.4 and 1. A Wilcoxon test was used for paired comparisons. Value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed with GraphPad Prism version 4.0 for Windows (GraphPad Software, San Diego, Calif). We estimated that we needed to include 16 patients to show an increase of $ScvO_2$ of 9% (SD, 6%) after increasing PaO_2 from 100 to 500 mmHg, assuming a median Hb level of 10 g/dL and median oxygen consumption of 200 mL/min, with an α risk of 5% and a power of 90%.

RESULTS

Characteristics of patients

Twenty patients formed the cohort $ScvO_2$, aged 63 (46–80) years, Simplified Acute Physiology Score (SAPS2) score 54 (42–58), 5 women and 15 men. Eleven had sepsis, five were trauma/burn patients, two had hemorrhagic shock, and two had cardiogenic shock. Twelve patients were under norepinephrine 0.5 (0.35–0.95) μg/kg per min, three received epinephrine 0.41 (0.35–0.47) μg/kg per min, and two received dobutamine 10 (10–10) μg/kg per min. Serum lactate level was 3.2 (1.8–4.3) mmol/L, platelets 166 (85–352) $\times 10^3$/L, serum bilirubin 14 (9–25) μmol/L, serum creatinine 125 (72–240) μmol/L. Eight patients formed the cohort $SjvO_2$, aged 32 (20–54) years, SAPS2 score 46 (34–57), five had a traumatic brain injury, two had stroke, and one had subarachnoid hemorrhage.

Oxygenation parameters

We observed that increasing FiO_2 from 0.4 (0.3–0.5) to 1 (1–1) leads to an increase of PaO_2 from 100 (85 – 124) mmHg to 387 (360–449) mmHg and a significant increase of $ScvO_2$ from 71% (69%–76%) to 84% (78%–88%) (Fig. 1). We found similar results with $SjvO_2$ when increasing FiO_2 in patients with brain injury (Fig. 1). The rise of $ScvO_2$ was not explained by changes in CO or Hb levels (5 [3.9–6.1] L/min vs. 5 (3.9–6.2) L/min and 11.1 (9.8–12.8) vs. 10.9 (9.8–12.7) g/dL, respectively, ns). Hemoglobin arterial oxygen saturation slightly increased from 0.97% (0.96%–0.98%) to 0.99% (0.98%–1.0%) ($P < 0.001$). Dissolved oxygen arterial content ($Ca_{dissolv}O_2$) rose significantly after increasing the FiO_2 from 0.30 (0.26–0.37) to 1.16 (1.08–1.35) mL and from 0.32 (0.23–0.45) to 1.47 (1.20–1.72) mL in the $ScvO_2$ group and the $SjvO_2$ group, respectively (Table 2; Fig. 2). However, estimated participation of the dissolved oxygen component (based on formula 6 in Table 1) revealed that it largely accounted for the rise of $ScvO_2$ (8.0% [5.9%–11.9%]) (Tables 1 and 2). Arterial carbon dioxide partial pressure ($PaCO_2$), venous carbon dioxide partial pressure ($PvCO_2$), arterial pH, and venous pH were not different between FiO_2 approximately 0.4 and 1. Fourteen patients had a third time point available, performed at FiO_2 0.5 or 0.6, allowing to plot $ScvO_2$ values against PvO_2 values and showing a sigmoidal relationship (Fig. 3).

DISCUSSION

Our study shows that dissolved oxygen can significantly influence the $ScvO_2$ value. Similar results were observed using

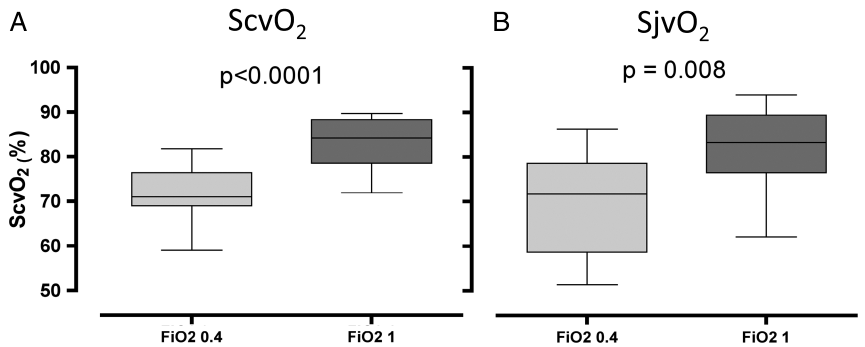

FIG. 1. **Evolution of measured $ScvO_2$ (A) and $SjvO_2$ (B) with increase of FiO_2.** Data presented in box and whisper plots (min-max).

TABLE 2. **Oxygenation parameters between FiO_2 40% and FiO_2 100% in the cohort $ScvO_2$**

Abbreviation	FiO_2 40% (30% – 50%)	FiO_2 100%	*P*
CO, L/min	5 (3.9–6.1)	5 (3.9–6.2)	0.76
Hb, g/dL	11.1 (9.8–12.8)	10.9 (9.8–12.7)	0.91
SaO_2, %	0.97 (0.96–0.98)	0.99 (0.98–1.0)	<0.001
PaO_2, mmHg	100 (85–124)	387 (360–449)	<0.0001
DO_2, mL O_2/min	712 (557–890)	761 (589–976)	0.44
CaO_2, mL O_2/mL	14.8 (13.0–14.8)	15.7 (14.3–18.2)	0.12
$Ca_{dissolv}O_2$, mL O_2/mL	0.30 (0.26–0.37)	1.16 (1.08–1.35)	<0.0001
PvO_2, mmHg	39 (36–44)	50 (45–57)	<0.0001
CvO_2, mL O_2/mL	11.0 (9.1–12.5)	12.0 (11.0–14.4)	0.05
$ScvO_2$, %	71 (69 –76)	84 (78–88)	<0.0001
Delta $ScvO_2$, %	—	9.3 (8.3–14.5)	—
Delta $Scv_{dissolv}O_2$, %	—	8.0 (5.9–11.9)	—

PaO_2, arterial PO_2; DO_2, oxygen delivery; VO_2, oxygen consumption, CaO_2, arterial oxygen content; $Ca_{dissolv}O_2$, arterial dissolved oxygen content; PvO_2, venous PO_2; CvO_2, venous oxygen content; $ScvO_2$, central venous oxygen saturation; Delta $ScvO_2$, variation of $ScvO_2$; Delta $Scv_{dissolv}O_2$, estimated variation of dissolved oxygen to the $ScvO_2$.

$SjvO_2$ in brain-injured patients, suggesting that it can also be applied at a regional circulation level. Our study highlights a well-known basic physiological principle, which has been overlooked in most reviews and textbooks that may lead to misinterpretation of $ScvO_2$. These misinterpretations of the determinant of $ScvO_2$ might arise from the oversimplification of the determinants of $ScvO_2$ with PaO_2 omission (leaving CO, SaO_2, and Hb level as sole determinants). We therefore believe that the results of our study can reach an important educational target in providing evidence for careful reading of the determinant of $ScvO_2$: PaO_2 should not be neglected when interpreting the $ScvO_2$ value.

The $ScvO_2$ has been widely included in goal-directed therapy algorithms both in critically ill patients and patients undergoing major surgery. These algorithms propose to optimize systemic hemodynamics to reach $ScvO_2$ greater than 70% and improve oxygen delivery (5). Because most textbooks and reviews proposed to neglect dissolved oxygen as part of O_2 content, PaO_2 is not included in most formulae showing the main determinants of $ScvO_2$ {i.e., $ScvO_2 = SaO_2 - [VO_2 / (CO \times Hb \times 1.34)]$} (2,6). Likewise, most observational studies did not mention the PaO_2 level in their results. For example, an observational study from Hernandez et al. showed a $ScvO_2$ increase from 61.8% ± 12.6% to 68.9% ± 12.2% when in critically ill patients were intubated and mechanically ventilated (7). The authors did not find any correlation between increase of $ScvO_2$ and changes in SaO_2, although blood gas were obtained 15 min after mechanical ventilation with $FiO_2 = 1$, a situation where high PaO_2 values might have accounted for the rise of $ScvO_2$. Because PaO_2 was not reported, it became difficult to conclude on this point. This is true for many studies testing and measuring $ScvO_2$ as an algorithm target (1, 8–10).

The range of $ScvO_2$ changes associated with the increase in FiO_2 (~9%–10%) can be seen modest when compared with those associated with CO or SaO_2 level. Indeed, because of the sigmoid shape of the oxygen-Hb dissociation curve, modest changes in PvO_2 can induce significant changes in $ScvO_2$. However, this range of $ScvO_2$ variation appears relevant in the light of current recommendation for resuscitation of patients with severe sepsis (i.e., to reach $ScvO_2$ >70%) (5). Furthermore, it is reasonable to expect a more pronounced effect of dissolved O_2 content when CO and Hb level are low (11).

The aim of the study was not to evaluate the potential benefit of increasing PaO_2 for improving tissue oxygenation but to appreciate the influence of variations in PaO_2 on $ScvO_2$ to raise awareness of intensivists while using the $ScvO_2$ as a hemodynamic target. However, different studies have used high inspiratory fraction of O_2 and dissolved O_2 as factors to improve

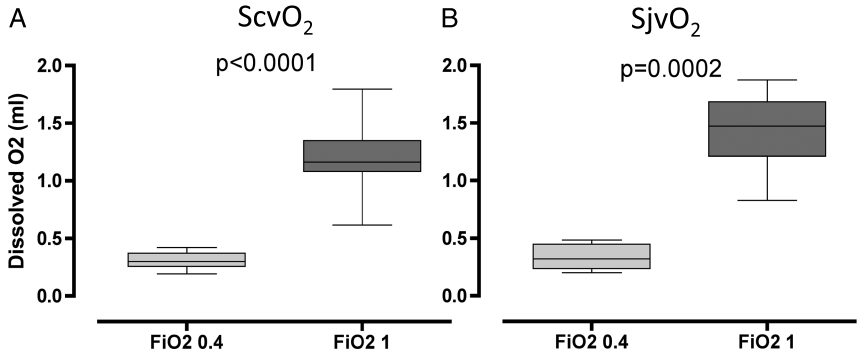

FIG. 2. **Evolution of the dissolved fraction of oxygen after increasing FiO_2 from 0.4 to 1 in the $ScvO_2$ cohort (A) and the $SjvO_2$ cohort (B).** Data presented in box and whisper plots (min-max).

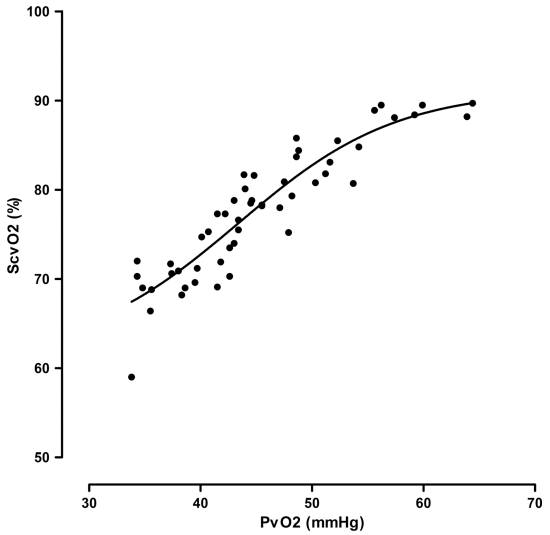

FIG. 3. **Plot of PvO_2 and $ScvO_2$ across a range of FiO_2 from 0.4 to 1 in 20 patients showing a sigmoidal relationship (54 measures).** These data highlight the expected sharp rise in $ScvO_2$ for modest changes in PvO_2 when PaO_2 increases.

tissue oxygen tension, illustrating that the amount of dissolved O_2 content may participate in tissue oxygenation. Yu et al. (12) observed a significant increase of tissue PO_2 (PtO_2) in critically ill patients after an oxygen challenge test (i.e., increase FiO_2 to 100%), illustrating the better oxygen delivery to tissue after increasing FiO_2. Likewise, Dyson et al. (13) observed a significant rise of PtO_2 in animal breathing at $FiO_2 = 1$ compared with room air. Although this study was not designed to assess the role of high FiO_2 to increase DO_2, this question merits to be prospectively addressed.

Our study has several limitations. The cohort size is small. The sizing was, however, fitting well with the sample size calculation, and the results are sustained by a strong physiological basis. It is unlikely that increasing the sample size would modify the results. Second, VO_2 was not measured. However, our patients were considered stable, nonstimulated, and under sedation, making a significant change in VO_2 between measurements unlikely.

Our study has direct clinical implications. In addition to CO and Hb levels as key determinant of $ScvO_2$ or organ SvO_2, our study shows that PaO_2, when varying significantly, is also to be taken into account when interpreting changes in $ScvO_2$. It can therefore be recommended to assess the impact of each therapeutic intervention (e.g. fluid loading, inotropes or vasopressors infusion, blood transfusion) at a constant FiO_2 and avoid significant variations in PaO_2.

In conclusion, our study shows that increasing dissolved oxygen content can notably influence $ScvO_2$ and $SjvO_2$ values in intensive care unit patients.

REFERENCES

1. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345(19):1368–1377, 2001.
2. Walley KR: Use of central venous oxygen saturation to guide therapy. *Am J Respir Crit Care Med* 184(5):514–520, 2011.
3. Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM: Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. *Chest* 95(6):1216–1221, 1989.
4. Clavier N, Schurando P, Raggueneau JL, Payen DM: Continuous jugular bulb venous oxygen saturation validation and variations during intracranial aneurysm surgery. *J Crit Care* 12(3):112–119, 1997.
5. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, et al.: Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. *Intensive Care Med* 39(2):165–228, 2013.
6. Teboul J-L, Hamzaoui O, Monnet X: SvO_2 to monitor resuscitation of septic patients: let's just understand the basic physiology. *Crit Care* 15(6):1005, 2011.
7. Hernandez G, Peña H, Cornejo R, Rovegno M, Retamal J, Navarro JL, Aranguiz I, Castro R, Bruhn A: Impact of emergency intubation on central venous oxygen saturation in critically ill patients: a multicenter observational study. *Crit Care* 13(30):R63, 2009.
8. Trzeciak S, Dellinger RP, Parrillo JE, Guglielmi M, Bajaj J, Abate NL, Arnold RC, Colilla S, Zanotti S, Hollenberg SM, Microcirculatory Alterations in Resuscitation and Shock Investigators: Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med* 49(1):88–98, 2007.
9. Bracht H, Hänggi M, Jeker B, Wegmüller N, Porta F, Tüller D, Takala J, Jakob SM: Incidence of low central venous oxygen saturation during unplanned admissions in a multidisciplinary intensive care unit: an observational study. *Crit Care* 11(1):R2, 2007.
10. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA; Emergency Medicine Shock Research Network (EMShockNet) Investigators: Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 303(8):739–746, 2010.
11. He H-W, Liu D-W, Long Y, Wang X-T, Chai W-Z, Zhou X: The transcutaneous oxygen challenge test: a noninvasive method for detecting low cardiac output in septic patients. *Shock* 37(2):152–155, 2012.
12. Yu M, Morita SY, Daniel SR, Chapital A, Waxman K, Severino R: Transcutaneous pressure of oxygen: a noninvasive and early detector of peripheral shock and outcome. *Shock* 26(5):450–456, 2006.
13. Dyson A, Stidwill R, Taylor V, Singer M: The impact of inspired oxygen concentration on tissue oxygenation during progressive hemorrhage. *Intensive Care Med* 35(10):1783–1791, 2009.