Use of Central Venous Oxygen Saturation to Guide Therapy

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The use of pulmonary artery catheters has diminished, so that other technologies are emerging. Central venous oxygen saturation measurement (Scv_{O_2}) as a surrogate for mixed venous oxygen saturation measurement ($S\bar{v}_{O_2}$) is simple and clinically accessible. To maximize the clinical utility of Scv_{O_2} (or $S\bar{v}_{O_2}$) measurement, it is useful to review what the measurement means in a physiologic context, how the measurement is made, important limitations, and how this measurement may be helpful in common clinical scenarios. Compared with cardiac output measurement, $S\bar{v}_{O_2}$ is more directly related to tissue oxygenation. Furthermore, when tissue oxygenation is a clinical concern, $S\bar{v}_{O_2}$ is less prone to error compared with cardiac output, where small measurement errors may lead to larger errors in interpreting adequacy of oxygen delivery. Scv_{O_2} should be measured from the tip of a central venous catheter placed close to, or within, the right atrium to reduce measurement error. Correct clinical interpretation of $S\bar{v}_{O_2}$, or its properly measured Scv_{O_2} surrogate, can be used to (*1*) estimate cardiac output using the Fick equation, (*2*) better understand whether a patient's oxygen delivery is adequate to meet their oxygen demands, (*3*) help guide clinical practice, particularly when resuscitating patients using validated early goal directed therapy treatment protocols, (*4*) understand and treat arterial hypoxemia, and (*5*) rapidly estimate shunt fraction (venous admixture).

Keywords: early goal directed therapy; cardiac output; Fick equation; shunt fraction; oxygen extraction ratio

Several studies assessing pulmonary artery catheter use failed to demonstrate benefit (1–3). Consequently, the use of pulmonary artery catheters to monitor critically ill patients and to guide therapy has diminished substantially (4). Some have suggested that the problem was not so much with the pulmonary artery catheter as with inadequate knowledge and interpretation (5). To fulfill the perceived clinical need for similar measurements a number of new technologies have emerged, including echocardiography (6), ultrasonic cardiac output monitors (7), arterial pulse pressure analysis techniques (8, 9), impedance techniques (10, 11), alternative dye dilution techniques (12), and so on, to provide alternative/additional measurements. In the absence of clinical trials analogous to those for pulmonary artery catheters, we do not know if these alternative/additional measurements are beneficial (13). To avoid a repeat of the pulmonary artery catheter story, it is important to maximize our knowledge of alternative/additional approaches so that we measure and interpret arising parameters in a way that maximizes clinical utility.

One remarkably simple alternative/additional measurement for which there is some evidence of clinical utility (14–17) is the measurement of central venous oxygen saturation (Scv_{O_2})—a surrogate measure of mixed venous oxygen saturation ($S\bar{v}_{O_2}$). Further evaluation is underway (18–20). To maximize the clinical utility of Scv_{O_2} (or $S\bar{v}_{O_2}$) measurement, it is useful to review what the measurement means in a physiologic context, how the measurement is made, important limitations, and how this measurement may be helpful in common clinical scenarios.

FIRST, DO WE NEED TO KNOW CARDIAC OUTPUT?

Adequate tissue oxygenation is essential for normal organ function. The amount of oxygen delivered to the tissues is flow (cardiac output in L blood/min) multiplied by oxygen-carrying capacity (mL O_2/L blood). Thus, cardiac output is important, but is not the only factor in determining adequacy of tissue oxygenation. Metabolic demand, hemoglobin concentration, and body size are three highly variable parameters that dramatically alter the "critical cardiac output" from minute to minute, over time in the same patient, and between patients, respectively. Adequacy of tissue oxygenation is, instead, determined by the balance between oxygen delivered to tissues (D_{O_2}) and oxygen consumption by the tissues (V_{O_2}). This balance is reflected by the fraction of delivered oxygen that the tissues consume ($ER_{O_2} = V_{O_2}/D_{O_2}$) or by the related variable (*see below*) venous oxygen saturation ($S\bar{v}_{O_2}$—how much of the delivered oxygen is left over after the tissues consume oxygen).

In contrast to a highly variable "critical cardiac output," many studies in many clinical states involving many different organs find a more stable and useful measurement reflecting tissue oxygenation to be the "critical oxygen extraction ratio," $ER_{O_2}crit$. Since $ER_{O_2} = V_{O_2}/D_{O_2}$, when D_{O_2} decreases relative to V_{O_2}, ER_{O_2} increases. When D_{O_2} falls further (decreasing cardiac output, oxygen carrying capacity, or arterial saturation) and is inadequate to meet V_{O_2} demand, ER_{O_2} exceeds a threshold that is identified by evidence of tissue hypoxia and anaerobic metabolism, including increasing lactate production and impaired organ function. This critical threshold is $ER_{O_2}crit$. $ER_{O_2}crit$ is approxmately 0.7 in normal healthy whole animals (21, 22) and regionally is approximately 0.7 in skeletal muscle (23, 24), approximately 0.7 in gut (21, 25), approximately 0.7 in heart (26), and approximately 0.7 in brain (27, 28) (*see* DISCUSSION OF DISEASE STATES, below).

Direct cardiac output measurement is essential in assessing a number of cardiovascular disease states. However, when addressing the issue of inadequate tissue oxygenation a measure reflecting tissue oxygen extraction, ER_{O_2}, may be more informative.

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$S\bar{v}_{O_2}$ IS SIMPLY RELATED TO ERO_2

The Fick equation states that:

$$CO = Vo_2/(Ca_{O_2} - Cv_{O_2}), \quad (Eq.\ 1)$$

where Ca_{O_2} and Cv_{O_2} are the oxygen contents of arterial and venous blood, respectively. Rearranging yields:

$$CO \times Ca_{O_2} - Vo_2 = CO \times Cv_{O_2}. \quad (Eq.\ 2)$$

Since $Do_2 = Ca_{O_2} \times CO$ this can be can be rewritten, after dividing both sides by Do_2, as:

$$1 - ERo_2 = (CO \times Cv_{O_2})/(CO \times Ca_{O_2}). \quad (Eq.\ 3)$$

Note that $Cx_{O_2} = 1.34 \times Hgb \times Sx_{O_2}$ if dissolved oxygen is ignored. Cancelling common terms on the right hand side of Equation 2 and rearranging yields:

$$S\bar{v}_{O_2} = (1 - ERo_2) \times Sa_{O_2}. \quad (Eq.\ 4)$$

In clinical practice Sao_2 is often kept quite constant and often greater than 0.9, so that:

$$S\bar{v}_{O_2} \approx 1 - ERo_2. \quad (Eq.\ 5)$$

This simple relationship indicates that $S\bar{v}_{O_2}$ measurement is directly related to ERO_2 and can be used to help determine whether a patient or individual organs are close to ERO_2crit, where evidence of inadequate oxygen delivery and organ dysfunction occur.

TECHNICAL ISSUES

When Does $S\bar{v}_{O_2}$ Measurement Perform Well/Not Well?

When assessing the utility of any measurement it is important to consider the interpretation of the measurement in the face of measurement errors—related to a sensitivity analysis. For cardiac output measurement and $S\bar{v}_{O_2}$ measurement, this can be illustrated by considering the Fick equation. Examination of this relationship (Figure 1) suggests that when cardiac output is high, errors in cardiac output measurement result in only minor errors in estimates of $S\bar{v}_{O_2}$; which reflects adequacy of tissue oxygenation. However, when cardiac output is low the curve is steep (Figure 1), so that small measurement errors in cardiac output lead to large errors in estimates of adequacy of tissue oxygenation. In other words, when cardiac output is high (and generally not much of a clinical issue), cardiac output measurements are technically excellent. When cardiac output is low (and therefore a crucial clinical issue), cardiac output measurements are technically poor in reflecting tissue oxygenation. In contrast, when cardiac output is high, $S\bar{v}_{O_2}$ measurement error leads to large errors in Fick cardiac output estimates. When cardiac output is low, $S\bar{v}_{O_2}$ measurement error does not substantially impact the estimate of cardiac output. Thus, $S\bar{v}_{O_2}$ measurement performs poorly when it is clinically irrelevant (high cardiac output states), but technically performs well in clinically relevant situations in which oxygen delivery may be inadequate.

Is Scv_{O_2} an Adequate Surrogate for $S\bar{v}_{O_2}$? Important Limitations

Multiple investigators have compared true $S\bar{v}_{O_2}$ with Scv_{O_2} measured in blood drawn from a thoracic central venous line (29–37). (Parenthetically, femoral venous blood is not mixed and not downstream of any vital organs and therefore it would be erroneous to use this value to interpret anything except oxygenation of the distal leg.) In general, a good but not perfect correlation is observed (38) (Figure 2A) with Scv_{O_2} overestimating $S\bar{v}_{O_2}$ by 3 to 8% (39–41), a difference that decreases in low cardiac output states. Change in Scv_{O_2} may correlate more closely with change in $S\bar{v}_{O_2}$ (36), although this remains imperfect (37, 39). More recently, Kopterides and coworkers (40) investigated the role of placement of the tip of the central venous catheter. When the tip was 15 cm away from the inlet of the right atrium, Scv_{O_2} overestimated $S\bar{v}_{O_2}$ by 8%, consistent with previous reports. However, when the tip of the central venous catheter was advanced to the right atrium, Scv_{O_2} now was an excellent surrogate for $S\bar{v}_{O_2}$, overestimating $S\bar{v}_{O_2}$ by 1% (Figure 2B). Thus, when care is taken in the placement of the central venous catheter (Figure 3), Scv_{O_2} becomes a reasonable estimate of $S\bar{v}_{O_2}$ (36, 40).

Thus, Scv_{O_2} is not $S\bar{v}_{O_2}$ (41), and the relationship between these two variables changes with catheter placement, between low flow and high flow states, and can clearly be influenced by relative changes in superior and inferior vena caval flow and coronary sinus flow. Thus, Scv_{O_2} is only an approximation of $S\bar{v}_{O_2}$, and potential differences must be kept in mind when using and interpreting Scv_{O_2} measurements. Figure 2A illustrates these differences which, for individual measurements, can be quite discrepant.

CLINICAL USE OF $S\bar{v}_{O_2}$

Correct clinical interpretation of $S\bar{v}_{O_2}$, or its properly measured Scv_{O_2} surrogate, can be used to (*1*) estimate cardiac output, (*2*) better understand a patient's physiologic state, (*3*) help resuscitate patients using validated treatment protocols and help identify patients at risk of weaning failure, (*4*) understand and treat arterial hypoxemia, and (*5*) rapidly estimate shunt fraction (venous admixture).

$S\bar{v}_{O_2}$ Can Be Used to Easily Estimate Cardiac Output Using the Fick Equation

The Fick equation can be simplified by ignoring the small contribution of dissolved oxygen and by indexing variables to body surface area. Then $CI = Vo_2I/\{Hgb \times 1.34 \times (Sao_2 - S\bar{v}_{O_2})\}$, where CI is cardiac index ($L/min/m^2$), Vo_2I is oxygen consumption index, and 1.34 ml O_2/gram Hgb is the amount of oxygen bound to hemoglobin and is a physical constant (theoretically 1.39 but, in practice closer to 1.34 due to a small fraction of reduced hemoglobin or carbon monoxide binding). Since Vo_2I is relatively constant at rest, Hgb is relatively constant in patients not briskly bleeding, 1.34 is a physical constant, and Sao_2 is kept relatively constant (90–100%) by typical ICU nursing protocols, the truly variable parameters in this equation are CI and $S\bar{v}_{O_2}$. Examination of the Fick equation shows that a decrease in $S\bar{v}_{O_2}$ indicates a decrease in CI, and an increase in $S\bar{v}_{O_2}$ indicates an increase in CI.

When having a rough estimate of CI is helpful in understanding the physiologic state of the circulation, this simplified Fick equation can be used at the bedside using readily available measurements. Note that the a typical resting value of Vo_2I in humans is approximately 120 to 140 ml $O_2/min/m^2$ and the amount of O_2 bound to each gram of Hgb is approximately 1.34 so that the ratio of typical Vo_2I to 1.34 is about 100. Thus, the Fick equation can be simplified further to a working version for resting patients of:

$$CI \approx 100/Hgb \times 1/(Sa_{O_2} - S\bar{v}_{O_2}) (SI\ Hgb\ units\ of\ grams/L)\ or$$
$$CI \approx 10/Hgb \times 1/(Sa_{O_2} - S\bar{v}_{O_2}) (Hgb\ units\ of\ grams/dL) \quad (Eq.\ 6)$$

For example, if Hgb is 100 g/L, arterial pulse oximeter saturation is 0.95, and Scv_{O_2} is 0.70, then $CI \approx 100/100 \times 1/(0.95 -$

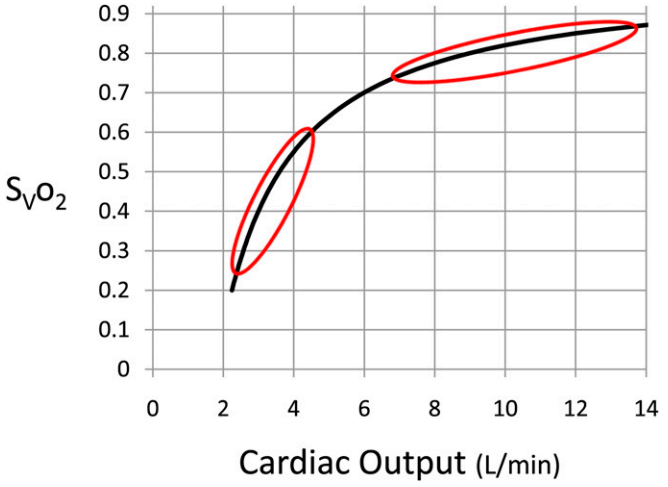

Figure 1. The Fick equation relating $S\bar{v}_{O_2}$ to cardiac output is plotted for Vo_2 = 220 ml/min, Hgb = 90 g/L, and Sao_2 = 100%. Where the curve is relatively flat, small errors in $S\bar{v}_{O_2}$ measurement are associated with large errors in the calculation of Fick cardiac output and its clinical interpretation. However, in this region of the Fick equation relationship, cardiac output is generous so that tissue oxygenation is generally not a major clinical issue. Where the curve is relatively steep the reverse is true. Small errors in cardiac output measurement result in substantial errors in interpretation of $S\bar{v}_{O_2}$. Since $S\bar{v}_{O_2}$ is directly related to tissue oxygenation ($S\bar{v}_{O_2} \approx 1 - ERo_2$) cardiac output measurement may not give clear guidance in assessing adequacy of tissue oxygenation. This is the region of the Fick equation relationship where tissue oxygenation is a major clinical issue. Therefore, when it counts, $S\bar{v}_{O_2}$ is less subject to error than cardiac output in assessing adequacy of oxygen delivery and tissue oxygenation.

$0.70) = 1/0.25 = 4$ L/min/m^2. If Scv_{O_2} drops to 0.45, then CI $\approx 1/0.5 = 2$ L/min/m^2. Using approximations and the Fick equation in this way can provide rapid and valuable clinical insight. *Post hoc* correction upward of Scv_{O_2} by approximately 5% could be considered but, to be clear, this is not a measurement of cardiac index; it is a "quick and dirty" approximation to aid clinical insight. When a technically correct value of cardiac output is required, then the above approximations are inappropriate (41) and direct measurements of Vo_2I and $S\bar{v}_{O_2}$ are required.

$S\bar{v}_{O_2}$ Can Be Interpreted Using Vo_2/Do_2 Relationships

What is a high $S\bar{v}_{O_2}$ value and what is a low value? $S\bar{v}_{O_2}$ gives information regarding the balance between oxygen delivery and oxygen consumption (Figure 4). The onset of anaerobic metabolism is characterized by a critical oxygen extraction ratio, ERo_2crit. In whole animal studies, in individual organ studies, and in human studies, the critical oxygen extraction ratio is approximately 70% (21–28). While relatively constant in health, ERo_2crit decreases in a number of critical illnesses (42) that are characterized by an impaired ability of the tissues to extract oxygen; importantly including sepsis (22, 24, 25). Impaired ability of the tissues to extract oxygen may be due to the observed increased heterogeneity of microvascular and macrovascular blood flow, related shunting of oxygen past the tissues (24, 43–45), and impaired ability of cells and their mitochondria to utilize oxygen (46). When tissue oxygen extraction capability is impaired, as it is during sepsis, ERo_2crit can fall to 50% in animal studies (47) and in the human heart (48, 49). Since $S\bar{v}_{O_2} \approx 1 - ER$ (when arterial oxygen saturation is $\sim$ 100%), it follows that the critical $S\bar{v}_{O_2}$ is approximately 30% in otherwise healthy individuals but can be 50% in patients who have severe sepsis or in other patients with impaired tissue oxygen extraction capability (Figure 4). In rare patients with extreme vasodilatory shock or following mitochondrial poisoning, cardiac output can be high and $S\bar{v}_{O_2}$ may be very high (> 85%), yet lactate levels may be elevated and shock and organ dysfunction persist. Oxygen extraction capacity in these patients is clearly very poor—reflected by a very high $S\bar{v}_{O_2}$ and a correspondingly very low ERo_2crit.

These considerations lead to an understanding of different $S\bar{v}_{O_2}$ values. $S\bar{v}_{O_2}$ over 70% generally is adequate and normal. $S\bar{v}_{O_2}$ less than 50% is low and, depending on tissue oxygen extraction capabilities, could be approaching values associated with ERo_2crit. In studying the critical oxygen delivery point in dying patients, we observed that patients cannot live for much more than a few minutes to an hour below this critical threshold (42). $S\bar{v}_{O_2}$ less than 50% and certainly less than 40% should generally be carefully considered and acted upon. $S\bar{v}_{O_2}$ values between 50% and 70% are somewhat low but, by themselves, do not lead to firm conclusions and must

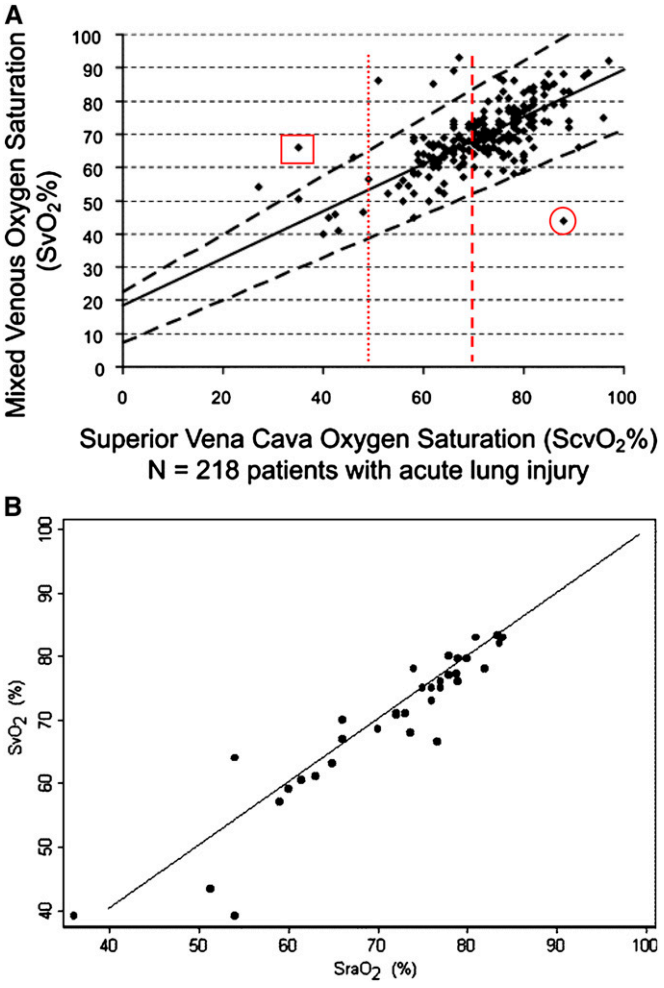

Figure 2. (*A*) Using data from a large number of patients in ARDSnet trials, Grissom and colleagues measured the relationship between Scv_{O_2} and $S\bar{v}_{O_2}$. Scatter around the line of identity illustrates the difference between these two measurements (38). When Scv_{O_2} is greater than 70% (*vertical dashed line*), $S\bar{v}_{O_2}$ is generally more than about 60%, although exceptions can occur (*point in circle*). When Scv_{O_2} is less than 50% (*vertical dotted line*), $S\bar{v}_{O_2}$ is generally low, although exceptions can occur (*point in square*). (*B*) When Scv_{O_2} is measured in blood drawn from the right atrium, the relationship between Scv_{O_2} and $S\bar{v}_{O_2}$ improves substantially (40).

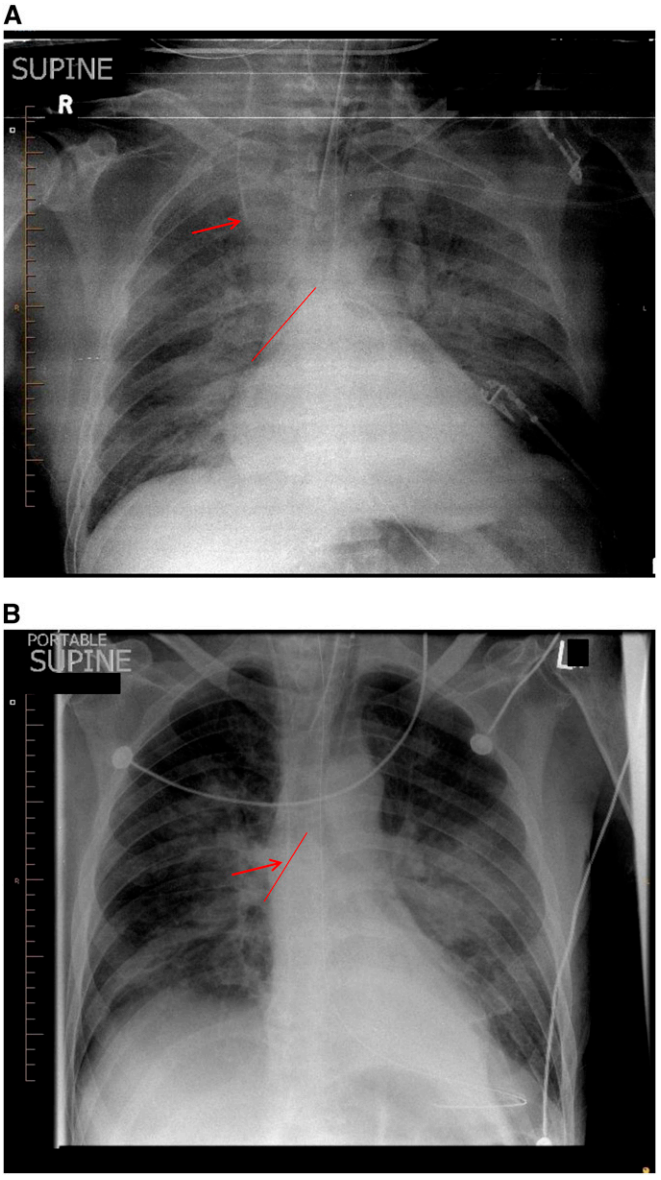

Figure 3. (*A*) When the central venous catheter tip (*red arrow*) is far from the right atrium, Scv_{O_2} is a poor surrogate for $S\bar{v}_{O_2}$, and substantial errors can occur. (*B*) When the central venous catheter tip (*red arrow*) is at the entrance of (*solid red line*), or in, the right atrium, Scv_{O_2} is a much better estimate of $S\bar{v}_{O_2}$.

be interpreted in the context of adequacy of tissue oxygenation. Is organ function OK? Should/can cardiac output or Hgb or Sao_2 be increased? Should/can oxygen demand be reduced using sedation or paralysis? Excessively high $S\bar{v}_{O_2}$ may indicate a high cardiac output but may also reflect very poor tissue oxygen extraction capacity. Consequently, very high and very low $S\bar{v}_{O_2}$ are associated with increased mortality (14).

Scv_{O_2} Has Clinical Utility in Early Goal Directed Therapy and in Weaning Protocols

Although the use of Scv_{O_2} and $S\bar{v}_{O_2}$ to assess and manage patients is grounded in firm physiological principles, evidence that routine measurement of Scv_{O_2} affects or predicts outcomes is only emerging. Two clinical scenarios in which evidence of clinical utility of Scv_{O_2} has been reported are in early shock resuscitation protocols (16) and in weaning patients from mechanical ventilation (50). Confirmation is now being tested in clinical trials.

The Surviving Sepsis Campaign Guidelines (51) endorse the elements of early goal directed therapy (EGDT) (16) protocols for resuscitation of septic shock patients. Similar physiologically targeted rapid resuscitation approaches are helpful in other shock states. The initial publication by Rivers and colleagues (16) many years ago, plus many subsequent "before/after" reports, lend evidence to support these protocols. Multiple large randomized controlled trials of EGDT and variants are now underway to more carefully test these concepts (18–20).

$S\bar{v}_{O_2}$ plays a central role in EGDT and related protocols. The shared elements in all of these protocols are, first, that resuscitation should be performed in a timely manner—time is tissue. Second, volume resuscitation is a fundamental initial step and must be adequate. Third, resuscitation must achieve a reasonable mean arterial pressure so that a sufficient arterial pressure head is available to allow redistribution of the cardiac output to vital organs. Finally, after these first goals have been achieved, it is necessary to ask: is oxygen delivery adequate? In many EGDT protocols this issue is addressed by measuring Scv_{O_2} or $S\bar{v}_{O_2}$. However, it may also be reasonable to address the same question by measuring lactate clearance (15)—same question, slightly different approach. Assessment of organ function is also important when assessing adequacy of tissue oxygenation; for example, measurement of urine output is incorporated into EGDT. An Scv_{O_2} greater than 70% is the original EGDT target and, as a component of River's EGDT (16), results in a substantial reduction in mortality with a number needed to treat to prevent one death (NNT) of approximately 6 (16). Thus, EGDT is a remarkably effective therapeutic approach and $S\bar{v}_{O_2}$ plays the important role of testing the final crucial question of whether oxygen delivery is adequate.

Teixeira and coworkers have recently found that among a variety of clinical parameters, Scv_{O_2} was the best clinical predictor of weaning failure (50). Difficult-to-wean patients who failed a 2-hour spontaneous breathing trial were followed daily until they successfully completed the spontaneous breathing trial. Scv_{O_2} and a large number of standard ventilatory, blood gas, and hemodynamic variables were measured before and 30 minutes into the spontaneous breathing trial. Then patients were extubated. Only Scv_{O_2} (and consequently ER_{O_2}) differed significantly between patients with extubation success versus extubation failure. A decrease in Scv_{O_2} of more than 4.5% during the spontaneous breathing trial had a sensitivity of 88% and a specificity of 95% in predicting extubation failure. Validation of these results is required.

$S\bar{v}_{O_2}$ Impacts Arterial Oxygenation in the Setting of Shunt/Venous Admixture

In the setting of shunt lung disease (or equivalent venous admixture through $\dot{V}/\dot{Q}$ mismatch), mixed venous oxygen saturation plays a major role in determining arterial oxygen saturation (Figure 5). The corollary of this observation is that, in this shunt setting, therapeutic maneuvers that increase mixed venous oxygen saturation will increase arterial oxygen saturation substantially (in proportion to the degree of shunt; i.e., big shunt, big $S\bar{v}_{O_2}$ effect). Thus, when high $F_{I_{O_2}}$, positive airway pressure, ventilator modes, nitric oxide, prone positioning, and other maneuvers are inadequate to achieve adequate arterial oxygenation, one more degree of therapeutic freedom is available—focus on $S\bar{v}_{O_2}$. That is, when all lung-related approaches are exhausted in treating the hypoxemic patient, increasing D_{O_2} (increasing cardiac output or oxygen-carrying capacity) and decreasing V_{O_2} (e.g., sedation, paralysis) will increase $S\bar{v}_{O_2}$ and,

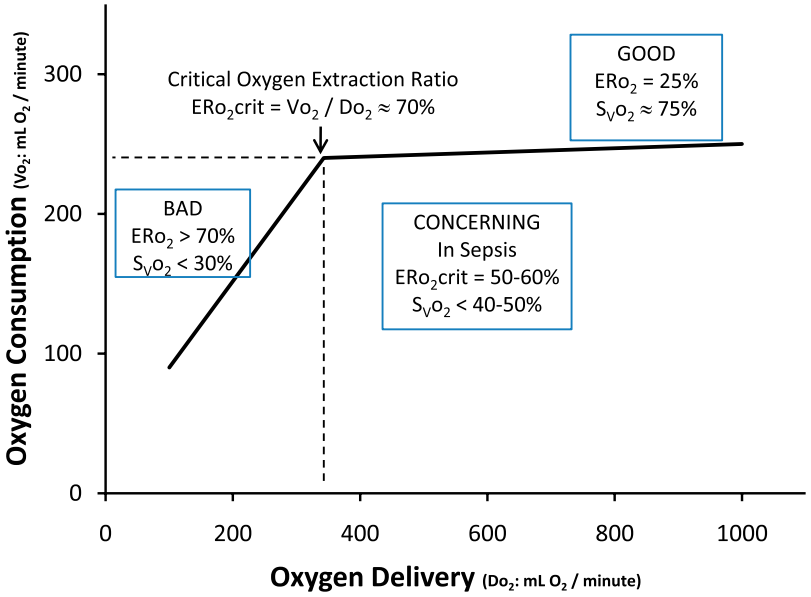

Figure 4. The relationship between oxygen delivery and oxygen consumption is used to frame the interpretation of $S\bar{v}_{O_2}$ values using the further knowledge that $S\bar{v}_{O_2} \approx 1 - ERo_2$. At rest in health, cardiac output may be approximately 5 L/min and oxygen-carrying capacity of fully saturated blood (Ca_{O_2}) is approximately 200 ml O_2/L of blood. Therefore, the amount of oxygen being delivered to the tissues is Do_2 = cardiac output × $Ca_{O_2} = 5 \times 200 =$ 1,000 ml O_2/min. At rest, whole body oxygen consumption (Vo_2) is about 250 ml O_2 per minute. That is, about 25% of the oxygen delivery was consumed so that the oxygen extraction ratio is 25% and the remainder, $S\bar{v}_{O_2}$, is 75% (assuming an arterial saturation of ~ 100%). If cardiac output or hemoglobin decrease, then Do_2 decreases but Vo_2 will remain relatively constant, since basal metabolic rate at rest is relatively unchanged (*flat portion* of the relationship). ER necessarily increases. Since it is not possible to extract more oxygen than is delivered (Vo_2 must be less than Do_2), it means that at some very low Do_2, Vo_2 must also decrease (*down-sloping portion* of the relationship). This is the onset of anaerobic metabolism characterized by a rising lactate and signs of shock and organ dysfunction.

consequently, increase arterial oxygen saturation. Finally and more recently, $S\bar{v}_{O_2}$ can also be raised directly using extracorporeal lung support.

As a corollary, when an arterial desaturation event occurs in the setting of high shunt fraction it is important to consider, in addition to lung-related events, that a reduction in $S\bar{v}_{O_2}$ may contribute. A reduction in $S\bar{v}_{O_2}$ may occur rapidly as a result of a sudden drop in cardiac output (e.g., due to arrhythmia or other cardiac event), as a result of a decrease in venous return (e.g., due to positioning of a relatively hypovolemic patient, etc.), or as a result of an increase in oxygen consumption (e.g., due to muscle activity). Rapid spontaneous resolution of arterial oxygen saturation further increases the probability that the desaturation event was related to low $S\bar{v}_{O_2}$, since the above causes are often transient. This knowledge may help detect the cause and prevent recurrence. When a desaturation event occurs in the setting of low shunt fraction, then a contribution by $S\bar{v}_{O_2}$ is less likely and the desaturation event is more often lung-related. Mucous plug, aspiration, FI_{O_2} regulation, endotracheal tube patency, ventilator circuit malfunction, pneumothorax, and so on become more likely explanations.

This line of reasoning helps quickly diagnose and treat desaturation events, but depends upon a prior knowledge of shunt fraction. How can shunt fraction be often and easily estimated so that it is part of routine critical care practice?

$S\bar{v}_{O_2}$ Can Be Used to Quickly Estimate Shunt Fraction

The equation for shunt fraction is:

$$\text{Shunt fraction} = \dot{Q}S/\dot{Q}T = (Cc_{O_2} - Ca_{O_2})/(Cc_{O_2} - Cv_{O_2}), \quad (Eq.\ 7)$$

where Cc_{O_2} is the oxygen concentration in maximally saturated pulmonary end-capillary blood (i.e., $Sc_{O_2} = 1$). Ignoring dissolved oxygen, this can be simplified to:

$$\text{Shunt fraction} = (1 - Sa_{O_2})/(1 - Sv_{O_2}).$$

For example, when pulse oximeter oxygen saturation is 90% and $S\bar{v}_{O_2}$ is 60%, the shunt fraction is $(1 - 0.9)/(1 - 0.6) = 25\%$, or when pulse oximeter oxygen saturation is 85% and $S\bar{v}_{O_2}$ is 70%, the shunt fraction is $(1 - 0.85)/(1 - 0.7) = 50\%$. With this simple equation in mind, bedside estimates of the clinical effect of diuresis, PEEP, and other treatment strategies on shunt fraction becomes very straightforward.

LIMITATIONS

In view of the above features, $S\bar{v}_{O_2}$ can be a valuable and readily accessible measure in managing critically ill patents where adequacy of tissue oxygenation is an issue. In this regard, $S\bar{v}_{O_2}$ is superior to cardiac output measurements and indeed, can be used to estimate cardiac output using the Fick equation. However, when the clinical issue is cardiac function, then other approaches such as echocardiography are far superior to $S\bar{v}_{O_2}$. The ability of Scv_{O_2} measurements to estimate $S\bar{v}_{O_2}$ is imperfect and depends on catheter placement, patient anatomy, and

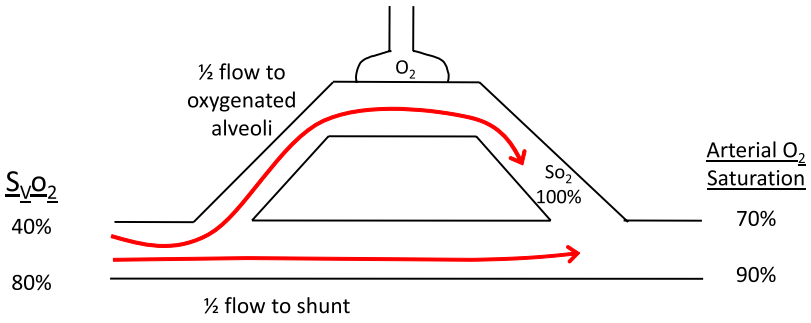

Figure 5. The contribution of $S\bar{v}_{O_2}$ to arterial hypoxemia in the setting of significant shunt (or $\dot{V}/\dot{Q}$ mismatch) is illustrated. The effect of a large change in $S\bar{v}_{O_2}$ is shown to highlight the impact of $S\bar{v}_{O_2}$. In this example, when the shunt fraction is 50%, half of every increase in $S\bar{v}_{O_2}$ will be reflected in Sao_2. Thus, an increase (exaggerated in this example to illustrate the effect) of $S\bar{v}_{O_2}$ from 40% to 80% will increase Sao_2 from 70% to 90%. This increase in Sao_2 is clinically highly significant, since Sao_2 of 70% over the course of several hours results in hypoxic death even in healthy mammals (26), while an Sao_2 of 90% is completely compatible with life.

physiologic state. This should always be kept in mind when interpreting Scv_{O_2} measurements. When a true mixed venous oxygen saturation is essential, pulmonary artery catheter placement is required.

Scv_{O_2} and $S\bar{v}_{O_2}$ measurements should never be interpreted in isolation. Rather, clinical context must always be considered. For example, $S\bar{v}_{O_2}$ over 70% is generally a good indicator. Yet in the setting of extreme vasodilatory shock or following mitochondrial poisoning where organ function is poor and lactate is rising, an $S\bar{v}_{O_2}$ of 90% provides no comfort (14). In these readily apparent clinical contexts, a high $S\bar{v}_{O_2}$ suggests that tissue oxygen extraction capacity is severely impaired and/or regional tissue hypoxia (e.g., gut ischemia) is present.

Is it necessary to measure central venous oxygen saturation continuously using a fiberoptic catheter, or do intermittent measurements (e.g., blood samples) suffice? This depends on clinical context. In a setting in which clinically important minute-to-minute changes that would otherwise go undetected are possible (e.g., specific operating room scenarios), then continuous measurement may be helpful. Baulig and coworkers report significant differences between continuous fiberoptic measurements and intermittent measurements (52). This additional source of error must be considered when interpreting continuous measurements, and can be minimized by careful attention to drift and calibration issues of the continuous measurement instrument. In other settings in which changes over hours need to be identified, intermittent measurements are often sufficient. For intermediate time-course settings, such as rapid resuscitation of shock, either approach can be used successfully.

SUMMARY

When adequacy of tissue oxygenation is a key issue, the balance between oxygen delivery and oxygen consumption must be considered. $S\bar{v}_{O_2}$ reflects this balance directly while cardiac output does not. Therefore, $S\bar{v}_{O_2}$ may be a more informative clinical measure. $ER_{O_2}crit$, reflecting the onset of tissue hypoxia, is a well-understood and stable parameter. Since $S\bar{v}_{O_2} \approx 1 - ER_{O_2}$, this knowledge can be used to understand critical $S\bar{v}_{O_2}$ values. Scv_{O_2} plays a central role in EGDT protocols, which appear to greatly improve patient outcomes. In addition, $S\bar{v}_{O_2}$ is important in understanding arterial desaturation events; intimately linked to shunt fraction. Understanding the role of $S\bar{v}_{O_2}$ provides an additional (non-lung) degree of freedom when treating severe arterial hypoxemia. Measurements of Scv_{O_2} are often readily available, since a thoracic central line is often needed as part of care in critically ill patients. Attention to placement of the tip of the central line near or at the right atrium increases the accuracy of Scv_{O_2} in reflecting $S\bar{v}_{O_2}$. Thoughtful measurement and interpretation of $S\bar{v}_{O_2}$ can contribute substantially to successful patient management.

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References

1. Connors AF Jr., Speroff T, Dawson NV, Thomas C, Harrell FE Jr., Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, *et al.* The effectiveness of right heart catheterization in the initial care of critically ill patients: support investigators. *JAMA* 1996;276:889–897.
2. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ, Laporta DP, Viner S, Passerini L, Devitt H, *et al.* A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003;348:5–14.
3. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, Brampton W, Williams D, Young D, Rowan K. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-MAN): a randomised controlled trial. *Lancet* 2005;366:472–477.
4. Wiener RS, Welch HG. Trends in the use of the pulmonary artery catheter in the United States, 1993–2004. *JAMA* 2007;298:423–429.
5. Vincent JL, Pinsky MR, Sprung CL, Levy M, Marini JJ, Payen D, Rhodes A, Takala J. The pulmonary artery catheter: in medio virtus. *Crit Care Med* 2008;36:3093–3096.
6. Beaulieu Y, Marik PE. Bedside ultrasonography in the ICU: Part 1. *Chest* 2005;128:881–895.
7. Meyer S, Todd D, Wright I, Gortner L, Reynolds G. Review article: non-invasive assessment of cardiac output with portable continuous-wave Doppler ultrasound. *Emerg Med Australas* 2008;20:201–208.
8. McGee WT, Horswell JL, Calderon J, Janvier G, Van Severen T, Van den Berghe G, Kozikowski L. Validation of a continuous, arterial pressure-based cardiac output measurement: a multicenter, prospective clinical trial. *Crit Care* 2007;11:R105.
9. Cannesson M, Attof Y, Rosamel P, Joseph P, Bastien O, Lehot JJ. Comparison of FloTrac cardiac output monitoring system in patients undergoing coronary artery bypass grafting with pulmonary artery cardiac output measurements. *Eur J Anaesthesiol* 2007;24:832–839.
10. Fellahi JL, Caille V, Charron C, Deschamps-Berger PH, Vieillard-Baron A. Noninvasive assessment of cardiac index in healthy volunteers: a comparison between thoracic impedance cardiography and doppler echocardiography. *Anesth Analg* 2009;108:1553–1559.
11. Zoremba N, Bickenbach J, Krauss B, Rossaint R, Kuhlen R, Schalte G. Comparison of electrical velocimetry and thermodilution techniques for the measurement of cardiac output. *Acta Anaesthesiol Scand* 2007; 51:1314–1319.
12. Linton RA, Band DM, Haire KM. A new method of measuring cardiac output in man using lithium dilution. *Br J Anaesth* 1993;71:262–266.
13. Van den Oever HL, Murphy EJ, Christie-Taylor GA. USCOM (ultrasonic cardiac output monitors) lacks agreement with thermodilution cardiac output and transoesophageal echocardiography valve measurements. *Anaesth Intensive Care* 2007;35:903–910.
14. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI. Multicenter study of central venous oxygen saturation (Scvo(2)) as a predictor of mortality in patients with sepsis. *Ann Emerg Med* 2010; 55:40–46 e41.
15. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010;303:739–746.
16. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345: 1368–1377.
17. Rivers E. Mixed vs central venous oxygen saturation may be not numerically equal, but both are still clinically useful. *Chest* 2006;129:507–508.
18. Protocolized care for early septic shock (PROCESS). (Accessed July 21, 2011.) Bethesda, MD: ClinicalTrials.gov; [received 18 July 2007; updated 27 July 2010]. Available from: http://clinicaltrials.gov/ct2/show/NCT00510835?term=00510835&rank=1
19. Protocol-driven hemodynamic support for patients with septic shock (Accessed July 21, 2011.) Bethesda, MD: ClinicalTrials.gov; [received 9 June 2006; updated 23 August 2010]. Available from: http://clinicaltrials.gov/ct2/show/NCT00335907?term=00335907&rank=1
20. Australasian resuscitation in sepsis evaluation randomised controlled trial (ARISE) (Accessed July 21, 2011.) Bethesda, MD: ClinicalTrials.gov; [received 10 September 2009]. Available from: http://clinicaltrials.gov/ct2/show/NCT00975793?term=00975793&rank=1
21. Nelson DP, King CE, Dodd SL, Schumacker PT, Cain SM. Systemic and intestinal limits of O_2 extraction in the dog. *J Appl Physiol* 1987;63: 387–394.
22. Samsel RW, Nelson DP, Sanders WM, Wood LD, Schumacker PT. Effect of endotoxin on systemic and skeletal muscle O_2 extraction. *J Appl Physiol* 1988;65:1377–1382.
23. Bredle DL, Samsel RW, Schumacker PT, Cain SM. Critical O_2 delivery to skeletal muscle at high and low Po_2 in endotoxemic dogs. *J Appl Physiol* 1989;66:2553–2558.
24. Humer MF, Phang PT, Friesen BP, Allard MF, Goddard CM, Walley KR. Heterogeneity of gut capillary transit times and impaired gut

oxygen extraction in endotoxemic pigs. *J Appl Physiol* 1996;81:895–904.
25. Nelson DP, Samsel RW, Wood LD, Schumacker PT. Pathological supply dependence of systemic and intestinal O_2 uptake during endotoxemia. *J Appl Physiol* 1988;64:2410–2419.
26. Walley KR, Becker CJ, Hogan RA, Teplinsky K, Wood LD. Progressive hypoxemia limits left ventricular oxygen consumption and contractility. *Circ Res* 1988;63:849–859.
27. Weyne J, De Ley G, Demeester G, Vandecasteele C, Vermeulen FL, Donche H, Deman J. Pet studies of changes in cerebral blood flow and oxygen metabolism after unilateral microembolization of the brain in anesthetized dogs. *Stroke* 1987;18:128–137.
28. Frykholm P, Andersson JL, Valtysson J, Silander HC, Hillered L, Persson L, Olsson Y, Yu WR, Westerberg G, Watanabe Y, *et al*. A metabolic threshold of irreversible ischemia demonstrated by pet in a middle cerebral artery occlusion-reperfusion primate model. *Acta Neurol Scand* 2000;102:18–26.
29. Rivers EP, Ander DS, Powell D. Central venous oxygen saturation monitoring in the critically ill patient. *Curr Opin Crit Care* 2001;7: 204–211.
30. 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* 1989;95:1216–1221.
31. Scalea TM, Holman M, Fuortes M, Baron BJ, Phillips TF, Goldstein AS, Sclafani SJ, Shaftan GW. Central venous blood oxygen saturation: an early, accurate measurement of volume during hemorrhage. *J Trauma* 1988;28:725–732.
32. Baquero Cano M, Sanchez Luna M, Elorza Fernandez MD, Valcarcel Lopez M, Perez Rodriguez J, Quero Jimenez J. Oxygen transport and consumption and oxygen saturation in the right atrium in an experimental model of neonatal septic shock [in Spanish]. *An Esp Pediatr* 1996;44:149–156.
33. Schou H, Perez de Sa V, Larsson A. Central and mixed venous blood oxygen correlate well during acute normovolemic hemodilution in anesthetized pigs. *Acta Anaesthesiol Scand* 1998;42:172–177.
34. Scheinman MM, Brown MA, Rapaport E. Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. *Circulation* 1969;40:165–172.
35. Berridge JC. Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation. *Br J Anaesth* 1992;69:409–410.
36. el-Masry A, Mukhtar AM, el-Sherbeny AM, Fathy M, el-Meteini M. Comparison of central venous oxygen saturation and mixed venous oxygen saturation during liver transplantation. *Anaesthesia* 2009;64:378–382.
37. Ho KM, Harding R, Chamberlain J, Bulsara M. A comparison of central and mixed venous oxygen saturation in circulatory failure. *J Cardiothorac Vasc Anesth* 2010;24:434–439.
38. Grissom CK, Morris AH, Lanken PN, Ancukiewicz M, Orme JF Jr., Schoenfeld DA, Thompson BT. Association of physical examination with pulmonary artery catheter parameters in acute lung injury. *Crit Care Med* 2009;37:2720–2726.
39. Lorentzen AG, Lindskov C, Sloth E, Jakobsen CJ. Central venous oxygen saturation cannot replace mixed venous saturation in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2008;22:853–857.
40. Kopterides P, Bonovas S, Mavrou I, Kostadima E, Zakynthinos E, Armaganidis A. Venous oxygen saturation and lactate gradient from superior vena cava to pulmonary artery in patients with septic shock. *Shock* 2009;31:561–567.
41. Chawla LS, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M. Lack of equivalence between central and mixed venous oxygen saturation. *Chest* 2004;126:1891–1896.
42. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, Cunningham KF, Russell JA, Walley KR. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA* 1993;270:1724–1730.
43. Walley KR. Heterogeneity of oxygen delivery impairs oxygen extraction by peripheral tissues: theory. *J Appl Physiol* 1996;81:885–894.
44. Ospina-Tascon G, Neves AP, Occhipinti G, Donadello K, Buchele G, Simion D, Chierego ML, Silva TO, Fonseca A, Vincent JL, *et al*. Effects of fluids on microvascular perfusion in patients with severe sepsis. *Intensive Care Med* 2010;36:949–955.
45. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med* 2004;32:1825–1831.
46. Protti A, Singer M. Bench-to-bedside review: potential strategies to protect or reverse mitochondrial dysfunction in sepsis-induced organ failure. *Crit Care* 2006;10:228.
47. Herbertson MJ, Werner HA, Russell JA, Iversen K, Walley KR. Myocardial oxygen extraction ratio is decreased during endotoxemia in pigs. *J Appl Physiol* 1995;79:479–486.
48. Cunnion RE, Schaer GL, Parker MM, Natanson C, Parrillo JE. The coronary circulation in human septic shock. *Circulation* 1986;73:637–644.
49. Dhainaut JF, Huyghebaert MF, Monsallier JF, Lefevre G, Dall'Ava-Santucci J, Brunet F, Villemant D, Carli A, Raichvarg D. Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. *Circulation* 1987; 75:533–541.
50. Teixeira C, da Silva NB, Savi A, Vieira SR, Nasi LA, Friedman G, Oliveira RP, Cremonese RV, Tonietto TF, Bressel MA, *et al*. Central venous saturation is a predictor of reintubation in difficult-to-wean patients. *Crit Care Med* 2010;38:491–496.
51. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, *et al*. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296–327.
52. Baulig W, Dullenkopf A, Kobler A, Baulig B, Roth HR, Schmid ER. Accuracy of continuous central venous oxygen saturation monitoring in patients undergoing cardiac surgery. *J Clin Monit Comput* 2008;22: 183–188.