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Review
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Central and Mixed Venous O_2 Saturation

Guillermo Gutierrez
Pulmonary, Critical Care and Sleep Medicine Division, The George Washington University Medical Centre, Washington, D.C., USA

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Abstract

Mixed and central venous oxygen saturations are commonly used to ascertain the degree of systemic oxygenation in critically ill patients. This review examines the physiological basis for the use of these variables to determine systemic extraction ration, oxygen consumption and tissue oxygenation, and also understand the role they may play in the early treatment of septic individuals.

Keywords: Critical illness, hemodynamics, oxygenation, sepsis

Introduction

The quest for mixed venous oxygenation ($S_{mv}O_2$).

In the latter part of the 19th Century, Adolf Fick (1821–1901) proposed his famous Fick's Principle, whereby cardiac output could be estimated by calculating the ratio of systemic O_2 consumption $(VO_2)_{sys}$, measured from the expired gases, to the arterio-venous O_2 content difference.

$$\text{Cardiac Output}=(VO_2)_{sys}/([O_2]_a-[O_2]_{mv}) \quad (1)$$

This formula requires blood samples from both arterial and pulmonary artery to calculate the O_2 content as:

$$[O_2]_{mv}=13.9\times S_{mv}O_2\times[Hb]+0.031\times PO_2 \text{ mL } L^{-1} \quad (2)$$

Where [Hb] indicates the haemoglobin concentration (gram dL^{-1}).

Since, at the time, there was no safe way to obtain access to pulmonary artery blood in humans, the cardiac output could not be calculated by Fick's Principle. This situation changed in 1929 when Werner Forssman (1904–1979) demonstrated that a catheter could be passed safely into the right atrium. One year later, Otto Klein (1881–1968) became the first individual to use Forssman's technique to measure cardiac output by Fick's Principle. A decade later, André Cournand (1895–1988) and Dickinson Richards (1895–1973) perfected the technique of right heart catheterisation and reported that they were able to leave a pulmonary artery catheter in place for a length of time with no harm to the patient. In 1970, Jeremy Swan (1922–2005) and William Ganz (1919–2009) developed a flow-directed pulmonary artery catheter (PAC) that could be inserted into the pulmonary artery without fluoroscopic guidance, allowing for ready and safe access to mixed venous blood in the ICU (1).

Paradoxically, the PAC also eliminated the need to measure $S_{mv}O_2$, since cardiac output now could be measured accurately by thermo-dilution. On the other hand, the unhindered access to pulmonary artery blood resulted in $S_{mv}O_2$ becoming one of the most commonly monitored physiological measures in the ICU, although its clinical utility remains a topic of intense and continuing debate. This review will discuss the utility, or lack thereof, of $S_{mv}O_2$ and of central venous blood O_2 saturation ($S_{cv}O_2$) in the care of the critically ill patient.

Corresponding Author: Guillermo Gutierrez E-mail: ggutierrez@mfa.gwu.edu

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Clinical and Research Consequences

$S_{mv}O_2$ is a measure of O_2 extraction ratio.

Systemic O_2 consumption is nowadays estimated by the 'reverse' Fick's Method, as the product of cardiac output (Q) (measured by thermo-dilution) and the O_2 content difference.

$$(VO_2)_{Sys}=Q([O_2]_a-[O_2]_{mv})\ mL\ min^{-1} \quad (3)$$

It should be noted that the above expression does not account for pulmonary O_2 consumption, since the deep bronchial veins drain on the left side of the circulatory system, either via the pulmonary vein or directly into the left atrium. Therefore, the reverse Fick's Method can underestimate $(O_2)_{Sys}$ in conditions associated with substantial pulmonary O_2 consumption, such as acute lung injury (2).

Defining the rate of O_2 delivered to the tissues per unit time $(O_2)_{Sys}$ as,

$$(DO_2)_{Sys}=Q\times[O_2]_a\ mL\ min^{-1} \quad (4)$$

One can calculate the efficiency of O_2 uptake by the tissues, i.e., the O_2 extraction ratio $(ERO_2)_{Sys}$, as:

$$(ERO_2)_{Sys}=(VO_2)_{Sys}/(DO_2)_{Sys} \quad (5)$$

The clinical interpretation of $(ERO_2)_{Sys}$ requires detailed knowledge of the physiological conditions prevailing at the time of its measurement. $(ERO_2)_{Sys}$ at rest is approximately 20–30%, but increases to 60% or higher with high intensity exercise (3). Conversely, in a critically ill individual, an $(ERO_2)_{Sys}$ of 60% is associated with severe and perhaps irreversible anaerobic metabolism (4).

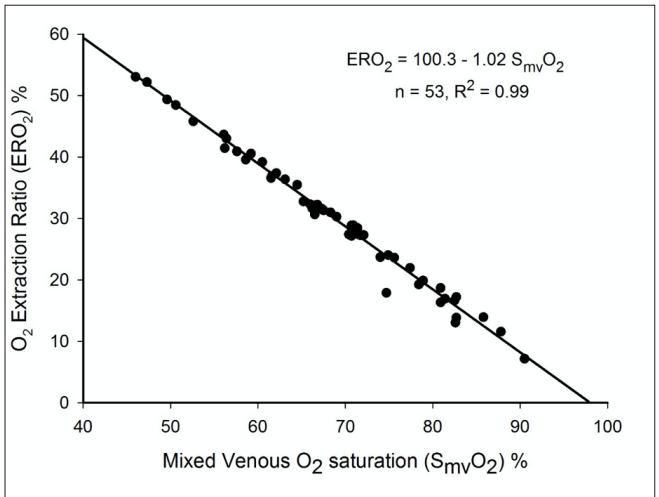

Figure 1. Systemic O_2 extraction ratio (ERO_2) as a function of mixed venous O_2 saturation ($SmvO_2$) for a heterogeneous cohort of critically ill patients (n=53). The solid line represents the linear correlation (R2= 0.99; p<0.01)

Neglecting the contribution of plasma PO_2 to blood O_2 content yields an expression for $(ERO_2)_{Sys}$ in terms of $S_{mv}O_2$ and S_aO_2, as:

$$(ERO_2)_{Sys}=(1-S_{mv}O_2/S_aO_2) \quad (6)$$

Figure 1 illustrates the close relationship between $(ERO_2)_{Sys}$ and $S_{mv}O_2$. The graph was developed using data from a cohort of critically ill patients (n=53) (5).

Since S_aO_2 in critically ill patients is usually constrained to the narrow range of 90–100%, for all practical purposes, as illustrated by Figure 1, $(ERO_2)_{Sys}$ becomes a complementary function of $S_{mv}O_2$, as:

$$(ERO_2)_{Sys}\approx(100-S_{mv}O_2\%) \quad (7).$$

The foregoing analysis shows that $S_{mv}O_2$ is a reliable indicator of $(ERO_2)_{Sys}$, thus providing a useful insight on the balance between $(DO_2)_{Sys}$ and $(VO_2)_{Sys}$. The clinical significance of changes in $(ERO_2)_{Sys}$ depends on prevalent physiological conditions. Low $(ERO_2)_{Sys}$ values may result from either a decrease in $(DO_2)_{Sys}$ or an increase in $(VO_2)_{Sys}$, although in resting ICU patients it is the former that is usually prevalent. It should be emphasised that central venous O_2 saturation ($S_{cv}O_2$) cannot be used to calculate $(ERO_2)_{Sys}$, since the resulting value would apply exclusively to organs located in the upper body.

$S_{mv}O_2$ as a measure of cardiac output

Further manipulation of equations (1) and (2) shows the complex relationship that exists between cardiac output and $S_{mv}O_2$. This relationship must also take into account other physiological variables, namely, the haemoglobin concentration and $(O_2)_{Sys}$.

$$Q=(VO_2)_{Sys}/[13.9\cdot[Hb]\cdot(S_aO_2-S_{mv}O_2)] \quad (8)$$

This relationship is a source of considerable uncertainty when using $S_{mv}O_2$ as an estimate of Q, as exemplified by Figure 2, where we again used the data from the patient cohort portrayed in Figure 1. Clearly, there is a positive relationship between Q and $S_{mv}O_2$, but this correlation is weak (R^2=0.24), making it difficult to predict one from the other. For example, according to Figure 2, a value of 70% for $S_{mv}O_2$ may correspond to cardiac output values between 3 L $minute^{-1}$ and 12 L $minute^{-1}$.

The poor correlation between $S_{mv}O_2$ and Q has been noted in studies performed under diverse clinical conditions, including the induction of anaesthesia (6), congestive heart failure (7), and septic shock (8). Using continuous measures of $S_{mv}O_2$ that were obtained by reflectance spectrophotometry to calculate Q has also proven disappointing, because it was found to ac-

curately predict changes in cardiac output only 50% of the time (9).

From a practical standpoint, however, as long as $(VO_2)_{Sys}$, [Hb], and S_aO_2 remain relatively constant, a decrease in $S_{mv}O_2$ in a critically ill individual is likely to reflect a lower cardiac output, rather than indicate increases in tissue O_2 requirements.

$S_{mv}O_2$ and right-to-left pulmonary shunt fraction

The right-to-left pulmonary shunt fraction (Q_{Shunt}/Q_{Total}) is estimated with the patient breathing 100% F_IO_2 as:

$$\frac{Q_S}{Q_T} = \frac{[O_2]_c - [O_2]_a}{[O_2]_c - [O_2]_{mv}} \quad (9)$$

where $[O_2]_c$ represents the idealised pulmonary capillary O_2 content and is calculated from the alveolar air equation. Some researchers have proposed substituting O_2 saturations for O_2 contents in eq. 10 as a bedside estimate of Q_S/Q_T (10), as:

$$\frac{Q_S}{Q_T} = \frac{1 - S_aO_2}{1 - S_{mv}O_2} \quad (10)$$

This equation will underestimate Q_S/Q_T and its use should be discouraged.

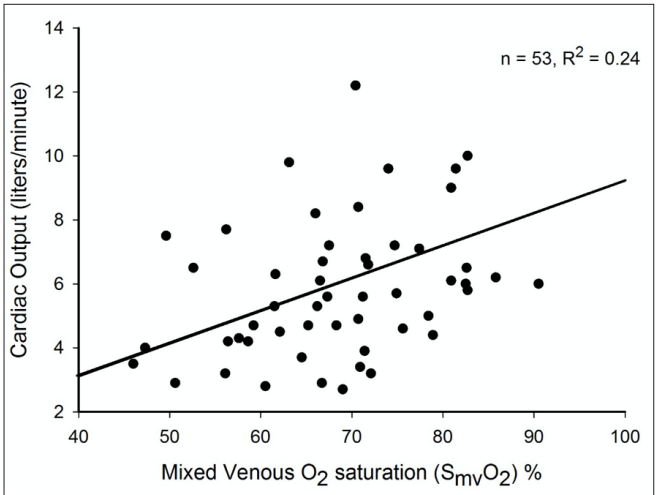

Figure 2. Cardiac output (Q) as a function of mixed venous O_2 saturation ($S_{mv}O_2$) for the patient cohort shown in Figure 1 (n=53). The solid line represents the linear correlation (R2=0.24; p<0.01)

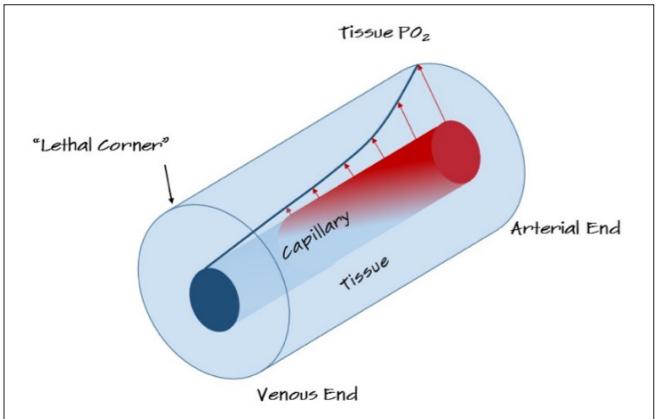

Figure 3. Krogh's cylinder model of capillary-tissue oxygenation

$S_{mv}O_2$ as a measure of tissue oxygenation

In 1919, August Krogh (1874–1949) developed a model of microcirculation to quantify the process of O_2 transfer from capillaries to tissue parenchyma (11), with tissues represented by a cylinder surrounding a single, non-branched capillary (Figure 3). The red blood cells (RBC) release O_2 into the capillary plasma and from there it diffuses radially into the tissues. Among the variables that determine plasma PO_2 are the rate of O_2 dissociation from haemoglobin, the O_2 solubility in plasma, and the capillary transit time, with the latter being defined as the ratio of capillary length to RBC velocity. The transit time increases with greater capillary cross-sectional area and decreases with faster blood flow.

Tissue O_2 uptake, or O_2 flux, is driven primarily by plasma PO_2. As RBCs traverse the length of the capillary, haemoglobin-bound O_2 and plasma PO_2 are depleted. According to Krogh's model, the capillary plasma PO_2 and O_2 flux reach a nadir at the venous end, giving rise to a region labelled the 'lethal corner', where tissues are at risk of hypoxia.

An important assumption of Krogh's model is the equivalence between end-capillary and venous blood PO_2. This assumption provides the physiological basis for the notion that venous SO_2 is a marker of tissue oxygenation. Extension of the Kroghian theory to the body as a whole provides the foundation for assuming that $S_{mv}O_2$ is a marker of global tissue oxygenation. This is a precarious and often incorrect assumption, since it fails to consider the intricate macro- and microcirculatory adjustments that are attendant to sepsis and hypoxaemia.

The elegant simplicity of Krogh's model provides a lucid physiological construct for the process of tissue oxygenation, but fails to account for the spatial and temporal heterogeneity of the microcirculation. Second order processes, including capillary recruitment, O_2 diffusion between adjacent capillaries, time-dependent haemoglobin O_2 unloading, and perpendicular and counter-current flow combine to produce a remarkably homogeneous distribution of tissue, one lacking 'lethal corners'. It is possible that the intestinal villi and the renal medulla, organs characterised by a peculiar vascular arrangement of counter-current flow, may have regions akin to the 'lethal corner', where cells exist on the edge of hypoxia, vulnerable to even mild ischaemic or hypoxic insults (12).

Another factor conflicting with the use of $S_{mv}O_2$ as a marker of peripheral organ oxygenation is that $S_{mv}O_2$ results from mixing the venous effluents of all organs in the right heart chambers. As such, it can be defined as the flow-weighted average of all venous effluents SO_2 as:

$$S_{mv}O_2 = \Sigma [S_vO_2]_i \times Q_i/Q \quad (11).$$

Where $[S_vO_2]_i$ and Q_i represent venous SO_2 and flow from various organs. According to equation 11, organs having the greatest venous outflow are the primary determinants of $S_{mv}O_2$. As a result, under certain pathological conditions such as sepsis, patients could have normal or even elevated $S_{mv}O_2$ values, along with simultaneously experiencing tissue hypoxia.

For example, the loss of regional microcirculatory control could apportion a greater Q_i to some tissue beds, such as resting skeletal muscle with its enormous capacity for auto-regulation. Skeletal muscle is an organ capable of inducing a 7-fold increase in blood flow by trebling the number of open capillaries by capillary recruitment (13). This is a beneficial response during exercise, as it directs the bulk of the cardiac output towards the working skeletal muscles. During critical illness, however, a misdirected increase in blood flow to *resting* skeletal muscle would result in a muscle venous effluent of high SO_2, potentially overwhelming the hypoxic signals emanating from under-perfused organs, such as the gut and kidneys. This is a condition termed as 'covert tissue hypoxia' (14), and is defined by a normal or even elevated $S_{mv}O_2$ in conjunction with regional tissue hypoxia, as it may occur in patients with sepsis or septic shock.

Alternatively, low $S_{mv}O_2$ values may occur in the absence of tissue hypoxia during aerobic exercise. Trained athletes are known to experience very low $S_{mv}O_2$, as low as 40%, prior to reaching the anaerobic threshold (15). Far from signalling tissue hypoxia, these low $S_{mv}O_2$ values reflect the ability of trained skeletal muscles to maintain aerobic metabolism by extracting O_2 maximally from capillaries.

Another confounder in the interpretation of $S_{mv}O_2$ vis-à-vis tissue oxygenation is the manner by which O_2 is lowered. Animals subjected to decreases in O_2 by hypoxaemia or by isovolaemic anaemia reach a state of anaerobiasis at similar $(O_2)_{sys}$ levels, which is defined as the critical O_2 delivery level $(O_2)_{critical}$. Remarkably, $S_{mv}O_2$ is much lower in hypoxemia than in isovolaemic anaemia at $(O_2)_{critical}$ (16), a phenomenon that has also been noted at the organ level (17). This is because resting skeletal muscle preparations that are exposed to hypoxaemia and isovolaemic anaemia show similar tissue PO_2 distributions and $O_{2critical}$, but significantly different S_vO_2 values.

To summarise, the relationship of $S_{mv}O_2$ to tissue PO_2 is tenuous at best, and the values for $S_{mv}O_2$ being ≥70% do not guarantee adequate tissue oxygenation. The fundamental issue in caring for critically ill patients is to discern the level of regionalO_2 required to sustain aerobic ATP turnover rate by all cells, in all organs, at all times. This information, however, cannot be gained from measuring the $S_{mv}O_2$.

Can we use central venous SO_2 in place of mixed venous SO_2?

$S_{cv}O_2$ has been proposed as a surrogate for $S_{mv}O_2$ (18), which begs the question of how reliable $S_{cv}O_2$ is as an estimate of $S_{mv}O_2$. The right atrium (RA) is a complex hydrodynamic chamber where venous blood of different provenances mix together. The resulting $S_{mv}O_2$ is the flow-weighted average of blood SO_2 from the inferior vena cava (IVC), the superior vena cava (SVC), and the coronary sinus (CS).

Studies in children with heart defects gave an impetus to the development of formulas to estimate $S_{mv}O_2$ based on SVC and IVC blood samples drawn nearly simultaneously. The expression (19) gaining the widest acceptance is:

$$S_{mv}O_2 = \frac{3S_{svc}O_2 + S_{IVC}O_2}{4} \quad (12)$$

This expression was derived empirically and does not imply a physiological model of RA blood mixing. Its utility is constrained to the range of measured SO_2 values and the clinical conditions present at the time of blood sampling. It, however, does point to the large influence of $S_{cv}O_2$ on $S_{mv}O_2$, further suggesting these variables may be closely correlated. It should be noted that Eq. 13 does not account for the contribution of CS blood towards the development of $S_{mv}O_2$. The O_2 saturation of CS blood ($S_{CS}O_2$) is usually low, nearly 40% (20), but given its low flow relative to cardiac output, the effect of $S_{CS}O_2$ on $S_{mv}O_2$ is likely to be modest at best. On the other hand, $S_{CS}O_2$ may play a role in determining the direction (or sign) of the SO_2 gradient, defined here as the difference between $S_{cv}O_2$ and $S_{mv}O_2$, as:

$$\Delta SO_2 = S_{cv}O_2 - S_{mv}O_2 \quad (13)$$

Some have proposed that subtracting 5% from $S_{cv}O_2$ may help to obtain an accurate estimate of $S_{mv}O_2$ (21), but the notion that $S_{cv}O_2$ and $S_{mv}O_2$ are separated by a fixed SO_2 % value is not supported by clinical data (5).

The ΔSO_2 gradient develops as blood from the SVC mixes with IVC and CS blood. This gradient is not constant, but may vary widely from patient to patient, and in the same patient at different times, in response to changes in the clinical condition. A complete understanding of the relative influences on ΔSO_2 of IVC and CS blood is hindered by a lack of

clinical data. A study on patients with pulmonary hypertension (22) showed similar $S_{IVC}O_2$ and $S_{cv}O_2$, with a ΔSO_2 of 4.4%, suggesting that mixing with CS blood of lower SO_2 is the likely mechanism that results in positive ΔSO_2 gradients.

Studies measuring both SO_2 and lactate concentrations in SVC and PA blood report positive ΔSO_2 gradients accompanied by a step-down in lactate concentration from SVC to PA (23). Lactate is a preferred myocardial substrate and its concentration in CS blood is usually low, giving further credence to the role played by CS blood in generating ΔSO_2. This observation raises the interesting possibility of ΔSO_2 being capable of providing useful insight into myocardial O_2 utilisation in some patients.

The clinical significance ΔSO_2 is not clear. A multicentre study of post-operative and medical ICU patients measured ΔSO_2 at 6-hour intervals (24) and found a strong association between survival and a positive ΔSO_2. Conversely, studies in cardiac surgery patients suggest that a *negative* ΔSO_2 gradient is associated with better outcomes and less inotropic support requirements (25).

In summary, measures of $S_{cv}O_2$ are not reliable surrogates for $S_{mv}O_2$, especially with regards to septic patients, where the influence of IVC and CS blood on $S_{mv}O_2$ may predominate. Further, the notion that $S_{mv}O_2$ may be estimated by subtracting 5% from $S_{cv}O_2$ is not supported by clinical data. However, in certain conditions in which the pathophysiology is well understood, it may be possible to ascertain alterations in systemic O_2 extraction from measures of $S_{cv}O_2$, particularly if it is measured continuously (26).

$S_{mv}O_2$ and $S_{cv}O_2$ as predictors of morbidity and mortality

Studies in critically ill patients relating morbidity and mortality to measures of $S_{mv}O_2$ or $S_{cv}O_2$ are remarkably few in number. Moreover, the nature of the data is ambiguous, given that poor ICU outcomes may occur with either high or low $S_{mv}O_2$ or $S_{cv}O_2$ values.

There appears to be consensus that mortality is greater in patients with $S_{mv}O_2$ or $S_{cv}O_2$ values of <70%, although the boundary between decedents and survivors varies according to the study. A study in patients with septic shock (n=20), in which $S_{mv}O_2$ was measured continuously with fiberoptic PACs, noted increased mortality for patients with a preponderance of $S_{mv}O_2$ readings <65% (27). A retrospective case-control analysis (28) of septic patients with pre-existing left ventricular dysfunction (n=166) showed decedents with a lower initial mean $S_{mv}O_2$ than survivors (61% vs. 70%). This was somewhat confusing, as the control group (n=168) showed decedents with similar $S_{mv}O_2$ as survivors (70% vs. 71%). Greater mortality rate (29% vs. 17%) was also noted in patients with $S_{cv}O_2$ <60%, who had been admitted to a multidisciplinary ICU (n=98) (29). Similarly, patients with septic shock (n=363) were found to experience greater mortality rates when the ICU admission occurred at an $S_{cv}O_2$ <70% (38% vs. 27%) (30).

To complicate matters further, high $S_{cv}O_2$ values are also have been associated with greater ICU mortality. In a secondary analysis of septic patients (31), using data culled from prospectively collected registries (n=619) showed patients with both low and high $S_{cv}O_2$ (<70% or >89%) having greater mortality rates than patients with a 'normal' range of $S_{cv}O_2$ (70% to 89%). A retrospective study of 169 septic patients revealed that patients with 'high' or 'low' admission $S_{cv}O_2$ values (78.8% and 51.1%, respectively) experienced significantly higher mortalities than those with 'normal' $S_{cv}O_2$ (70.9%) (32).

Perhaps the time during which a patient is exposed to a low $S_{mv}O_2$ or $S_{cv}O_2$ carries more weight regarding the outcome than sporadic decreases in saturation. A retrospective analysis of septic shock patients (n=111) found that decreases in $S_{mv}O_2$ <70% for a significant amount of time during their first 24 ICU hours was associated with greater mortality (33%) (33).

The majority of surgical and trauma studies show an association between low values for $S_{mv}O_2$ and $S_{cv}O_2$ and post-operative complications. A retrospective analysis of 488 post-operative cardiac patients found a greater incidence of both post-operative complications and mortality (9.4%) for patients with a $S_{mv}O_2$ level of <55% on arrival to the ICU (34). Patients with a cardiac index of <2.0 $L.min^{-1}m^{-2}$ following coronary artery bypass grafting (CABG; n=36), experienced low $S_{mv}O_2$ values (58.5% vs. 63.7% in control) and a prolonged course of stay in the ICU (35). Decreases in $S_{cv}O_2$ have been independently associated with post-operative complications following major surgery (n=117) (36). Patients experiencing complications had lower $S_{cv}O_2$ during surgery (63% vs. 67%).

However, as we have noted in septic and general ICU patients, the relationship of post-operative complications to low $S_{cv}O_2$ measurements is not clear cut. Greater mortality rates also have been noted in patients undergoing elective cardiac surgery (n=205) with either low (<61%) or high (>77%) $S_{cv}O_2$ values (37).

Given the uneven ability of $S_{cv}O_2$ to provide a forecast of the outcome, some researchers advocate combining early measures of $S_{cv}O_2$ with either blood lactate concentration ([Lac]) or with lactate clearance. Blood lactate concentration ([Lac]) may be more reliable as a predictor of post-surgical complications than $S_{cv}O_2$. Patients following CABG (n=629) had fewer complications when [Lac] measured <3.9 mmol/L, irrespective of $S_{cv}O_2$ values (38).

A study in septic shock patients showed no difference in mortality when therapy aimed at increasing lactate clearance to ≥10% was compared to that of raising $S_{cv}O_2$ to ≥70% (n=150 each group) (39). A subsequent study by the same investigators (40) (n=203) showed that achieving a lactate clearance of ≥10% was more strongly associated with survival than achieving a $S_{cv}O_2$ value of ≥70%.

Decreases in $S_{mv}O_2$ or $S_{cv}O_2$ levels are prone to reflect increased extraction by the respiratory muscles, therefore, monitoring these variables during the process of weaning patients from mechanical ventilation appears to be useful. A study in haemodynamically stable ICU patients undergoing weaning (n=73) found that a decrease in $S_{cv}O_2$ > 4.5% was the only independent predictor of re-intubation (41). When $S_{mv}O_2$ was monitored continuously, weaning failure (n=8) was associated with progressive declines in $S_{mv}O_2$, in contrast to weaning success (n=11), where the $S_{mv}O_2$ did not change (42).

$S_{cv}O_2$ as a guide to resuscitation in sepsis

The concept of pathologic supply dependency during sepsis arose from the confluence of two observations. The first observation is that [Lac] usually increases in sepsis, which may be interpreted as the activation of anaerobic glycolysis by tissue hypoxia. The second observation is that increasing $(DO_2)_{Sys}$ in septic patients is usually associated with greater $(VO_2)_{Sys}$ (43). These observations gave rise to the concept of 'pathologic supply dependency', implying that septic tissues experience a 'covert' hypoxic condition (44), which is unmasked by increases in $(DO_2)_{Sys}$ accomplished either by a dobutamine-mediated rise in cardiac output (45) or by the transfusion of blood (46). A clinical trial tested this hypothesis in a heterogeneous ICU population in which one group (n=253) was targeted to achieve a high cardiac index and another (n=257) was set to maintain $S_{mv}O_2$ at ≥70%. Neither group, however, showed improved survival when compared to the control group (47).

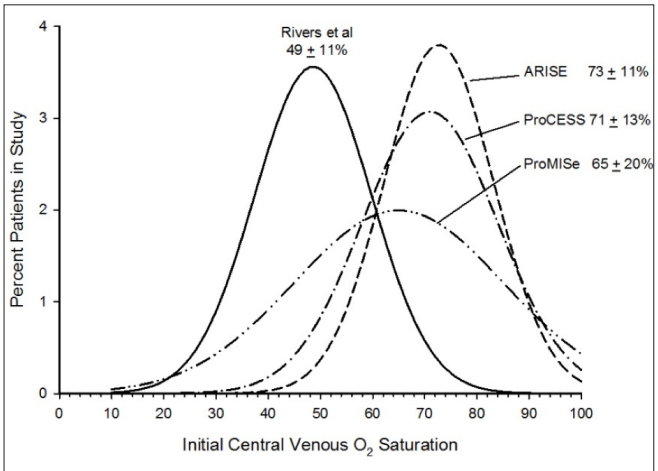

Figure 4. Hypothetical $S_{cv}O_2$ Gaussian population distributions derived from the mean±standard deviation values published in various Early Goal Directed Therapy (EGDT) trials

Several years later, a study was conducted in septic shock patients (n=263) that emphasised alacrity in therapeutic response. Treatment was dictated by a resuscitation algorithm called Early Goal Directed Therapy (EGDT) implemented during the patient's initial 6 hours in the hospital (48), in which therapy was in part guided by $S_{cv}O_2$ measured continuously with a spectrophotometric central venous catheter. Among the treatment arms of the EGDT algorithm was the maintenance of $S_{cv}O_2$ ≥70% mediated by increases in $(O_2)_{Sys}$ with fluids, RBC transfusions and dobutamine. The study showed a substantially lower mortality (30.5% vs. 46.5%) in patients treated with EGDT.

Three large prospective randomised studies enrolling a total of 4,183 patients tested the hypothesis that EGDT improves ICU survival in septic patients. All three of these trials, The Protocolized Care for Early Septic Shock (ProCESS) (49), the Autralasian Resuscitation Sepsis Evaluation (ARISE) (50), and the Protocolised Management of Sepsis (ProMISe) (51) have failed to show a survival advantage by implementing EGDT.

Without delving into all possible causes leading to the divergent outcomes of the initial EGDT study and the recent trials, it may be instructive to examine one aspect of these trials heretofore ignored. It concerns the low initial $S_{cv}O_2$ values reported in the initial. EGDT study of 49±11%. By most standards these are very low $S_{cv}O_2$ values, and quite different from those found in a Dutch multicentre study that reported <1% of septic patients having $S_{cv}O_2$ <50% within 6 hours of hospital admission (52). Moreover, initial $S_{cv}O_2$ values were 71±13% in the ProCESS, 73±11 % in the ARISE, and 65±20% in the ProMISe study.

Figure 4 depicts the Gaussian functions corresponding to these initial $S_{cv}O_2$ values. Obviously, the $S_{cv}O_2$ distribution reported in the EGDT trial is substantially different from the others ($p<0.001$). This observation suggests that the cohort enrolled in the EGDT trial differed fundamentally from those enrolled in the subsequent negative trials.

A possible explanation for this discrepancy may be found by noting the location of the catheter in the SVC where $S_{cv}O_2$ is measured. The central venous catheter should lie with its tip in the SVC, below the anterior first rib, and above the RA. This places the infrared spectrophotometer fibreoptic sensor just below the opening of the azygos vein, a unilateral vessel carrying blood from the posterior intercostal muscle and the diaphragmatic veins.

Patients in the original EGDT study experienced considerable respiratory distress, with 53% requiring invasive mechanical ventilation, compared to the values of 26%, 20%, and 22% for patients in the ProCESS, ARISE, and ProMISe trials, respectively. Increased work by the respiratory muscles, particularly by the intercostal muscles, results in blood of very low O_2 saturation being discharged by the azygos vein into the SVC, which is in close proximity to the oximeter sensor. Therefore, it is likely that the $S_{cv}O_2$ values reported in the EGDT trial reflected increased work of breathing and not global tissue hypoxia, further suggesting that the correct therapy was by way of mechanical ventilation, not RBC transfusion or dobutamine infusion. Supporting this hypothesis was a study of septic patients showing increases in $S_{cv}O_2$ from 64% to 71%, before and after applying mechanical ventilation (53).

To summarise, it appears that $S_{cv}O_2$-guided resuscitation does not improve the survival of septic patients. On the other hand, the early application of some treatment modalities, such as the early administration of antibiotics, low tidal volume mechanical ventilation, and rapid fluid infusion with the reversal of hypotension can improve survival in cases of severe sepsis or septic shock (54).

Conclusion

The ideal ICU monitored variable must meet each of the following parameters: (1) easy to measure; (2) easy to interpret; (3) amenable to treatment; and (4) measured non-invasively. Pulse oximetry is the quintessential monitoring device that meets all these criteria. $S_{cv}O_2$ monitoring, on the other hand, falls far short of this expectation.

$S_{cv}O_2$ is relatively easy to measure, either intermittently or continuously, with a fiberoptic catheter. However, due to its invasiveness, the decision to insert a central venous catheter solely for the purpose of measuring $S_{cv}O_2$ should be tempered by the risk associated with the procedure.

Changes in $S_{mv}O_2$ are inversely related to changes in systemic ERO_2. The same concept applies to $S_{cv}O_2$ regarding upper body organs. As previously reviewed, however, $S_{cv}O_2$ is not easy to interpret. Experienced clinicians might also be confused by the information conveyed by $S_{cv}O_2$. Perhaps the continuous monitoring of $S_{mv}O_2$ or $S_{cv}O_2$ is useful in selected cases where the patient's pathophysiology is well understood, such as when there is cardiomyopathy with reduced cardiac output. This is not the case in most other conditions that affect critically ill individuals, particularly in cases of severe sepsis, in which both high and low $S_{mv}O_2$ or $S_{cv}O_2$ values carry a dire prognosis.

Lastly, not knowing the pathophysiological processes responsible for alterations in $S_{cv}O_2$ in sepsis, as well as lacking a clearly defined therapeutic response, greatly diminish the clinical utility of this monitored variable. Whether the aim is to decrease O_2 consumption by mechanical ventilation or increase O_2 delivery by transfusing RBCs or infusing dobutamine, it cannot be easily discerned from measures of $S_{cv}O_2$.

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