

REVIEW

Central venous oxygenation: when physiology explains apparent discrepancies

Pierre Squara

Abstract

Central venous oxygen saturation ($ScvO_2$) >70% or mixed venous oxygen saturation (SvO_2) >65% is recommended for both septic and non-septic patients. Although it is the task of experts to suggest clear and simple guidelines, there is a risk of reducing critical care to these simple recommendations. This article reviews the basic physiological and pathological features as well as the metrological issues that provide clear evidence that SvO_2 and $ScvO_2$ are adaptative variables with large inter-patient variability. This variability is exemplified in a modeled population of 1,000 standard ICU patients and in a real population of 100 patients including 15,860 measurements. In these populations, it can be seen how optimizing one to three of the four $S(c)vO_2$ components homogenized the patients and yields a clear dependency with the fourth one. This explains the discordant results observed in large studies where cardiac output was increased up to predetermined $S(c)vO_2$ thresholds following arterial oxygen hemoglobin saturation, total body oxygen consumption needs and hemoglobin optimization. Although a systematic $S(c)vO_2$ goal-oriented protocol can be statistically profitable before ICU admission, appropriate intensive care mandates determination of the best compromise between $S(c)vO_2$ and its four components, taking into account the specific constraints of each individual patient.

Introduction

A recent review of the literature concluded that 'central venous oxygen saturation ($ScvO_2$) is a very important measurement, which can be easily taken in a critical care environment by both medical and nursing staff. It provides an understanding of the patient's oxygen delivery, oxygen consumption and cardiac output. It has a key

role within early goal-directed therapy and has been shown to decrease mortality when taken and analyzed appropriately' [1]. Indeed, $ScvO_2 > 70\%$ or mixed venous oxygen saturation (SvO_2) >65% is recommended for both septic and non-septic patients [2-4].

There is no debate that a major task of experts is to determine clear and simple rules for the early treatment of life-threatening disorders. As a consequence of the worldwide promotion of these recommendations, however, there is a risk of reducing intensive care to these simple protocols. The objective of this review is to highlight the basic physiological and pathological features as well as the metrological issues that provide clear evidence that, in reality, and for each specific patient, SvO_2 and $ScvO_2$ are complex dynamic variables that may not always provide an appropriate cutoff for all clinical settings [5-7]. This may explain that targeting unique $S(c)vO_2$ thresholds may balance positive and negative effects and may produce hazardous results in large studies.

The fundamental equilibrium

The *sine qua non* condition for adequate energy supply is that the circulatory system transports to each cell enough oxygen (O_2), nutrients, and chemicals to ensure their aerobic respiration [8,9]. 'Adequate' means that, at any time, the difference (gap) between the expected metabolic needs minus the real O_2 consumption (VO_2) must not exceed energy storage. This basic equilibrium can be conveniently formulated as:

$$VO_2(\text{measured}) = VO_2\text{needs} - VO_2\text{gap} \quad (1)$$

For any cell, tissue, and organ, VO_2 is the difference between arterial and venous O_2 flows. For the whole body, if we ignore the O_2 dissolved in the plasma water, which represents only a few percent of the total O_2 blood content, if we consider that arterial and venous blood flows are represented by the cardiac output (CO), and if we assume that

Correspondence: pierre.squara@orange.fr
Clinique Ambroise Paré, 27 boulevard Victor Hugo, 92200 Neuilly-sur-Seine, France

arterial and venous blood flow have a similar hemoglobin concentration (Hb), then we can write:

$$VO_2 = CO \times Hb \times 1.34 \times (SaO_2 - SvO_2) \quad (2)$$

where VO_2 is in $ml/minute.m^2$, CO is in $L/minute.m^2$, Hb is in g/L , and arterial oxygen hemoglobin saturation (SaO_2) and SvO_2 are the ratios of arterial and venous oxygenated Hb over the total Hb per blood unit and, therefore, dimensionless percentages. The constant 1.34 is the carrying capacity of the oxygenated Hb in milliliters of O_2 per gram. This equation can be reformulated as a function of each variable, but its reformulation as a function of SvO_2 is one of the most popular because SvO_2 measurements are precise, accurate, time responsive and quite easy to monitor [10,11]. Figure 1 shows that the relationships between SvO_2 and its components are not equivalent and not necessarily linear. As a consequence, a large change in one variable may be compensated by a

small change in another - for example, small changes in low CO that are compensated for by large changes in SvO_2 and large changes in high CO that are compensated for by small changes in SvO_2 :

$$SvO_2 = SaO_2 - VO_2 / (CO \times Hb \times 1.34) \quad (3)$$

If we replace the measured value of VO_2 by its two hidden components seen in [1], we find:

$$SvO_2 = SaO_2 - VO_{2needs} / (CO \times Hb \times 1.34) + VO_{2gap} / (CO \times Hb \times 1.34) \quad (4)$$

The purpose of the circulatory system, eventually supported by intensive care, is to nullify the VO_2 gap; at equilibrium, therefore, Equation 4 can be written:

$$SvO_2 = SaO_2 - VO_{2needs} / (CO \times Hb \times 1.34) \quad (5)$$

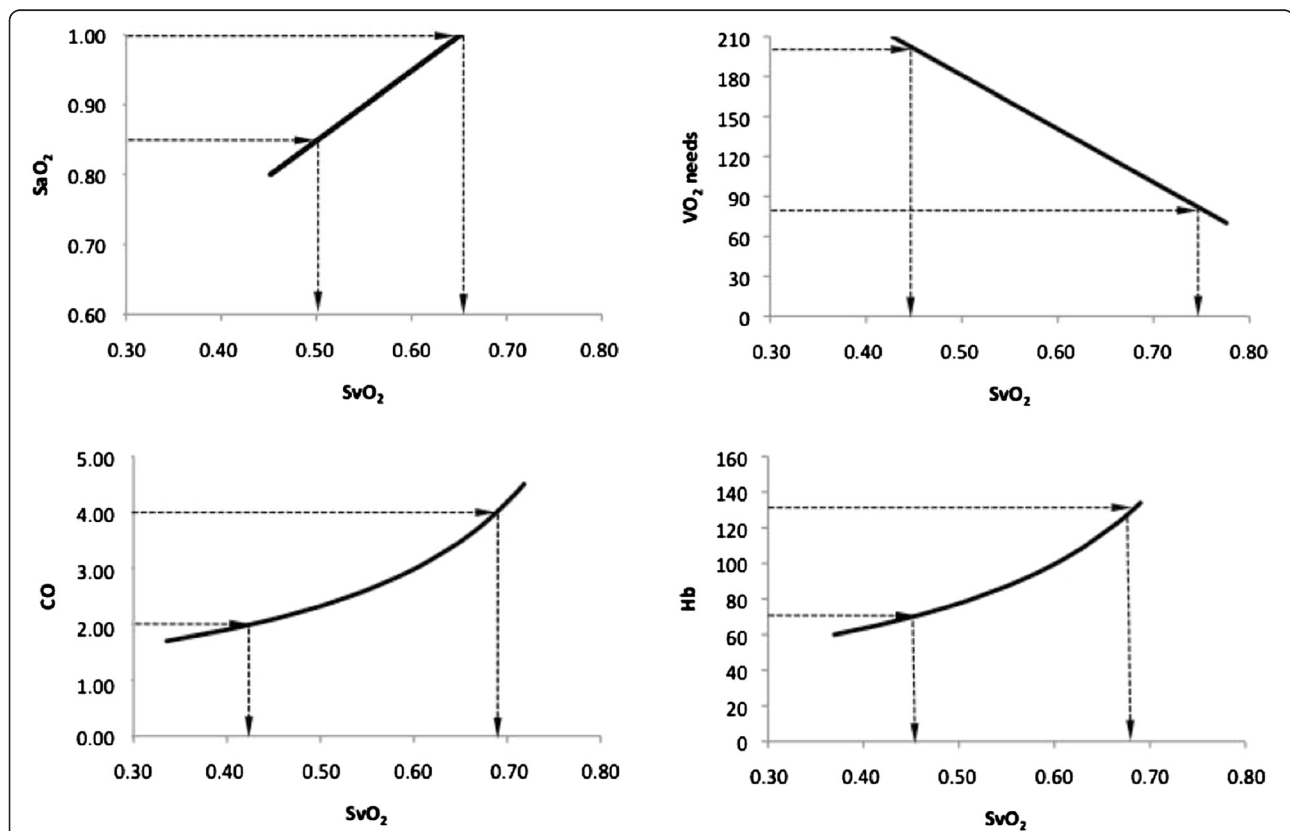


Figure 1 Relationships between mixed venous oxygen hemoglobin saturation and its components. To create these curves, we modeled a standard ICU population of 1,000 patients (Excel, Microsoft) with normal distribution of arterial oxygen hemoglobin saturation (SaO_2 ; 0.95 ± 0.05 limited to 1) and normal distributions of total body oxygen consumption (VO_2) needs (140 ± 30 $ml/minute.m^2$), cardiac output (CO ; 3.0 ± 0.5 $L/minute.m^2$) and hemoglobin concentration (Hb ; 100 ± 15 g/L). Only one of the four components was sequentially changed (Y-variables) to look at its specific relationship with mixed venous oxygen saturation (SvO_2) (X-variable). When unchanged, variables were set to their mean value. The horizontal arrows indicate the fluctuations of the Y-variable around its mean value (± 2 standard deviations). The vertical arrows show the corresponding fluctuations of SvO_2 . We can see that reference ranges (mean $\pm 2SD$) of SaO_2 , VO_2 needs, CO , and Hb are compensated for by a 26%, 50%, 47%, and 40% change in SvO_2 , respectively. Thus, CO is not necessarily the predominant component of SvO_2 except when low (left, flat part of the relationship).

where ${}^e\text{SvO}_2$ is the expected SvO_2 to maintain the equilibrium.

In reality, the 'two hands of equality' in Equation 5 fluctuate around the equilibrium. When SvO_2 is superior to the right hand, a VO_2 gap is created, and when below, the gap is restored. If we subtract Equation 5 from Equation 4, we can see that the difference $\text{SvO}_2 - {}^e\text{SvO}_2$ (ΔSvO_2) is related to the VO_2 gap:

$$\Delta\text{SvO}_2 = \text{VO}_2 \text{ gap} / (\text{CO} \times \text{Hb} \times 1.34) \quad (6)$$

Physiological adaptation

Any change in metabolic needs triggers active neuro-hormonal regulation to enable the actual VO_2 to equalize to the VO_2 needs as soon as possible. Under basal metabolic conditions, VO_2 needs depend mostly on age, gender, height and weight [12-14]. In the resting state, physiological changes in the basal metabolism are mostly due to digestion and body temperature. A normal meal usually increases the metabolic rate by 4 to 10% and each degree change in temperature over or under 37°C alters VO_2 needs by 13% [8]. Consequently, the expected VO_2 of resting patients may be easily computed or found from normative tables.

This VO_2 adaptation to metabolic needs is primarily achieved by stimulus-induced catecholamine secretion modulating global CO and its distribution. SaO_2 is maintained close to 1 by the ventilation drive triggered by brain receptors. When low, Hb is also improved, albeit slowly, by iron mobilization, [15] kidney secretion of erythropoietin, [16] and the release of young red blood cells [17,18]. In contrast, no regulatory loop has been observed for maintaining the mixed venous oxygen partial pressure or SvO_2 within specific ranges. Therefore, SvO_2 seems to be a variable that passively follows the regulation of its components. For any change in VO_2 needs, the tissue residual partial pressure of O_2 represents the final adjustment between O_2 delivery and uptake and determines the change in SvO_2 . The proportional contributions of CO and SvO_2 to the changes in VO_2 strongly depend on body position, blood volume, and the protocol for increasing the requirements. In the following, we will assume that in ICU patients, lying supine, with acceptable blood volume, two-thirds of the change in VO_2 is achieved by a parallel change in CO and one-third by an anti-parallel change in SvO_2 [19-23]. This allows us to derive the expected adaptive values of SvO_2 as a function of age, gender and temperature (Figure 2). The two-thirds to one-third balance, observed in cases of physiologic stress, should be seen as a pivotal value in critical situations. In case of limited CO for any reasons, necessary compensation

would be reached by a proportional decrease in SvO_2 and vice versa.

The adaptive physiological variability of SvO_2 that maintains VO_2 equal to needs can also be shown by its frequency distribution in large populations of steady-state patients (Figure 3). We can see that the expected SvO_2 is often below 65% in both modeled and real anesthetized patients. In real, non-anesthetized patients, other physiological contributors to metabolic needs, such as digestion, pain, discomfort, stress, inflammation, increased work of breathing, and so on, additionally increase this heterogeneity.

Pathological changes

When the VO_2 gap exceeds the tissue O_2 reserve, the cell moves from aerobic to anaerobic metabolism, leading to tissue hypoxia and dysoxia [24,25]. This can be first observed when the right-hand side of Equation 5 is excessively low (low SaO_2 , high VO_2 needs, low CO or low Hb), such that SvO_2 cannot decrease proportionally to maintain the equilibrium and a difference occurs between limited SvO_2 and very low ${}^e\text{SvO}_2$.

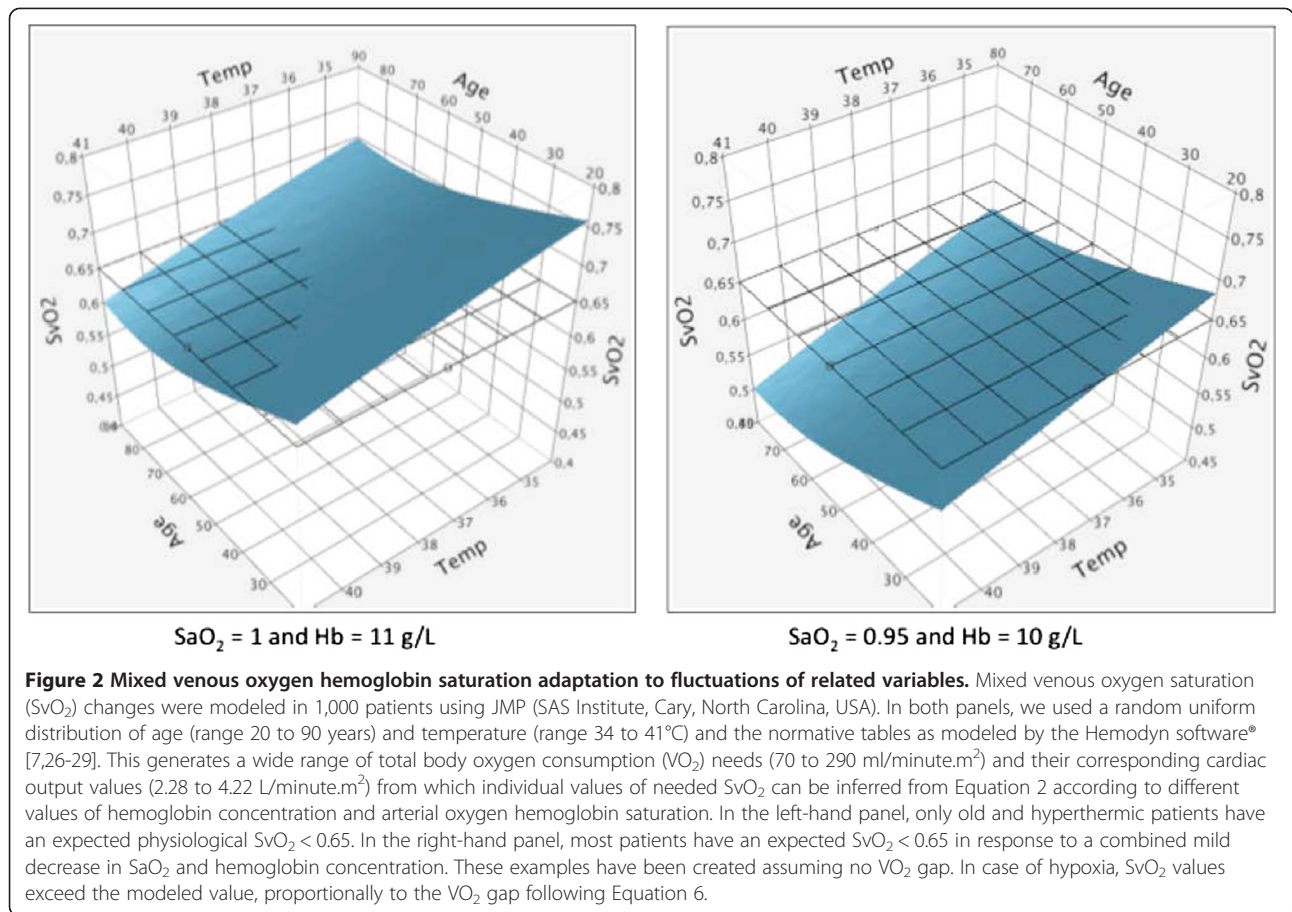
A second pathological situation is observed in the case of impaired tissue O_2 convection between hemoglobin and mitochondria, such that the arterial blood flow is not sufficiently unloaded and SvO_2 increases over ${}^e\text{SvO}_2$. This can be seen when the O_2 gradient is low due to a deficit in utilization (for example, from mitochondrial blockage, cyanide poisoning, and so on) and/or when O_2 tissue diffusion is impaired by an excessive distance or a reduced surface area (for example, in the presence of edema, inflammation, microclots, reduced capillary density, anatomical and/or functional shunts). In septic shock or in late stage shock caused by any mechanism, SvO_2 cannot decrease sufficiently due to a combination of these elementary mechanisms [7,26-29].

In both situations, the parallel changes in SvO_2 , CO and Hb predicted by Equation 3 may be lost since VO_2 is expected to increase as well up to its needed value.

Except in experimental conditions, these two pathological situations are usually combined [30]. We can reasonably speculate that, depending on the initial mechanisms of shock, its magnitude, and the adaptive possibilities of each patient, SvO_2 will cover a wide range of values and will not provide by itself clear indications for guiding therapy. The same considerations will also lead to significant discordance between different studies according to the heterogeneity of their populations for each of the elementary mechanisms described above [31].

Metrological considerations

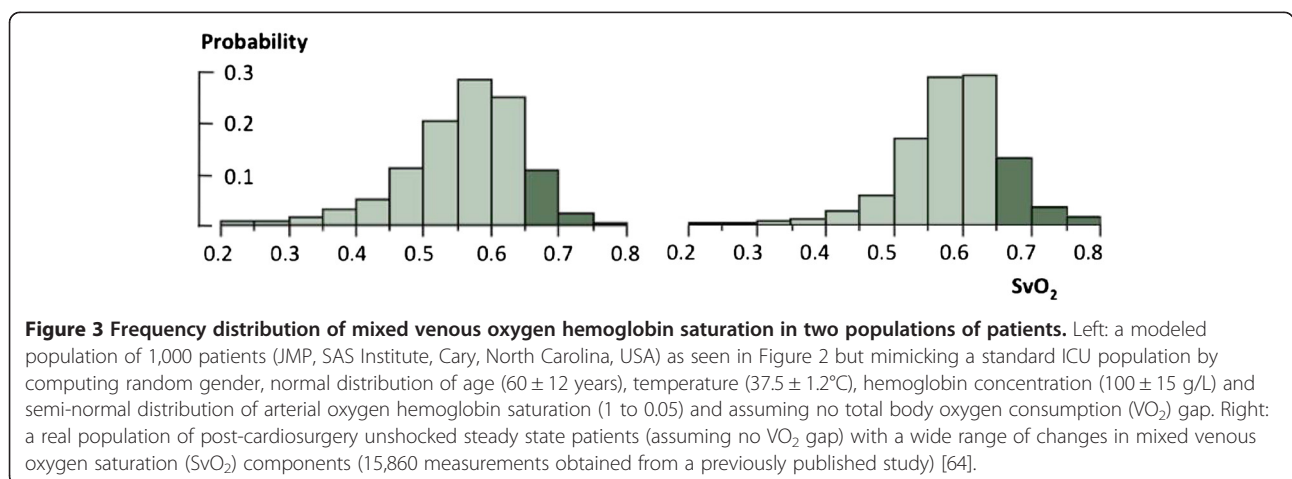
The reference method for assessing SvO_2 requires mixed venous blood sampling through a pulmonary artery



catheter and direct measurement of hemoglobin saturation using a multi-wavelength spectrophotometer (co-oximeter) [32]. When the blood sampling procedure is correct and the sample is immediately analyzed using a properly calibrated co-oximeter, the SvO₂ measurement is accurate (bias <0.5%), precise (2 standard deviations (SD)/mean = 1.3%) and linear (R² = 1) [33,34]. Even with

such good performance indices, however, the least significant change in a unique measurement ($2\sqrt{2} \times 2SD/\text{mean}$) is 3.7%, meaning that a SvO₂ value of 65% needs to change to >68.7% or <61.3% to have a 95% chance of being real.

Continuous monitoring of SvO₂ using a fiber-optic sensor placed at the tip of a pulmonary catheter has



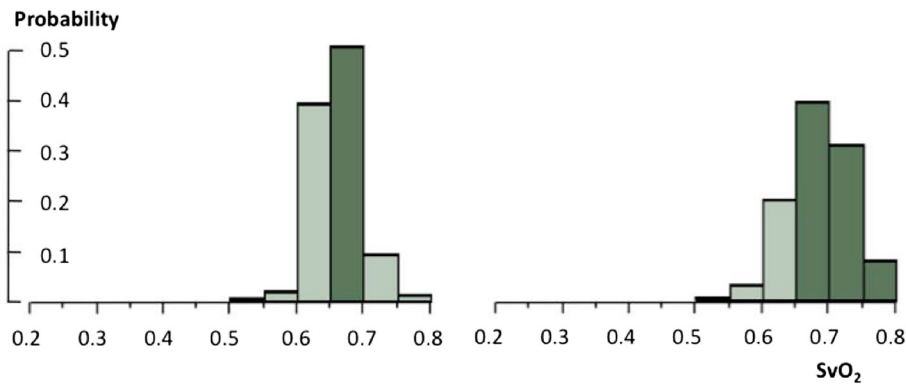


Figure 4 Frequency distribution of mixed venous oxygen hemoglobin saturation in two populations of 'optimized' patients according to the protocol of Rivers and colleagues [52]. The left-hand panel represents the population of 1,000 patients as seen in Figure 3 but total body oxygen consumption needs and cardiac output (CO) were set at 120% and 130% of the expected values at basal metabolism for modeling septic conditions. Other variables were distributed as reported by Rivers and colleagues: age = 67 ± 17.4 years, 50.8% male sex ratio, temperature = $35.9 \pm 3.2^\circ\text{C}$, hemoglobin concentration (Hb) $>100 \pm 15$ g/L and arterial oxygen hemoglobin saturation (SaO₂) >0.93 . The right-hand panel represents the same real population of post-cardiosurgery patients as shown in Figure 3 but restricted to CO >1.3 basal values, Hb $>100 \pm 15$ g/L and SaO₂ >0.93 (8,067 measurements). SvO₂, mixed venous oxygen saturation.

acceptable accuracy (bias $<1\%$) when properly calibrated and recalibrated using a co-oximeter [35]. The precision is necessarily lower ($2\text{SD}/\text{mean} >5\%$) [10,11], but is compensated by a very fast response (almost instantaneous) [36], allowing averaging of several elementary measurements (N) in a few milliseconds and decreasing the standard error of the mean ($2\text{SD}/\sqrt{N}$). Averaging 10 elementary measurements when continuously monitoring SvO₂ allows the same least significant changes to be achieved as when analyzing a unique mixed venous blood sample.

At the turn of the century, it was suggested that ScvO₂ should be used as a surrogate of SvO₂, owing to the fact that it is easier and less invasive to insert a central line than a pulmonary catheter. ScvO₂ is similar to SvO₂ in normal patients, being about 2 to 3% lower because many of the vascular circuits that drain into the inferior vena cava may have non-oxidative phosphorylation (renal, portal, hepatic blood flows) and therefore extract less O₂ [37,38]. However, several studies have shown that ScvO₂ may not predict SvO₂ in patients suffering shock, depending on the O₂ flows and O₂ extractions of the different tissue compartments, and where measurements are taken [39-43]. The coefficient of variation ($2\text{SD}/\text{mean}$) between ScvO₂ and SvO₂ may exceed $\pm 20\%$ [44,45]. Even paired changes in ScvO₂ and SvO₂ are not necessarily parallel; they were only found in 55% of cases in one study [45]. It is only when considering trend lines that changes in ScvO₂ and SvO₂ become more consistent [46].

Clinical evidence

Finally, there is a huge body of evidence (often with a degree of mathematical evidence) that SvO₂ values vary

widely in ICU patients, either for physiological, pathological or metrological reasons. Therefore, the appropriate SvO₂ for achieving an adequate body energy supply is specific to each individual patient and to its specific time-evolving situation. There is no basic evidence for targeting any clear-cut SvO₂ value. From the considerations listed above, it seems more appropriate to tune a multivariate compromise represented by an acceptable range of the four SvO₂ component trend lines with the objective of fulfilling global and local metabolic needs. This compromise must be assessed in terms of predicted benefit and risk of any change.

A variety of clinical evidence has provided us with a message in accordance with these fundamentals, showing no interest in targeting specific values of SvO₂ and/or ScvO₂ in large populations of patients [47-49]. However, other studies have presented indisputable evidence that targeting a specific value of SvO₂/ScvO₂ can be of interest for lactate clearance [50], morbidity [51], and mortality [52]. Accordingly, the Surviving Sepsis Campaign recommends maximizing mixed or central venous oxygen saturation [2]. The contradiction is apparent. As previously mentioned and detailed above, all results can be predicted by the homogeneity/heterogeneity of the patient population.

In the Rivers and colleagues' study [52], which is the main reference for the hemodynamic recommendations of the Surviving Sepsis Campaign, the population was homogenized as much as possible before targeting the ScvO₂. The study included early septic shock before ICU admission, and thus compared patients at the same phase of pathological evolution. In addition, the therapeutic protocol, including sedation, mechanical ventilation and fraction of inspired oxygen adjustment,

resulted in a decrease in VO_2 needs and the maximization of SaO_2 . Hemoglobin was also increased when necessary by blood transfusion. Heart rate and central venous pressure were optimized, thus improving CO as much as possible. Under these conditions, if a low ScvO_2 was found instead of an expected high value, even taking into consideration a possible discordance between ScvO_2 and SvO_2 , the probability of insufficient CO was high and use of inotropes was consistent with the basic physiology. This is illustrated in Figure 4, where we used the same populations as shown in Figure 3 but with the distributions of the SvO_2 components mimicking those of the study by Rivers and colleagues. In these homogenized populations, the SvO_2 distribution is obviously narrower. If Hb, SaO_2 and VO_2 are homogenized, ScvO_2 and/or SvO_2 are necessarily more influenced by CO.

From the modeled population seen in Figure 4, we can simulate the increase in CO required to reach a target SvO_2 of >65% (presumably equivalent to $\text{ScvO}_2 > 70\%$). Such an increase would be required in 39.5% of the patients, up to 1.2 L/minute. m^{-2} (average 0.17 ± 0.16), which seems to be a reasonable objective.

However, the Surviving Sepsis Campaign recommended a target Hb of 70 to 90 g/L whereas in Rivers and colleagues' study the hematocrit was increased up to 30%, which represents an Hb >100 g/L. This has major consequences for SvO_2 . If we consider again the population modeled in Figure 4, reducing Hb from 100 to 90 g/L displaces the frequency distribution leftwards and it would be more difficult to target SvO_2 to >65%. The simulation shows that an increase in CO would be necessary for 79.5% of the patients, up to 1.7 L/minute. m^2 , with an average increase of 0.39 ± 0.24 . If targeting Hb to 70 g/L, an increase in CO would be necessary for 98.7% of the patients, up to 2.7 L/minute. m^2 with a mean increase of 1.30 ± 0.44 . All these estimations are derived with constant VO_2 needs, ignoring the caloric effects of increasing CO [53]. Therefore, targeting the same SvO_2 objective as Rivers and colleagues without targeting the same Hb has strong consequences for CO stimulation. Finally, SvO_2 must be viewed as a compromise. Increasing Hb may have favorable [54] or detrimental effects [55]. Increasing CO may also have positive [56,57] or negative results [58-61]. The final decision depends, therefore, on the specific conditions and limitations of each patient. This statement is reinforced by two recent reports. In the study of Jones and colleagues [62] management to increase lactate clearance was equivalent to targeting specific ScvO_2 values in septic shock. Moreover, the ProCESS trial has shown that, in academic hospitals, the Rivers and colleagues' protocol was not superior to usual care despite significant increases in blood transfusion, dobutamine and vasopressor use [63]. The comparable mortality may

only be explained by an absence of impact on mortality of these interventions, which seems unlikely, or by the fact that targeting a unique ScvO_2 value in heterogeneous patients may balance positive and negative effects. Whether a unique SvO_2 or ScvO_2 goal would be beneficial or not depends, therefore, on the quality of care in the control group and on the inter-individual dispersion of the difference between the target and the optimal ScvO_2 value allowing VO_2 needs to be met. We have seen that this optimal value may be far from a fixed target. These results should not discourage us from monitoring SvO_2 or ScvO_2 but encourage us to include these variables in a multimodal analysis.

Conclusion

Basic physiology tells us that SvO_2 is not a regulated variable but an adaptive variable depending on four elementary regulated components: VO_2 needs, SaO_2 , Hb and CO. Consequently, SvO_2 is widely fluctuating. There is no physiological argument for targeting particular values of SvO_2 (or its surrogate ScvO_2) by specific interventions except in homogenized populations, where optimizing one to three of the four SvO_2 components may yield a clear dependency with the fourth one. This explains the apparently contradictory results observed in large studies where CO was increased up to specific SvO_2 thresholds and confirms the basic physiology predicting large inter-patient variability. Although a systematic SvO_2 goal-oriented protocol can be statistically profitable before ICU admission, one would expect from any trained intensivist a more sophisticated, multivariate approach and a determination of the best compromise between SvO_2 and its components, taking into account the specific constraints of each individual patient.

Abbreviations

CO: Cardiac output; $^e\text{SvO}_2$: Expected SvO_2 ; Hb: Hemoglobin concentration; SaO_2 : Arterial oxygen hemoglobin saturation; ScvO_2 : Central venous oxygen saturation; SD: Standard deviation; SvO_2 : Mixed venous oxygen saturation; VO_2 : Total body oxygen consumption.

Competing interests

The author declares that he has no competing interests.

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