Mixed and Central Venous Oxygen Saturation

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Introduction

Central venous oxygen saturation ($ScvO_2$) and mixed venous oxygen saturation (SvO_2) have been used in the assessment and management of the critically ill for many years. $ScvO_2$ refers to hemoglobin saturation of blood in the superior vena cava and SvO_2 refers to the same measurement in blood from the proximal pulmonary artery. The earliest clinical reports of the use of such data were of $ScvO_2$ in the coronary care unit [1]. Following the introduction of the pulmonary artery catheter (PAC) in 1970 [2], the routine clinical use of both $ScvO_2$ and SvO_2 became possible.

Since that time various authors have utilized SvO_2 and $ScvO_2$ as therapeutic goals in clinical trials, initially without success [3]. However, as our understanding of the clinical relevance of $ScvO_2$ and SvO_2 has improved, use of these parameters has been associated with marked improvements in outcome [4]. As a result, there is renewed interest in the use of venous saturation, in particular as a hemodynamic goal in the use of goal-directed therapy. The aim of this chapter is to give an account of the physiology of SvO_2 and $ScvO_2$ in health and disease, describe the relationship between the two and explore the use of these parameters in interventional trials.

Techniques of Measurement of SvO_2 and $ScvO_2$

Venous saturation of blood can be measured in one of two ways. Either a sample of blood from the correct anatomical position can be taken and the venous saturation then measured (intermittent) or a continuous invasive catheter is used that measures the saturation of blood *in vivo*.

Intermittent Blood Sampling

The saturation of hemoglobin with oxygen is measured by spectrophotometry. The pattern of light absorption differs for oxygenated and de-oxygenated hemoglobin. The relative concentrations of each form may be calculated from absorption of light comprising two or more discrete wavelengths and a measurement of hematocrit. This technique, known as a co-oximetry, is employed in modern blood gas analyzers and allows the presence of methemoglobin and carboxyhemoglobin to be quantified as well.

Co-oximetry is a reliable technique, the main sources of error being the use of a diluted or unhomogenized blood sample. Blood sampling from the distal port of a 'wedged' PAC may provide a sample of pulmonary capillary rather than mixed venous blood [5]. Prior to the introduction of spectrophotometry, PvO_2 and $PcvO_2$ were measured and SvO_2 and $ScvO_2$ then calculated with the use of a nomogram [6]. This technique does not take account of changes either in hemoglobin affinity for oxygen or the presence of carboxyhemoglobin and methemoglobin, which may be clinically significant in the critically ill. Some older studies describing $ScvO_2$ and SvO_2 are therefore subject to a greater margin of error than subsequent research which utilized spectrophotometric techniques.

Indwelling Fiberoptic Catheter

By incorporating optical fibers into pulmonary artery and central venous catheters, the oxygen saturation of venous blood may be measured continuously without the need for intermittent blood sampling. The use of light of three wavelengths appears to be more reliable [7]. The main sources of error with this approach are malposition of the catheter and the catheter tip abutting a vessel wall. The latter is indicated by a signal on the display provided by some continuous spectrophotometry systems.

Physiology of SvO_2 and $ScvO_2$

Basic Determinants of SvO_2 and $ScvO_2$

The main determinants of the oxygen content of venous blood are the delivery of oxygen to the tissues (DO_2) and its consumption by the tissues (VO_2). DO_2 is determined by the oxygen content in arterial blood and cardiac output, whilst VO_2 is affected by a range of factors which relate to tissue respiration. This relationship may be expressed by re-arranging the Fick equation:

$$CvO_2 = CaO_2 - \frac{VO_2}{CO}$$

Where CvO_2 and CaO_2 are the oxygen contents in venous and arterial blood; these are determined by the concentration of oxgenated hemoglobin and the dissolved

Table 1. Factors influencing mixed and central venous oxygen saturation

Factors affecting oxygen delivery	Factors affecting oxygen consumption
Cardiac output	**Cytopathic hypoxia**
▪ Cardiogenic shock	▪ Sepsis
▪ Reduced circulating blood volume	▪ Cyanide poisoning
▪ Exercise	**Increased consumption**
Oxygen content	▪ Pyrexia
▪ Hypoxia/O_2 therapy	▪ Exercise
▪ Hyperbaric O_2 exposure	▪ Shivering
▪ Anemia/hemorrhage	**Reduced consumption**
▪ Carbon monoxide poisoning	▪ Sedation/anesthesia

oxygen content. Because at standard atmospheric pressure, the quantity of dissolved oxygen is very small it is acceptable and more convenient simply to measure hemoglobin saturation. SvO_2 and $ScvO_2$ reflect the physiology of the entire body and are global indicators of tissue oxygenation and function. It is important therefore to realize that regional changes in venous saturation may occur without an overall change in SvO_2.

A diverse range of factors may affect SvO_2 (Table 1) and it is important to emphasize the need to assess the cause of any derangement before initiating treatment based on an abnormal value. The presence of intra-cardiac shunt will greatly limit the significance of changes in either SvO_2 or $ScvO_2$.

What are the Normal Values of SvO_2 and $ScvO_2$?

The normal value of SvO_2 has been quoted as 70% [8], however the measurement of SvO_2 and $ScvO_2$ is invasive in nature and few data exist to describe normal values. Only two studies, of which we are aware, document values for these parameters in young healthy individuals. The first is one of the earliest studies of venous saturation and provides a detailed description of hemoglobin saturation in the superior and inferior vena cavae, right atria, right ventricles and pulmonary arteries of 26 healthy subjects breathing air. The mean values were 76.8% (SD±5.2%) in the superior vena cava and 78.4% (SD±2.6%) in the pulmonary artery [9]. The second assessed trends in $ScvO_2$ in response to orthosatatic hypotension and described a median baseline $ScvO_2$ of 75% (range 69–78%) in nine subjects [10].

The most useful indicator of normal values of venous saturation in clinical practice involved the measurement of $ScvO_2$ prior to induction of anesthesia in 23 patients scheduled for major abdominal surgery. This study suggests a median value of 69% (Range 53%–83%) rising to 72% (range 66%–83%) after fluid administration [11]. These recordings were taken breathing room air but one hour after oral diazepam given as premedication for anesthesia.

All other available data describe SvO_2 and $ScvO_2$ values during major surgery or intensive care unit (ICU) admission, frequently providing little or no data regarding FiO_2, depth of anesthesia or sedation. It is more logical therefore, to assume a normal range for these parameters rather than one discrete value. Taking into account the above data and the normal value for PvO_2 which is quoted as 5 kPa [6], SvO_2 and $ScvO_2$ would be expected to vary between 70% and 80% in healthy subjects. However, values may be as low as 65% in hospital in-patients who are not critically ill.

Relationship between SvO_2 and $ScvO_2$

The relationship between these two parameters is complex. The differences in VO_2 and DO_2 between the upper and lower regions of the body vary in health and disease. Drainage of coronary venous blood directly into the cardiac chambers via the coronary sinus and Thebesian veins also changes with myocardial work. Complete mixing of venous blood is not thought to occur until it reaches the right ventricle and, as a result, it is generally accepted that for reliable measurement of SvO_2, blood must be sampled from the pulmonary artery.

In healthy individuals, $ScvO_2$ is slightly lower than SvO_2 (76.8% vs 78.4%) [9], but this relationship changes in periods of cardiovascular instability. Scheinman

and co-workers performed the earliest comparison of $ScvO_2$ and SvO_2 in both hemodynamically stable and shocked patients [12]. In stable critically ill patients, $ScvO_2$ was similar to SvO_2 ($ScvO_2$ 54.7% SD ± 19.92% vs SvO_2 56.9% SD±21.16%, $p > 0.1$). In patients with heart failure, $ScvO_2$ was slightly higher than SvO_2 ($ScvO_2$ 61.8% SD±8.76% vs SvO_2 58.2% SD±8.74%, $p < 0.1$), whilst in shock patients the pattern was even more pronounced ($ScvO_2$ 58.0% SD ± 13.05% vs SvO_2 47.5% SD ± 15.11%, $p < 0.001$). The only other study to compare hemodynamically stable patients to those with shock describes similar findings [13]. In a more detailed study of a carefully defined group of patients with circulatory shock, mean $ScvO_2$ was again greater than SvO_2 although the range of values was large ($ScvO_2$ 74.2% SD ± 12.5% vs SvO_2 71.3% SD ± 12.7%) [14]. The largest series reported so far was a retrospective analysis of 3296 patients undergoing cardiac catheterization. Data were analyzed to identify the frequency of patients in whom $ScvO_2$ was more than 5% greater than SvO_2. This 'step-down' was identified in only 177 patients (5.4%). Whilst cardiac output was similar between the two groups, pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP) and serum creatinine were all significantly greater in the step-down group. The authors concluded that poor left ventricular performance and renal dysfunction might explain these findings [15].

Most authors attribute this pattern to changes in the distribution of cardiac output that occur in periods of hemodynamic instability. In health, blood in the inferior vena cava has a high oxygen content because the kidneys do not utilize much oxygen but receive a high proportion of cardiac output [16]. As a result, inferior vena caval blood has a higher oxygen content than blood from the upper body and SvO_2 is greater than $ScvO_2$ [9, 12, 13]. In shock states, blood flow to the splanchnic and renal circulations falls, whilst flow to the heart and brain is maintained [17]. This results in a fall in the oxygen content of blood in the inferior vena cava. As a consequence in shock states the normal relationship is reversed and $ScvO_2$ is greater than SvO_2 [12-14]. In two studies in hemodynamically stable patients, $ScvO_2$ was slightly greater than SvO_2 but the differences were small [18, 19].

Some studies have aimed simply to describe the degree of correlation between $ScvO_2$ and SvO_2 but do not stratify patients according to hemodynamic status. Because of the influence of changes in the distribution of cardiac output in critical illness these trials simply report a poor correlation and are difficult to interpret [20-22]. Experimental studies indicate a good association between these parameters, although absolute values differ [23, 24]. Two studies have utilized spectrophotometry techniques to simultaneously monitor $ScvO_2$ and SvO_2 in critically ill patients. Whilst both describe discrepancies between the two parameters, one reports useful similarity in trend between the two whilst the other suggests $ScvO_2$ to be an unreliable indicator of SvO_2 [25, 26].

The relationship between $ScvO_2$ and SvO_2 is not straightforward. In health, the two values are often similar in magnitude but this is not always the case during periods of critical illness. Many previous studies of the link between these two parameters aimed to provide a more easily obtained surrogate for SvO_2 to allow calculation of intra-pulmonary shunt (Qs/Qt) or VO_2. The relationship between $ScvO_2$ and SvO_2 is too inconsistent for this purpose. Contemporary practice involves the use of these variables not to quantify VO_2 but as therapeutic end-points in their own right. In the presence of abnormalities, absolute values for either $ScvO_2$ or SvO_2 may not be as important as trend in response to treatment. The use of $ScvO_2$ in particular, has developed renewed interest as it avoids the requirement for pulmonary artery catheterization, a technique which has been criticized in the past [27].

Right Atrial Oxygen Saturation

Where reported, the saturation of blood in the right atrium is very similar to that of the pulmonary artery [9, 12–14, 28]. As might be anticipated, there was a very poor association in children immediately following surgery for major atrial or ventricular septal defects [29]. Choice of optimal position for the tip of the central venous catheter is not straightforward. Placement of the catheter tip in the right atrium may be associated with perforation of cardiac chambers whilst not advancing the catheter far enough may be associated with a higher incidence of venous thrombo-embolism [30]. For $ScvO_2$ measurement the catheter tip should probably be situated in the superior vena cava just above the entrance to the right atrium.

Venous Oxygen Saturation in Pathological States

Patterns of SvO_2 and $ScvO_2$ derangement have been described in various pathological conditions. The causes of any abnormalities and the appropriate therapies required to correct them may differ widely. It is therefore important to consider each etiological group separately. The randomized trials that have utilized these parameters as hemodynamic goals are discussed separately.

Hypovolemia

The effects of circulatory disturbance due to hypovolemia have been described in both animals and humans. Reinhart et al. demonstrated fluctuations in SvO_2 and $ScvO_2$, which closely mirrored periods of hypoxia, hyperoxia, hemorrhage and subsequent resuscitation in anesthetized dogs. Values varied between 60% at baseline to 35% during periods of hypovolemia [24]. In another experimental study, a number of cardiovascular parameters were correlated with the extent of hemorrhage in dogs [31]. Central venous pressure (CVP), PAOP, arterial pressure and heart rate proved unreliable indicators but cardiac index, SvO_2 and $ScvO_2$ correlated well with the extent of blood loss. Whilst the values of SvO_2 and $ScvO_2$ were not identical, the trends were very similar throughout periods of hemodynamic change. In other experimental studies, oxygen saturations of blood from the jugular vein of rats and the right atria of rabbits have also correlated well with hemorrhage [32, 33]. Work in humans used orthostatic hypotension as a model of the cardiovascular disturbances associated with hypovolemia [10]. Median $ScvO_2$ fell from 75% at baseline to 60% at the onset of pre-syncopal symptoms. Over the same period, cardiac output fell from 4.3 to 2.7 l/min.

Clinical studies also suggest a role for the use of SvO_2 and $ScvO_2$ in the evaluation of traumatic shock. A small clinical series described derangements of SvO_2 in victims mainly of penetrating trauma [34]. Profound reductions, frequently below 30%, are described. SvO_2 rose above 60% in all four survivors but failed to do so in five of the six non-survivors. In a series of 26 major trauma victims, a value of $ScvO_2$ below 65% was not only a useful indicator of severity of blood loss but proved more reliable than conventional observations (heart rate, blood pressure, CVP) [35]. However, correlation with the extent of blood loss was not as strong as that found in experimental studies by the same author [31].

Both SvO_2 and $ScvO_2$ were lower in patients suffering in circulatory shock of various causes than a similar group of more stable patients. The data suggest that

other causes of hypovolemia also result in profound reductions in venous oxygen saturation [13]. Reductions in $ScvO_2$ to below 65% were frequent in a group of patients mainly suffering from septic shock [36]. The same author went on to show that, following initial resuscitation, a value of $ScvO_2$ below 65% combined with serum lactate greater than 2 mmol/l indicated the need for additional resuscitation [37]. In early severe sepsis, mean $ScvO_2$ at baseline was 49.2% (SD±13.3%) in the control group and 48.6% (SD±11.2%) in the intervention group of a randomized trial [4]. There is also some evidence to suggest reductions in $ScvO_2$ to below 65% are associated with a poor outcome following high-risk surgery [38].

Cardiac Failure and Myocardial Infarction

Patterns of SvO_2 and $ScvO_2$ derangement in cardiac failure and following myocardial infarction have been described extensively. The earliest clinical work on $ScvO_2$ was performed by Goldman, who correlated derangements of this parameter with severity of myocardial dysfunction and subsequent response to treatment. A 60% threshold was suggested as holding particular importance and indicated a number of patients suffering from occult heart failure. Reductions in $ScvO_2$ to below 45% were generally associated with cardiogenic shock [1, 39]. Subsequent studies have also described derangements in both $ScvO_2$ and SvO_2 in cardiac failure, cardiogenic shock and following myocardial infarction. Reductions indicate the severity of disease [12, 40], whilst trends provide an indication of cardiac output and reflect response to treatment [41–44]. One study showed reductions in PvO_2 to reflect hyperlactemia and poor outcome in severe cardiac and respiratory disease [45]. Two studies demonstrated the occurrence of abnormalities of SvO_2 in chronic heart failure and acute myocardial infarction but did not recommend the use of this parameter to guide therapy [46, 47].

Cardiopulmonary Arrest

A number of studies have employed $ScvO_2$ in the management of cardiac arrest [48–51]. Although animal studies of the relationship between $ScvO_2$ and SvO_2 during cardiopulmonary arrest are contradictory, $ScvO_2$ measurement still appears to be of value [52, 53]. In a series of 43 patients with cardiopulmonary arrest, at ten minutes after the loss of spontaneous circulation, PvO_2 was greater than 4.9 kPa in 12 out of 14 survivors, whilst all 29 non-survivors had a PvO_2 below 4.1 kPa [50]. In a series of 100 cases, $ScvO_2$ above 72% was found to be a reliable indicator of return of spontaneous circulation [51]. This is particularly helpful because clinical methods of detecting return of spontaneous circulation are known to be unreliable.

Cardiothoracic and Aortic Surgery

In cardiac surgery, studies which concentrate on SvO_2 values during surgery suggest changes occur before those of blood pressure or heart rate [54] and correlate well with changes in cardiac index (CI) [54, 55]. In a study of 19 patients undergoing cardiac or lung surgery, sustained falls in SvO_2 to below 65% were associated with a higher incidence of complications especially arrhythmias [56]. Other data suggest changes in SvO_2 during and after cardiac surgery provide a more reliable indication of VO_2 than of cardiac output [57]. This may reflect a higher variability

in VO_2 in the patients studied resulting from changes in anesthesia, sedation and invasive ventilation during the post-operative period. Changes in SvO_2 reflected specific events during lung transplantation, although the series was too small to draw any conclusions regarding the value of SvO_2 monitoring in this group [58].

SvO_2 monitoring during aortic surgery has also been described [59, 60]. The pattern of SvO_2 changes during the application and removal of aortic and femoral clamps appears complex. Reperfusion of the lower body following a variable period of ischemia results in large falls in SvO_2 which do not necessarily reflect a need for a change in cardiovascular management. There are few or no data regarding the monitoring of $ScvO_2$ during either cardiac or aortic surgery.

SvO_2 in Established Critical Illness

In respiratory failure, SvO_2 provided a useful indication of unsuspected problems with respiratory function resulting from sub-optimal patient position or coughing as well as guiding the choice of positive end-expiratory pressure (PEEP) and other respiratory management [61–64]. Some studies have concluded that SvO_2 monitoring provides no clear benefit in the management of mixed groups of critically ill patients [65, 66].

Interventional Trials Utilizing SvO_2 and $ScvO_2$ as Hemodynamic Goals

In common with other hemodynamic goals, interventional studies utilizing SvO_2 have shown conflicting results. The largest of these was a multicenter trial in a mixed group of critically ill patients [3]. Patients were randomized 48 hours after ICU admission to receive therapy targeted at maintaining $SvO_2 \geq 70\%$, $CI \geq 4.5$ l/min/m^2 or to the control group in whom a goal of 2.5–3.5 l/min/m was set for CI. These goals were then maintained for a five-day period.

At enrolment SvO_2, CI, DO_2, mean arterial pressure (MAP), and CVP were all similar between the groups. This remained the case at the end of the study period, with the exception of CI and DO_2, which were higher in the high CI group. Mean SvO_2 was between 67.3% and 69.7% in the three groups at enrolment and between 70.7% and 72.1% at the end of the study period. Similarly, the CI in the three groups was reasonable at enrolment (3.7–3.8 l/min/m) and normal or high at the end of the study period (control group 3.9 l/min/m, CI group 4.4 l/min/m, SvO_2 group 4.1 l/min/m). These figures suggest that flow related parameters were not so sufficiently deranged that further increases would alter outcome.

In peripheral vascular surgery, pre and post-operative goal directed hemodynamic therapy to achieve an SvO_2 of 65% did not alter outcome [67]. In this study, initial values for SvO_2 were low at enrolment and responded significantly in the intervention group (initial SvO_2 59.1%, final SvO_2 68.8%), but remained similar in the control group (initial SvO_2 59.1%, final SvO_2 63.8%). The outcome in this trial cannot therefore be attributed to the adequacy of therapy.

SvO_2 has been used successfully as a hemodynamic goal in cardiac surgical patients [68]. For the first eight hours after surgery, patients received either standard care or therapy to achieve a target for SvO_2 of 70% combined with a goal for serum lactate of below 2 mmol/l. Median hospital stay was shorter in the intervention group (6 vs 7 days, $p < 0.05$). Morbidity was also reduced in the intervention group (1.1% vs 6.1%, $p < 0.01$). Mean SvO_2 was 67% in both groups on arrival in the ICU

but made significantly greater improvement in the intervention group (intervention group 71%±4% vs control group 69%±5, $p < 0.001$).

Rivers and colleagues utilized $ScvO_2$ to guide cardiovascular management in early severe sepsis and septic shock [4]. Two hundred and sixty-three patients were randomized to receive either six hours of standard care or fluid and inotropic support to achieve a target for $ScvO_2$ of 70% prior to ICU admission. In-hospital mortality was 30.5% in the intervention group and 46.5% in the control group ($p = 0.009$). The authors attribute this outcome improvement to a substantial reduction in episodes of 'sudden cardiovascular collapse'. Immediately following the trial period, patients receiving goal-directed therapy had higher mean $ScvO_2$ (goal-directed therapy group 70.4% SD±10.7% vs. Control group 65.3% SD±11.4%), lower serum lactate and lower mean APACHE II scores indicating less severe organ dysfunction.

Regardless of the hemodynamic goal chosen, goal-directed therapy is generally successful when employed in the resuscitation of patients at high risk of hypovolemia. Optimal benefit seems to result from short periods of goal-directed therapy applied at an early stage in the evolution of circulatory shock. Outcome from interventional trials utilizing SvO_2 and $ScvO_2$ as hemodynamic goals are also consistent with this concept. When appropriately applied, measurement of either $ScvO_2$ or SvO_2 may provide a valuable guide to circulatory management. $ScvO_2$ monitoring is particularly convenient as it allows the use of goal-directed therapy without recourse to the PAC or other forms of cardiac output measurement.

Conclusion

SvO_2 and $ScvO_2$ appear to be useful indicators of disease severity and response to treatment in cardiovascular disturbances of various causes, although the utility of venous saturation in the calculation of VO_2 and Qs/Qt has been discounted. The relationship between the two parameters is complex and varies in health and disease. However, this does not appear to prevent the use of either in the assessment and management of the critically ill. Whilst cardiac output appears to be the single most important determinant of SvO_2 and $ScvO_2$, other factors must also be taken into account. Factors which influence VO_2 are of particular relevance as considerable changes in invasive ventilation, anesthesia and sedation may be made during a period of critical illness.

A primary aim of management of the critically ill is the maintenance of adequate tissue perfusion. Because of the challenges of measuring tissue function, we employ surrogate markers of tissue perfusion and function e.g., blood pressure, cardiac output, and serum lactate, each of which has limitations. The evidence regarding the use SvO_2 and $ScvO_2$ suggests that, in carefully chosen situations, they are also effective tools in the assessment and management of tissue perfusion in the critically ill.

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