Published in final edited form as:

Ann Emerg Med. 2010 January ; 55(1): 40–46.e1. doi:10.1016/j.annemergmed.2009.08.014.

Multi-Center Study of Central Venous Oxygen Saturation (ScvO₂) as a Predictor of Mortality in Patients with Sepsis

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Abstract

Study Hypothesis—Abnormal (both low and high) central venous saturation (ScvO₂) is associated with increased mortality in Emergency Department (ED) patients with suspected sepsis.

Methods—Secondary analysis of four prospectively collected registries of ED patients treated with Early Goal Directed Therapy (EGDT) based sepsis resuscitation protocols from 4 urban tertiary care hospitals. Inclusion criteria: 1) sepsis; 2) hypoperfusion defined by SBP < 90 mmHg or lactate ≥ 4 mmol/L; and 3) EGDT therapy treatment. ScvO₂ levels were stratified 3 groups: hypoxia (ScvO₂ <70%); normoxia (71% - 89%); and hyperoxia (90 - 100%). The primary exposures were initial ScvO₂ and maximum ScvO₂ achieved with the primary outcome as in-hospital mortality. Multivariate analysis was performed.

Results—There were 619 patients who met criteria and were included. For the maximum ScvO₂, compared to the mortality rate in the normoxia of 96/465 (21%; 17 - 25%), both the hypoxia mortality rate 25/62 (40%; 29 - 53%) and hyperoxia mortality rate 31/92 (34%; 25 - 44%) were significantly higher, which remained significant in a multivariate modeling. When the initial ScvO₂ measurement was analyzed in a multivariate model, only hyperoxia was significantly higher.

Conclusions—The maximum ScvO₂ value achieved in the ED (both abnormally low and high) was associated with increased mortality. In multivariate analysis for initial ScvO₂, the hyperoxia group was associated with increased mortality, but not the hypoxia group. This study suggests that future research aimed to target methods to normalize high ScvO₂ values via therapies that improve microcirculatory flow or mitochondrial dysfunction may be warranted.

Introduction

Background

Sepsis, defined as the presence of infection with an associated systemic response, exists on a continuum of severity progressing from sepsis (infection with an pro-inflammatory response)

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Author Contributions: All authors (JVP, NIS, AJ, DG, RCA, and ST) participated in the conception of the study, study design, and data collection. JVP and NIS oversaw the final data compilation and statistical analysis. All authors participated in the drafting of the manuscript into its final form.

to severe sepsis (sepsis plus acute organ dysfunction) to septic shock (sepsis plus tissue hypoperfusion). Sepsis is the 10th leading cause of death in the United States with in-hospital mortality rates of 30% (1,2). Unfortunately, until recently, numerous therapies to treat sepsis failed to improve mortality. In 2001, Rivers et al. demonstrated that early goal-directed therapy (EGDT), consisting of fluid resuscitation, vasoactive interventions, and transfusions based on hemodynamics and other physiologic parameters, resulted in an absolute mortality reduction of 16% (3). The EGDT protocol balances systemic oxygen delivery with oxygen demand by using targeted endpoints (or goals) as part of a standardized resuscitation protocol. The three main resuscitation targets are preload (measured by central venous pressure), perfusion (mean arterial pressure), and tissue hypoxia (central venous oxygen saturation (ScvO₂)). To better understand EGDT and the importance of improving global tissue hypoxia, one must understand the significance of the ScvO₂ measurement.

Central venous oxygen saturation values are obtained by measuring the oxygen saturation in venous blood returning to the heart. In simple form, it represents the balance between oxygen delivery and oxygen consumption. The story is more complex, however, as mechanisms of oxygen supply (macrocirculatory flow), distribution (microcirculatory flow), and processing (mitochondrial function) must all function at an adequate level to maintain normal physiology. Thus, a low ScvO₂ may indicate a decrease in oxygen delivery, an increase in oxygen extraction, or a combination of the two. In the EGDT protocol, a low ScvO₂ is addressed through oxygen delivery optimization by improving arterial oxygen saturation, cardiac output, or oxygen carrying capacity to increase oxygen delivery. Accordingly, one may broadly categorize deficiencies in oxygen exchange into three types of failure: 1) macrocirculatory failure, 2) microcirculatory failure, and 3) mitochondrial failure. Macrocirculatory failure is typically assessed through parameters such as central venous pressure (CVP), mean arterial pressure (MAP), cardiac index and ScvO₂. (3) A deficiency in any of these parameters can result in an inadequacy in the net amount of oxygen delivered to the tissues. The cause of microcirculatory failure is multifactorial and includes physiologic shunting, maldistributed flow, increased microvascular permeability, and microvascular thrombosis. In some instances, there may be adequate macrocirculatory flow but microcirculatory failure prevents the oxygen from reaching tissues (4). Finally, in mitochondrial failure, oxygen is presented to the cell but the mitochondria are dysfunctional and unable to process the oxygen (5,6). In the latter two cases, the ScvO₂ may actually be elevated—a condition referred to as tissue *dysoxia*. In these cases, increasing oxygen supply will not ameliorate the problem.

Importance

While ScvO₂ measurement is recommended by evidence based practice guidelines and medical professional organizations, multiple challenges limit its adoption into standard practice. Although guidelines recommend normalizing ScvO₂, it is based on the assumed association between ScvO₂ and mixed venous oxygen saturation (SvO₂) and studies compared patients receiving an entire protocol against those who did not (7). The clinical impact of abnormally low and high ScvO₂ values in patients who receive the same protocol are not well characterized. The notion of abnormally elevated ScvO₂ levels representing hypoxia at the cellular level has been reported (5), but there is little evidence in support of its clinical significance. Furthermore, since the EGDT-based protocol aims to correct a low ScvO₂ level through a titrated resuscitation, it is not clear whether the initial ScvO₂ level and/or the maximum ScvO₂ achieved have an association with mortality.

Goals of This Investigation

In this manuscript we sought to test the hypothesis that an abnormal (both low and high) ScvO₂ is associated with increased mortality in Emergency Department (ED) patients with

septic shock. As a secondary objective, we sought to determine whether the initial ScvO₂ and/or the maximum ScvO₂ achieved were associated with mortality.

Materials and Methods

Study Design and Setting

This study was a secondary analysis of four prospectively collected registries of patients treated with EGDT based sepsis resuscitation protocols from 4 urban tertiary care hospitals. The registries were collected from ED patients and the methodologies have been previously reported (8-11). Each of the studies were initially independent single institution, prospective initiatives; however, the patient selection characteristics (see below) were identical and the EGDT based resuscitation portion of the protocols were also identical across the sites, making it easy and appropriate to combine the different registries. The respective Institutional Review Boards approved the initial data collection and the Beth Israel Deaconess Medical Center IRB approved subsequent research outlined in this proposal.

Selection of Patients and Data Collection

Eligible patients were ED patients ≥ 18 years old who met the following criteria: 1) suspected infection; 2) ≥ 2 systemic inflammatory response syndrome criteria; 3) hypoperfusion defined by SBP < 90 mmHg after fluid challenge or lactate ≥ 4 mmol/L; and 4) treated with EGDT therapy. Data elements included *demographics*: age and gender, *physiologic variables*: initial ScvO₂ and maximum ScvO₂ during six hours of EGDT, *co-morbidities*: hypertension (HTN), coronary artery disease (CAD), diabetes mellitus (DM), cancer, human immunodeficiency virus (HIV), chronic obstructive pulmonary disease (COPD), and alcoholism, *source of infection*: pneumonia (PNA), urinary tract infection (UTI)/pyelonephritis, meningitis, skin infection, intra-abdominal infection, and line infection.

Methods of Measurement

The primary exposures were initial and maximum ScvO₂ with the primary outcome as in-hospital mortality. The initial ScvO₂ was the ScvO₂ upon initial insertion of the ScvO₂ catheter; the maximum ScvO₂ was the highest ScvO₂ recorded during the first 6 hours of EGDT treatment. The ScvO₂ levels were stratified into the clinically meaningful groups of hypoxia (ScvO₂ 0 – 70%), normoxia (70-89%), and hyperoxia (90 – 100%). These thresholds were selected apriori.

Data Analysis

Descriptive statistics were used to describe population means and proportions along with 95% confidence intervals. To determine the univariate relationship between hypoxia and hyperoxia to normoxia, the mortality rates for the respective groups were compared to determine statistical significance using Fisher's exact test, with alpha set at 0.017 using a Bonferonni correction ($0.05/3 = 0.017$) to adjust for multiple comparisons. We also performed a univariate analysis of the covariates that we collected using fisher's exact test, followed by a stepwise logistic regression (both automated and by-hand) retaining significance covariates ($p < 0.05$), to control for confounders in evaluating the relationship between ScvO₂ and mortality.

Results

There were a total of 619 patients who met criteria and were included in the study. The mean age of patients was 61 (+/- SD 17) years old, 46% were females, and there was a high prevalence of co-morbidities such as DM (29%), HTN (24%), and cancer (20%) (Table 1). The most common sources of infection were PNA (36%) and UTI/pyelonephritis (25%). The mean

ScvO₂ was initially 73% (+/- SD 13) and the overall mortality for all patients was 25% (95% confidence interval 21-28%).

Next, we evaluated the association of the initial ScvO₂ with outcome. The normoxia group mortality rate was 81/351 (23%; 95% CI: 19 - 28%), while the hypoxia group mortality rate was 56/223 (25%; 20 - 31%), and the hyperoxia group mortality rate was (14/45) (31%; 21 - 48%). (Figure 1) When looking at potential confounders across the 3 initial ScvO₂ groups such as age, co-morbidities, and source of infection, characteristics were relatively similar. For maximum ScvO₂ groups, hypoxia patients were slightly older, had higher rates of cancer, and lower rates of skin and line infections. (Table 2) We built a multivariate model for initial ScvO₂, and after adjusting for significant covariates of age, active cancer status, and the presence of a urogenital or line infection (which were less lethal than other infection sources), the hyperoxia group had a significantly higher mortality (OR2.0: 95% CI: 1.0 - 4.0) than the normoxia group, while the hypoxia group (OR1.1: 0.7 - 1.6) was not significantly higher. (Table 3, model 1) When considering the maximum ScvO₂ achieved in the ED, the presence of both hypoxia and hyperoxia was associated with a higher mortality rate compared to the normoxia group (figure 1). The hypoxia mortality rate 25/62 (40%; 29 - 53%) and hyperoxia mortality rate 31/92 (34%; 25 - 44%) were significantly higher than the normoxia rate 96/465 (21%; 17 - 25%), in a univariate analysis, as well as after adjusting for significant confounders of age, active cancer, and the presence of a line infection (less lethal than other sources) where the hyperoxia group had a 2.2 (1.3 - 3.7) odds of death and the hypoxia group had a 2.0 (1.1 - 3.6) odds of death (Table 3, model 2). The hypoxia and hyperoxia mortality rates in both initial and maximum ScvO₂ evaluations were similar to each other.

Interestingly, among the people who were normoxic throughout the 6 hours of observation, the mortality rate was 68/312 (22%; 95% CI: 18%-27%), whereas, among those who initially had hypoxia and never improved, the mortality rate was 25/62 (40%; 29-53%), and in those who were initially hypoxic and reached normoxia within 6 hours, the mortality rate was 28/151 (19%; 13-25%). Similarly, those who started with normoxia and became hyperoxic within 6 hours had a mortality rate of 13/39 (33%; 21-49%) and those who were always hyperoxic had a mortality rate of 8/26 (31%; 16-50%). While these figures are interesting, they should be considered hypothesis generating, so we do not formally test hypotheses of differences between the groups as: 1) they were not part of our primary analysis plan, and 2) we are underpowered to make definitive statements.

Limitations

Limitations of our study include the possibility of selection bias because our patient population was not consecutive, and we did not record, assess or compare specific characteristic of enrolled patients to missed patients. We were also subject to ascertainment bias if we missed an abnormal ScvO₂ that was not recorded. In addition, institutional variation in patient population may have affected the data. We also did not take into account the effects of therapies such as antibiotics, fluids, vasoactive agents, and steroids on the mortality outcome. We collected the ScvO₂ during the ED visit; however, this may have varied between individuals and we did not record the exact times. These patients were treated with an EGDT protocol which involves intensive monitoring, and, therefore, the results of this study may not be generalizable to all patients with sepsis managed by other strategies. Additionally, we did not record or adjust for specific therapies, so our mortality rates are subject to possible treatment effects. Also, as stated above, it is also important to recognize that there are other important causes of hypoxia and hyperoxia beyond oxygen deficiency that may confound our findings. Finally, this was a large cohort study, but was not specifically powered to the various subgroups tested; it is possible that larger patient numbers, especially with different cutoffs that highlight the extremes, may have yielded differences that we missed based on our numbers (type II error).

Discussion

Although the initial EGDT study targeting an $\text{ScvO}_2 > 70\%$ suggested a mortality benefit for normalizing ScvO_2 in septic patients(3), few studies have assessed the association of ScvO_2 (or mixed venous oxygen saturation (SvO_2)) with mortality in sepsis. One study found that non-survivors in sepsis had more episodes of SvO_2 desaturation ($<65\%$) than survivors suggesting a mismatch of oxygen supply and demand.(12) Another study found SvO_2 to be an independent predictor of mortality, but only after 48 hours in the ICU. (13) In a large cohort of EGDT patients, we have found on multivariate modeling that patients with initial ScvO_2 values demonstrating hyperoxia were associated with a worse in-hospital mortality than normoxia. For maximum ScvO_2 , values achieved during the first 6 hours of EGDT resuscitation, patients with hypoxic or hyperoxic ScvO_2 values had increased mortality rates compared to patients with normoxic values. These findings not only support the benefit of normalizing ScvO_2 in the EGDT protocol, but also highlight the potential significance of venous hyperoxia or impaired oxygen utilization in sepsis. One explanation is that while low ScvO_2 values may be a marker for macrocirculatory failure, high ScvO_2 values may reflect microcirculatory or mitochondrial failure. This finding supports further investigation into therapeutic interventions for patients with abnormal ScvO_2 values (figure 2).

Hypoxia or low ScvO_2 may be thought of as macrocirculatory failure in sepsis where oxygen delivery, whose components are cardiac output or oxygen carrying capacity, are inadequate to meet the oxygen uptake at the level of the tissues. This imbalance may occur either on the supply side (e.g. reduced cardiac output or low oxygen carrying capacity (hemoglobin)) or the demand side (e.g. increased metabolic demands from sepsis), or both. The EGDT algorithm focuses on increasing systemic oxygen delivery or improving macrocirculation by manipulating preload with intravenous volume expansion, afterload with vasoactive agents, cardiac contractility with dobutamine, and oxygen carrying-capacity with packed red blood cells. But even when macrocirculatory failure is corrected, microcirculatory and mitochondrial failure may still result in tissue dysoxia.

Our data also suggest that patients with both initial and high maximum ScvO_2 (hyperoxia) have worse outcomes supporting the concept of cellular hypoxia *despite* adequate macrocirculatory augmentation due perhaps to microcirculatory and mitochondrial failure during sepsis. High ScvO_2 values may represent an inability to exchange oxygen due to impaired flow in the small vessels. The microcirculation consists of interplay between arterioles, capillaries, and venules that respond to local metabolic demands and perfusion pressure. Microcirculatory alterations in sepsis arises from impaired vascular autoregulatory mechanisms and functional shunting of oxygen leading to tissue dysoxia (14-16). In addition, experimental studies have demonstrated decreased tissue capillary density and increased heterogeneity of perfusion in sepsis that leads to functional shunting of oxygen (15,16). Thus, even with adequate macrocirculatory flow, microcirculatory failure may prevent needed and available oxygen from reaching cells in vital organs.

Finally, hyperoxia may also represent the inability of cells to utilize the oxygen due to derangement of cellular respiration, coined 'cytopathic hypoxia' by Fink in 1997 (6). When there is decreased delivery of oxygen to tissue from hypoperfusion, anemia, or hypoxemia, we expect the amount of oxygen extracted to increase in order to keep up with the aerobic demands. However, if cellular respiration is disrupted, the ability of the tissues to process oxygen is impaired resulting in a high ScvO_2 . Evidence to support mitochondrial dysfunction in sepsis has been demonstrated in experimental studies (17-19). It is also important to recognize that there are other potential causes of hyperoxia beyond an ability to extract oxygen that may confound our findings and include: changes in temperature, reductions in oxygen utilization due to neuromuscular blockade, chronic disease (e.g. liver disease, congestive heart failure,

chronic obstructive pulmonary disease), the use of vasopressors, and ischemic bowel, amongst other confounders.

While EGDT focuses on the correction of a low ScvO₂ signifying impairment in macrovascular oxygen delivery, the finding that high ScvO₂ was also associated with increased mortality reminds us that tissue dysoxia may occur despite adequate global oxygen delivery, and that these abnormalities (e.g. microcirculatory or mitochondrial dysfunction) may represent a therapeutic target for future research investigations. For example, a resuscitation protocol might assess microcirculatory flow using videomicroscopy and use novel therapies to recruit microcirculatory blood flow. Or, one could assay for mitochondrial activity and use a novel (currently undefined) therapy that would stimulate mitochondrial activity. Until then, we need to look for other markers of impaired microcirculatory or mitochondrial dysfunction as well as therapeutic approaches targeting these deficiencies.

Acknowledgments

Grant Support: This study was supported in part by National Institutes of Health grants: HL091757 and GM076659 (NIS), the National Institutes of Health/National Institute of General Medical Sciences: K23GM83211 (ST), National Institutes of Health/National Institute of General Medical Sciences: K23GM076652 (AJ), research endowment from the Beatrice Wind Gift Foundation (DG).

Disclosures: Dr. Trzeciak has received research support from Novo Nordisk, Biosite, and Eli Lilly. Dr. Jones has received research support from Critical Biologics and Hutchinson Technology. Dr. Shapiro receives research grants from Hutchinson technologies, Eli Lilly, Inverness Medical, and is on the Eli Lilly Speaker's bureau.

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Figure 1. Maximum ScvO2 groups – The Association of Hypoxia, Normoxia, and Hyperoxia with Mortality

The figure above shows the mortality rates by ScvO2 groups of hypoxia (<70%), normoxia (70-90%), and hyperoxia (> 90%). There was a significant difference in comparing the mortality rates for the hypoxia group (40%; 29 – 53%) versus the normoxia group (21%; 17 – 25%) and hyperoxia group (34%; 25 – 44%) versus normoxia (21%; 17 – 25%).

Oxygen Utilization

Figure 2. Schema for Classification of Oxygen Supply and Utilization

This figure shows one approach to a general classification of the components of oxygen supply and utilization. More specifically, it may be used to better understand the types of failure that can occur, leading to cellular hypoxia. Oxygen supply, represented by the macrocirculation, is the oxygen contained in the blood leaving the heart. It is calculated as cardiac output (CO) $\times$ oxygen carrying capacity of the hemoglobin (Hb) $\times$ arterial oxygen saturation (SaO₂) $\times$ 13.4 (a constant). The microcirculation consists of the small arterioles and capillaries where oxygen exchange generally occurs, while the mitochondria are where the oxygen is processed once it reaches the cells. 1) Macrocirculatory failure occurs when there is not enough oxygen supplied to meet the needs of the cells and is usually caused by hypotension, anemia, or hypoxemia, often in the setting of increased oxygen demand of the tissues/vital organs. 2) Microcirculatory failure occurs when there is global, or more often regionalized, shunting of blood, producing a disruption in the ability of oxygen to flow through the microcirculation to reach metabolically active tissues. Finally, 3) Mitochondria failure occurs when oxygenated blood is delivered to the tissues but the mitochondria can not process the oxygen. The ScvO₂ measurement occurs after all three types of failure have occurred.

Table 1

	Alive (n=467)	Dead (n=152)	Total (n=619)
Age mean, (SD)	60 (+/-18)	65 (+/-16)	61 (+/-17)
Female Gender (%)	211(45)	75(49)	286(46)
Patient History, n (%)			
HTN	114 (24)	37 (24)	151 (24)
CAD	83 (18)	33 (22)	116 (19)
DM	142 (30)	37 (24)	179 (29)
Cancer	75 (16)	49 (32)	125 (20)
HIV	31 (7)	12 (8)	43 (7)
COPD	59 (13)	25 (16)	84 (14)
Alcoholism	16 (3)	5 (3)	21 (3)
Source of Infection, n (%)			
PNA	163 (35)	60 (39)	223 (36)
UTI/pyelonephritis	125 (27)	31 (20)	156 (25)
Meningitis	7 (2)	4 (3)	11 (2)
Skin infection	54 (12)	10 (16)	64 (10)
Intra abdominal	68 (15)	25 (16)	93 (15)
Line	29 (6)	2 (1)	31 (5)
Initial Physiologic Variables, n (%)			
ScvO2 mean (SD)	73% ($\pm$ 13)	73% ($\pm$ 14)	73% ($\pm$ 13)
Normoxia, n (%)	270 (58)	81 (53)	351 (57)
Hypoxia, n (%)	167 (36)	56 (37)	223 (36)
Hyperoxia, n (%)	30 (6)	15 (10)	45 (7)
Maximum Physiologic Variables, n (%)			
ScvO2 (SD)	80% ($\pm$ 9)	79% ($\pm$ 12)	80% ($\pm$ 10)
Normoxia, n (%)	369 (79)	96 (63)	465 (75)
Hypoxia, n (%)	37 (8)	25 (17)	62 (10)
Hyperoxia, n (%)	61 (13)	31 (20)	92 (15)
Initial Lactate, mean (SD)	4.2 ($\pm$ 2.9)	6.1 ($\pm$ 3.9)	4.7 ($\pm$ 3.3)

HTN=hypertension, CAD=coronary artery disease, DM=diabetes, HIV=human immunodeficiency, COPD=chronic obstructive pulmonary disease, PNA=pneumonia, UTI=urinary tract infection, ScvO2=central venous oxygen saturation.

Table 2 Maximum ScvO₂

	Hypoxia (n=62)	Hyperoxia (n=92)	Normoxia (n=465)
Age Mean; (SD)	66 (18)	59 (18)	61 (17)
Female Gender (%)	23 (37)	46 (50)	217 (47)
Patient History, n (%)			
HTN	16 (26)	25 (27)	110 (24)
CAD	15 (24)	18 (20)	83 (18)
DM	15 (24)	31 (34)	133 (29)
Cancer	21 (34)	16 (17)	88 (19)
HIV	5 (8)	5 (5)	33 (7)
COPD	4 (6)	15 (16)	65 (14)
Alcoholism	0 (0)	3 (3)	18 (4)
Source of Infection, n (%)			
PNA	23 (37)	38 (41)	162 (35)
UTI/pyelonephritis	17 (24)	18 (20)	121 (26)
Meningitis	2 (3)	1 (1)	8 (2)
Skin infection	2 (3)	9 (10)	53 (11)
Intra abdominal	6 (10)	18 (20)	69 (15)
Line	0 (0)	7 (8)	24 (5)
Initial Physiologic Variables, n (%)			
ScvO ₂ mean (SD)	55 % (±12)	85 % (±13)	73% (±11)
Maximum Physiologic Variables, n (%)			
ScvO ₂ mean (SD)	60% (±11)	93% (±3)	80 % (±6)
Initial Lactate, mean (SD)	6.2 (±3.2)	5.2 (±4.7)	4.3 (±2.8)

HTN=hypertension, CAD=coronary artery disease, DM=diabetes, HIV=human immunodeficiency, COPD=chronic obstructive pulmonary disease, PNA=pneumonia, UTI=urinary tract infection, ScvO₂=central venous oxygen saturation.

Table 3 Multivariate Models for association of Initial and Maximum ScvO₂ with Mortality

Model 1: Association of Initial ScvO₂ with Mortality		
Covariate	Odds Ratio	5% Confidence Interval
Hyperoxia group (initial)	2.0	(1.0 – 4.0)
Hypoxia group (initial)	1.1	(0.7 – 1.6)
Active Cancer	2.5	(1.6 – 3.8)
Age (years)	1.2	(1.1 – 1.4)
Line infection	0.2	(0.04 – 0.8)
Urogenital source	0.6	(0.4 – 0.98)
Model 2: Association of Maximum ScvO₂ with Mortality		
Covariate	Odds Ratio	5% Confidence Interval
Hyperoxia group (maximum)	2.2	(1.3 – 3.7)
Hypoxia group (maximum)	2.0	(1.1 – 3.6)
Active Cancer	2.5	(1.6 – 3.8)
Age (years)	1.2	(1.1 – 1.3)
Line infection	0.2	(0.04 – 0.8)

For model 1 above, the hypoxia group (ScvO₂ <70%) and hyperoxia (≥90%) groups were compared to the normoxia (70-89%) group as a reference. Bolded characteristics above represent statistical significance. The c-statistic for the model was 0.67. For model 2, the same comparisons within the ScvO₂ groups were made and the c-statistic for the model was 0.69.

Table 4 Initial ScvO₂

	Hypoxia (n=223)	Hyperoxia (n=45)	Normoxia (n=351)
Age Mean; (SD)	63 (17)	57 (20)	60 (17)
Female Gender (%)	97 (44)	23 (51)	166 (47)
Patient History, n (%)			
HTN	51 (23)	13 (29)	87 (25)
CAD	47 (21)	6 (13)	63 (18)
DM	70 (31)	13 (29)	97 (27)
Cancer	50 (22)	7 (16)	68 (19)
HIV	17 (8)	5 (11)	21 (6)
COPD	21 (9)	7 (16)	56 (16)
Alcoholism	4 (2)	2 (4)	15 (4)
Source of Infection, n (%)			
PNA	76 (34)	16 (36)	131 (37)
UTI/pyelonephritis	57 (26)	12 (27)	87 (25)
Meningitis	4 (2)	0 (0)	7 (2)
Skin infection	23 (10)	7 (16)	34 (10)
Intra abdominal	33 (15)	6 (13)	54 (15)
Line	15 (7)	3 (7)	13 (4)
Initial Physiologic Variables, n (%)			
ScvO ₂ mean (SD)	58% (±9)	93% (±3)	79% (±6)
Maximum Physiologic Variables, n (%)			
ScvO ₂ mean (SD)	73% (±11)	93% (±3)	82% (±3)
Initial Lactate, mean (SD)	4.8 (±3.0)	5.5 (±5.4)	4.4 (±3.1)

HTN=hypertension, CAD=coronary artery disease, DM=diabetes, HIV=human immunodeficiency, COPD=chronic obstructive pulmonary disease, PNA=pneumonia, UTI=urinary tract infection, ScvO₂=central venous oxygen saturation.