Intradialytic Central Venous Oxygen Saturation is Associated with Clinical Outcomes in Hemodialysis Patients

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Central venous oxygen saturation (ScvO\(_2\)) in the superior vena cava is predominantly determined by cardiac output, arterial oxygen content, and oxygen consumption by the upper body. While abnormal ScvO\(_2\) levels are associated with morbidity and mortality in non-uremic populations, ScvO\(_2\) has received little attention in hemodialysis patients. From 1/2012 to 8/2015, 232 chronic hemodialysis patients with central venous catheters as vascular access had their ScvO\(_2\) monitored during a 6-month baseline period and followed for up to 36 months. Patients were stratified into upper and lower two tertiles by a ScvO\(_2\) of 61.1%. Survival analysis employed Kaplan-Meier curves and adjusted Cox proportional hazards models. Patients in the lower tertiles of ScvO\(_2\) were older, had longer hemodialysis vintage, lower systolic blood pressure, lower ultrafiltration rates, higher leukocyte counts and neutrophil-to-lymphocyte ratios. Kaplan-Meier analysis indicated a shorter survival time in the lower tertiles of ScvO\(_2\) (P = 0.005, log-rank test). In adjusted Cox analysis, a 1 percent point decrease in mean ScvO\(_2\) was associated with a 4% increase in mortality (HR 1.04 [95% CI 1.01–1.08], P = 0.044), indicating that low ScvO\(_2\) is associated with poor outcomes. Research on the relative contributions of cardiac output and other factors is warranted to further elucidate the pathophysiology underlying this novel finding.

The mortality rate of hemodialysis (HD) patients is elevated compared to the normal population\(^1\). The primary cause of mortality is cardiovascular disease (CVD), and there is evidence that the mechanism for CVD in HD patients differ from the traditional CVD risk factors in the general population\(^2,3\). High ultrafiltration rates (UFR), episodes of intradialytic hypotension, presence of congestive heart failure (CHF) and left ventricular hypertrophy (LVH) are some of the factors that have been associated with increased mortality\(^4,5\). Additionally nocturnal hypoxemia in HD patients has been demonstrated to be associated with worse cardiovascular outcomes\(^6,7\).

Mixed venous oxygen saturation (SmvO\(_2\)) and central venous oxygen saturation (ScvO2) have been used in critical care to guide fluid resuscitation\(^8\). SmvO\(_2\) is the oxygen saturation in the pulmonary artery, which receives blood from the superior vena cava, the inferior vena cava, and the coronary sinus, and therefore reflects – in the absence of arterial venous shunts – the aggregated effects of oxygen delivery to and utilization by the entire body. ScvO\(_2\) from upper body central venous catheters (CVC) is the oxygen saturation of blood in the superior vena cava, which reflects the aggregate of oxygen delivery to and utilization by the upper body. Although resting SmvO\(_2\) and ScvO\(_2\) differ due to the higher oxygen extraction in the upper body, the time trends of SmvO\(_2\) and ScvO\(_2\) are comparable under most circumstances\(^9-11\). While the measurement of SmvO\(_2\) requires pulmonary artery catheterization, ScvO\(_2\) can be more easily obtained from a CVC.

ScvO\(_2\) is determined by oxygen delivery to and oxygen consumption of the arms, head, and upper portion of the torso; the former depends on the arterial blood oxygen content and the cardiac output (CO). At rest with stable arterial oxygen saturation (SaO\(_2\)), hemoglobin, and tissue oxygen consumption, ScvO\(_2\) can serve as a surrogate of CO. Poor oxygen delivery can be caused by decreased CO, e.g. from CHF or reduced cardiac preload, or decreased arterial oxygen content, e.g. due to anemia or hypoxemic states. Oxygen consumption is determined by metabolic status and is altered in sepsis, fever, exercise and sedation\(^12\). ScvO\(_2\) in the general population is poorly

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defined, as obtaining this measurement requires a CVC, and patients who require CVC placement are generally significantly ill. One study in healthy subjects found a ScvO₂ of 76.8 ± 5.2% during cardiac catheterization13. Studies in non-uremic populations, have found that abnormal ScvO₂ levels are associated with worse morbidity and mortality8, 14–18. ScvO₂ levels in HD patients have not been well described. In patients who have ESRD with CVC as vascular access, ScvO₂ can be easily and continuously obtained during HD treatments by using the Crit-Line monitor™ (CLM). The CLM is used routinely in Renal Research Institute HD units, which allowed us to investigate the ScvO₂ in maintenance HD patients. The goals of our study were to evaluate the baseline characteristics of patients with different levels of intradialytic ScvO₂ and to examine the associations between ScvO₂ and mortality.

Results

Baseline patient characteristics. The final analytical cohort comprised of 232 patients with 6,042 HD treatments and was derived after a deliberate step-by-step data cleaning process at the treatment level. Patients were only excluded in the event that they did not contribute sufficient data during baseline, either because of end of study, death, treatment modality change, recovery of renal function, or transfer to another dialysis facility (Fig. 1).

The initial population comprised of 579 patients with CVC as dialysis access, with a total of 15,792 HD treatments with ScvO₂ measurements from January 1, 2012 until August 31, 2015. We excluded 3,650 treatments (23%) as they had a mean ScvO₂ of greater than 85% and 25 treatments (0.16%) as they had a mean ScvO₂ of less than or equal to 25%. We also excluded 4,185 treatments (26.5%) that occurred after the 6-month baseline period. This left us with 579 patients and 7,937 HD sessions, from which we excluded 347 patients with 1,895 HD treatments from the subsequent analysis because they had less than the required 10 HD treatments with ScvO₂ recordings and/or less than 6 months of follow up (Fig. 1). Out of the 155 patients excluded for not having 6 months of follow up time, 79 were due to death.

In our study population, the mean age was 62.7 ± 15.7 years, dialysis vintage was 2.9 ± 4.6 years, 56% were white, 48.3% were male, 59% had diabetes mellitus (DM), 22% had CHF, and 10.3% had chronic obstructive pulmonary disease (COPD) (Table 1). Median follow-up time was 431 days.

During baseline, ScvO₂ was recorded in 26 ± 13.3 HD treatments per patient. On a population level the ScvO₂ was normally distributed with a mean of 58.7 ± 7.3%. Analysis of intradialytic ScvO₂ dynamics across all patients indicated that on average ScvO₂ slightly increased over the first 60 minutes of treatment, and then progressively declined below starting levels towards the end of HD (Fig. 2).

ScvO₂ as a dichotomous outcomes. Comparison of baseline characteristics between upper and lower tertiles. Patients were stratified into upper tertile (N = 78) and lower two tertiles (N = 154); a mean ScvO₂ level below 61.1% during baseline period separated the two groups. A comparison of baseline characteristics between upper and lower tertiles is presented in Table 1. The patients in the lower tertiles were older (66.0 ± 13.8 years vs 56.2 ± 17.3 years, P < 0.001), had longer dialysis vintage (3.3 ± 5.1 years vs 2.0 ± 3.6 years, P = 0.031),
Table 1. Baseline characteristics of all patients, lower tertiles and upper tertile. 95% CI, 95% confidence interval; SD, standard deviation; ScvO2, central venous oxygen saturation; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; UFV, ultrafiltration volume; IDWG, interdialytic weight gain; Hgb, hemoglobin; PTH, parathyroid hormone; NLR, neutrophil-to-lymphocyte ratio; n.a., not applicable. *t test. **Chi-square test. †Wilcoxon test.
Mortality between upper and lower tertiles. During the 36-month follow-up period, there were a total of 54 deaths, 45 in the lower two tertiles and 9 in the upper tertile. Mortality rate was 24.1/100 patient years in lower two tertiles and 9.0/100 patient years in upper tertile ($P = 0.005$). Univariate Kaplan-Meier analysis indicated a significantly shorter survival among lower tertile patients ($P = 0.0051$, log-rank test) (Fig. 3).

ScvO$_2$ as a continuous variable. In unadjusted Cox analysis, for every 1 percent point decrease in mean ScvO$_2$ there was an associated 6% increase in mortality (HR 1.06 (1.03–1.10)). There was no material change in the results after adjustment for age, gender, comorbidities (COPD and CHF), log vintage, inflammatory markers (albumin, NLR), hemoglobin and erythropoietin dose (HR 1.04 (1.01–1.08)) (Table 2).

Correlates of ScvO$_2$. Figure 4 depicts the relationship between ScvO$_2$ and patient characteristics that were found to differ between the two groups. Mean ScvO$_2$ across patients was plotted against age, log vintage, body mass index (BMI), interdialytic weight gain (IDWG) relative to post-HD weight, post-HD SBP, and NLR. As vintage was not normally distributed, it was log transformed. Age, BMI, log vintage and NLR were negatively associated with ScvO$_2$, while post-HD SBP and IDWG were positively correlated with ScvO$_2$. While all correlates were statistically significant except for ScvO$_2$ and log vintage ($P = 0.19$), correlation coefficients were relatively low.
Discussion

Our study indicates that in chronic HD patients with CVC as vascular access, lower ScvO₂ levels are associated with poorer survival.

Despite the relative ease with which ScvO₂ can be obtained in HD patients with CVC as access, to date only small studies have examined this key indicator of cardiac function. Cordtz et al.¹⁹ in 2008 evaluated 20 HD patients and classified them as either hypotension prone or hypotension resistant and measured their ScvO₂ at treatment initiation and end. The authors found a significant decrease in ScvO₂ in hypotension prone patients. Harrison et al.²⁰ investigated 18 HD patients and found a strong inverse correlation between ScvO₂ at the end of

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| Outcome                | Events | Crude¹ | Crude P | Minimally Adjusted² | Minimally Adjusted P | Fully Adjusted³ | Fully Adjusted P |
|------------------------|--------|--------|---------|----------------------|----------------------|-----------------|------------------|
| All-cause mortality    | 54     | 1.06   | <0.001  | 1.05                 | 0.003                | 1.04            | 0.0437           |

Table 2. Crude and adjusted hazard ratios for all-cause mortality for a 1% decrease in central venous oxygen saturation. HR, hazard ratio. ¹Unadjusted model. ²Adjusted for age, gender, chronic obstructive pulmonary disease and congestive heart failure. ³Adjusted for age, gender, chronic obstructive pulmonary disease, congestive heart failure, albumin, hemoglobin, erythropoietin dose, neutrophil to lymphocyte ratio, and log vintage.

Figure 4. Correlates of central venous oxygen saturation with respect to patient characteristics. Each point represents one patient; the depicted data points represent the respective parameter averages during the 6-month baseline period. (A) Age; (B) Log vintage; (C) Body mass index; (D) Interdialytic weight gain relative to post-dialysis body weight; (E) Post-dialysis systolic blood pressure; (F) Neutrophil-to-lymphocyte ratio.
dialysis and ultrafiltration volume normalized to post-HD body weight. A recent review of intradialytic oxygen saturation did not identify any previous research examining the association between ScvO₂ and patient survival 13.

In the study by Harrison et al., the mean ScvO₂ was 63.5 ± 13% pre-HD and 56.4 ± 8% post-HD 20, whereas in the study by Cordtz et al., the initial ScvO₂ was 52.2 ± 6.7% in hypotension prone and 49.7 ± 6.9% in hypotension resistant patients 19. While these studies focused on ScvO₂ at HD start and end, we examined ScvO₂ continuously throughout the HD session. The ScvO₂ levels found in our study are below the levels of ~70% observed in healthy subjects 13, but consistent with those reported in HD patients. The exact etiology of low intradialytic ScvO₂ in HD patients is not well established, but may be partially explained by the lower hemoglobin levels, and the higher prevalence of cardiac dysfunction and pulmonary hypertension in HD patients.

In our cohort, when ScvO₂ was assessed throughout the entire HD treatment, on average ScvO₂ increased slightly over the first hour and then progressively declined during the remaining treatment time. The determinants of ScvO₂ can be visualized by rearrangement of the familiar form of Fick's law and replacement of SmvO₂ with CO. Therefore we refrained from defining comparison groups based on ScvO₂ tertiles obtained from our large HD population, but rather used ScvO₂ tertiles obtained from our large HD population, as a continuous variable remained a significant predictor of mortality.

Our finding that patients with lower ScvO₂ were older may reflect the poorer cardiac function expected in older subjects. Of note, the prevalence of CHF increases with age, as does CHF mortality 22. While the correlation coefficients were low, we identified several significant correlations between ScvO₂ and patient variables such as the association between lower ScvO₂ levels and longer dialysis vintage. We speculate that this finding may be related to recurrent hemodynamic stress and cardiac injury caused by HD. McIntyre et al., demonstrated that HD induced RWMA in a subset of maintenance HD patients. While at baseline there was no difference in left ventricular ejection fraction (LVEF) between patients who developed RWMA and those that did not, at 1 year follow-up, the group of patients that developed RWMA during HD had significantly lower resting LVEF 23.

In our study, lower tertile patients had lower pre-HD and lower post-HD SBP, a finding possibly related to low CO. Of note, an association between low pre-HD SBP and mortality has been repeatedly shown 23, 24. It is interesting to note that in our study the prevalence of CHF did not differ between lower and upper tertiles. Unfortunately, no routine echocardiography assessments were available in our patients, so we cannot comment on the possibility of deficient documentation, classification or misdiagnosis of CHF. One intriguing possibility is that we may be identifying a group of patients without clinically overt signs and symptoms of CHF at rest, who however have reduced cardiac reserve or autonomic dysfunction and are unable to mount the necessary increase in sympathetic response and CO when faced with the hemodynamic stress of HD 25, 26.
The main limitation of our study is its observational nature, which prevents any conclusions related to causality. As mentioned earlier, routine echocardiograms are unfortunately not available in our study population, making potentially very insightful correlational analyses of ScvO₂ and cardiac structure and function impossible. Lastly, we appreciate that ScvO₂ measurements may be altered by changes in catheter tip position due to changes in body position; however, we have no indication that this may affect one of the two groups disproportionally and created any bias.

Considering a recent review of this topic, we believe that this is the largest study to date examining the epidemiology of ScvO₂ in maintenance HD patients. CVC are used as vascular access in the majority of U.S. patients starting HD. While this situation is certainly not desirable, the presence of a CVC allows us to measure ScvO₂, a vitally important physiological parameter. This additional diagnostic opportunity may be particularly important in the incident period, the time with the highest cardiovascular mortality rate. In fact, a recent study published by Mancini et al. demonstrates that variability in SaO₂ is associated with intradialytic hypotension. This supports the potential role of oxygen saturation monitoring during dialysis.

In conclusion, our research shows that routine measurement of ScvO₂ during HD provides a novel window into patients’ biology that may help to improve our care for this vulnerable patient population.

**Method**

**Population and study design.** This is a retrospective multi-center study of a cohort of maintenance HD patients from 17 facilities of the Renal Research Institute (RRI) across the United States between January 2012 and August 2015. In these clinics, CLM use is part of standard care. All patients were treated with bicarbonate dialysate and polysulfone membranes. Over 80% of patients had a prescribed dialysate temperature of 37°C. All patients who received HD via a CVC and had at least 6 months of clinical data and 10 dialysis treatments with eligible ScvO₂ recordings (definition of eligibility see below) were eligible for inclusion into the study. Therefore our study included both incident and prevalent HD patients. The CLM was rolled out into dialysis units in a staggered manner, and we used the first treatment with CLM data as start date of the patients’ 6 month baseline period. Since eligible patients had to contribute 6 months’ worth of data, by design only those patients who survived for at least 6 months were included into the study (Fig. 1). Patient characteristics were assessed over the baseline period, and mortality was assessed during a follow-up period for a maximum duration of three years. Figure 5 summarizes the study design. For group comparison patients were stratified based on the population ScvO₂ that separated the top tertile from the bottom two tertiles. Descriptive statistics of the ScvO₂ distribution showed a ScvO₂ of 61.1% to be the cut-off between these two groups. Patients were censored in the event of kidney transplantation, transfer to a non-RRI facility, dialysis treatment modality change, recovery of kidney function, or end of follow-up.

The study was approved by the New England Institutional Review Board (14–446) and conducted in accordance with the Declaration of Helsinki. Informed consent was not obtained as this was determined not to be human subject research, and we were working with de-identified data.

This study has been registered at clinicaltrials.gov (NCT02501044).

**Measurement of ScvO₂.** Intradialytic ScvO₂ measurements were obtained by the CLM. The CLM has been approved by the U.S. Food and Drug Administration (FDA) for the measurement of hematocrit, relative blood volume, and oxygen saturation in the extracorporeal dialysis circuit. The CLM measures oxygen saturation 9,000 times per minute and reports the mean of these measurements every minute. The manufacturer reported accuracy for oxygen saturation measurement is 2%. Patients’ mean, median, minimum, maximum, standard deviation, start-HD, end-HD ScvO₂ was calculated per treatment and then averaged across all treatments per patient and subsequently across patients. We chose to do our analysis using the mean ScvO₂ as there was low variability across treatments for each patient (mean coefficient of variability of 7.5 ± 4%).

**Clinical and laboratory data.** Laboratory measurements were done at Spectra East Laboratories (Rockleigh, NJ, USA). The results were downloaded to the RRI data warehouse and extracted to the study database. Continuous variables were averaged during the baseline period. BMI was calculated using post-HD dry weight.
Data eligibility. To ensure appropriate data quality, we included only treatments where mean ScvO₂ was below 85%, as higher values are incompatible with central venous blood. Mean ScvO₂ measurements less than 25% were excluded because they are considered incompatible with life. Additionally, data points with relative blood volume measurements above 102% were considered very unlikely, potentially due to saline administration, and hence excluded. This constituted 3% of all data points.

Comorbidities. CHF, DM, and COPD were defined using International Classification of Diseases - 9 (ICD-9) codes.

Statistical analysis. Continuous variables are presented as mean ± standard deviation (SD) if normally distributed and as median (25th, 75th percentile) otherwise. Categorical variables are presented as percentages of the respective group. Statistics of ScvO₂ variables were calculated on a HD treatment level and then aggregated on a patient level.

Baseline characteristics of exposed and unexposed were compared using chi-square test for categorical variables and two-sample t test for continuous variables, Wilcoxon Rank-Sum test were used for non-parametric variables. Survival characteristics were compared using Kaplan-Meier plots, log-rank test, and Cox proportional hazards models.

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and R 3.0.2 (libraries ggplot2, splines, survival, pspline; R Foundation for Statistical Computing, Vienna, Austria).

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Data Availability. Consolidated data may be shared with other scientists at their request.

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Author Contributions
P.K., S.T., and H.Z. designed the study. L.C., A.M.W., I.C., and D.F. were instrumental in the interpretation of the results. L.C. wrote the main manuscript text. H.Z. acquired data and performed all the statistical analysis. All authors contributed to the manuscript and approved the final version.

Additional Information
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