Association of Central Venous Oxygen Saturation Variability and Mortality in Hemodialysis Patients

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Keywords

Central venous oxygen saturation variability · Estimated upper body blood flow, cardiac output · All-cause mortality · Hemodialysis

Abstract

Background: Central venous oxygen saturation (ScvO₂) is correlated with cardiac output. In most patients, ScvO₂ declines during hemodialysis (HD) due to factors such as reduced preload, myocardial stunning, and intermittent arrhythmias. Previous research has shown that low ScvO₂ is associated with higher mortality in chronic HD patients. In this research, we tested the hypothesis that ScvO₂ variability is associated with all-cause mortality. **Methods:** We conducted a retrospective study in 232 chronic HD patients with central venous catheter as vascular access. ScvO₂ was recorded 1× per minute during dialysis using the Crit-Line monitor. A 6-month baseline comprising at least 10 dialysis treatments

with ScvO₂ recordings preceded a follow-up period of up to 3 years. The coefficient of variation (CV) of ScvO₂ (100 times the ratio of the standard deviation and mean of ScvO₂) served as a measure of ScvO₂ stability during baseline. Patients were stratified by median population CV of ScvO₂ during baseline, and survival during follow-up was compared between the 2 groups by Kaplan Meier and multivariate Cox analysis. The association between CV of ScvO₂ and all-cause mortality during follow-up was further assessed by Cox analysis with a spline term for CV of ScvO₂. **Results:** The mean CV ± standard deviation of ScvO₂ in our population was 6.1 ± 2.7% and the median was 5.3%. Univariate Kaplan-Meier analysis ($p = 0.043$) and multivariate Cox analysis (hazard ratio [HR] 1.16; $p = 0.0005$) indicated that a CV of ScvO₂ > 5.3% was significantly associated with increased mortality. In Cox analysis with spline term, a CV of ScvO₂ > 11% was associated with a significantly increased HR for all-cause mortality. **Conclusion:** High ScvO₂ variability during dialysis is associated with increased all-cause mortality.

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Introduction

Intradialytic morbid events are common and associated with poor outcomes [1, 2]. Ultrafiltration leads to a decline in circulating blood volume, which may result in intradialytic hypotension (IDH) and changes in tissue perfusion, potentially having a long-term structural and functional impact on vital organs, such as the brain and the heart [3]. Besides a decline in blood volume, IDH can also be caused by other pathologies such as myocardial stunning, diastolic or systolic dysfunction, valvular disease, arrhythmias, and autonomic dysfunction [4–15]. A decreased cardiac output (CO) is the terminal pathway in most of these entities. While it would be highly desirable to detect hemodynamic deterioration in a timely manner, there are no tools currently available to routinely assess CO during dialysis [16].

In critical care medicine, central venous oxygen saturation (ScvO₂) and mixed venous oxygen saturation (SmvO₂) are used as proxies of CO and tissue perfusion and are integrated in fluid resuscitation algorithms [17]. SmvO₂ 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 shunts – the aggregated effects of oxygen delivery and consumption of the entire body. ScvO₂ is the oxygen saturation in the superior vena cava, which reflects the aggregate of oxygen delivery and consumption of the upper body [18]. Previous studies have demonstrated that ScvO₂ trends with SmvO₂ in a range of settings. Oxygen delivery depends on the arterial blood oxygen content (the product of arterial oxygen saturation [SaO₂] and hemoglobin concentration [Hgb]) and the upper body blood flow (UBBF), respectively [19]. At rest, upper body oxygen uptake is stable and primarily determined by the brain. Several devices can measure ScvO₂ in a quasi-continuous fashion in patients who are dialyzed with a central venous catheter (CVC) as their vascular access. Previous research has shown that low ScvO₂ is associated with high ultrafiltration volume [20] and higher mortality [21] in chronic hemodialysis (HD) patients. In this study, we tested the hypothesis that intradialytic variability of ScvO₂, as a surrogate of UBBF and CO, is associated with all-cause mortality.

Methods

Population and Study Design

This is a retrospective multi-center database study conducted between January 2012 and August 2015 in a cohort of maintenance HD patients from 17 facilities of the Renal Research Institute (RRI)

in the United States. In these clinics, the use of the Crit-Line Monitor (CLM; Fresenius Medical Care, Waltham, MA, USA; see details below) is part of standard clinical care. All patients, either incident or prevalent, who received HD via a CVC and had at least 10 dialysis treatments with technically satisfactory ScvO₂ recordings during a 6-month baseline period were included in the study.

The need for informed consent was waived by the New England Institutional Review Board (14–446). The study was conducted in accordance with the Declaration of Helsinki.

Measurement of ScvO₂

Intradialytic ScvO₂ was measured using the CLM. The CLM has been approved by the U.S. Food and Drug Administration 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 1× per minute. The manufacturer-reported accuracy for oxygen saturation measurement is 2%. The CLM measurements were stored on a server located in the dialysis facility and later transferred to the RRI research data base. Average, minimum, maximum, median, standard deviation (SD) and coefficient of variation (CV) of ScvO₂ were calculated per treatment, averaged across all treatments per patient and subsequently across all patients.

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 RRI research data base.

Data Eligibility

To ensure appropriate data quality, we decided to include only treatments where mean ScvO₂ was below 85%, as higher values are outside the biologically plausible ScvO₂ range. Likewise, ScvO₂ measurements with an average below 25% were excluded as they are deemed incompatible with life. Additionally, data points with relative blood volume measurements above 102% were considered very unlikely and hence excluded. In total, 3% of all CLM data points were omitted.

Comorbidities

Congestive heart failure (CHF), diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) were defined using the International Classification of Diseases-9 codes.

Statistical Analysis

Descriptive statistics comprised means and standard deviation ($\pm$ SD) for continuous variables and percentages for categorical variables. ScvO₂ CV was calculated as 100 times the ratio of the SD and mean of ScvO₂.

All-cause mortality was recorded during follow-up. To explore the association between all-cause mortality and CV of ScvO₂, we built Cox proportional hazards models with spline terms that modeled the relationship between all-cause mortality and CV of ScvO₂. This spline analysis allowed us to identify CV of ScvO₂ levels that were associated with hazard ratios (HR) significantly different from 1.

For additional analyses we stratified patients into 2 groups based on their CV of ScvO₂ being above or below the population's median CV of ScvO₂. Survival characteristics were compared between those 2 groups using Kaplan-Meier plots and Cox propor-

tional hazards models. Minimally and fully adjusted Cox models complemented the crude survival analysis. Adjustment factors were selected based on their documented or hypothesized association with ScvO₂ and outcome. In the minimally adjusted model, we included age, sex, and the presence of CHF or COPD. In addition to these, the fully adjusted model included serum albumin and hemoglobin levels, the neutrophil-to-lymphocyte ratio as an indicator of inflammation [22], ultrafiltration rate (UFR), pre-dialysis systolic blood pressure (SBP), and race. 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 in August 2015.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R 3.0.2 (libraries ggplot2, splines, survival, pspline; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Patient Characteristics

Our study population comprised 232 patients with a mean age of 62.7 ± 15.7 years and a dialysis vintage of 2.9 ± 4.6 years. Fifty-six percent of the patients were white, 48.3% were male, 59.1% had DM, 22% had CHF, and 10.3% had COPD (Table 1). We recorded ScvO₂ in 26 ± 13.3 HD treatments per patient during the 6-month baseline period. Mean ScvO₂ was $58.7 \pm 7.3\%$, and the mean ScvO₂ CV was $6.1 \pm 2.7\%$ with a median of 5.3%. Mean ScvO₂ and mean ScvO₂ CV were inversely correlated ($r = -0.53$, $p < 0.001$; Fig. 1).

Baseline Characteristics in Groups Stratified by Median CV ScvO₂

Patients were stratified into 2 groups based on the median population baseline ScvO₂ CV of 5.3% (Table 1). We decided to use the median because a threshold for pathologic ScvO₂ CV is not known yet. Patients with a high ScvO₂ CV had lower pre-dialysis SBP (143.1 ± 22.9 vs. 149.8 ± 20.6 mm Hg, $p = 0.019$) and post-dialysis SBP (135.7 ± 19.1 vs. 144.9 ± 20.1 mm Hg, $p = 0.0004$). There was no statistically significant difference in comorbidities (DM, CHF, and COPD), interdialytic weight gain, UFR and ultrafiltration volume. Laboratory data, erythropoietin, and iron therapy did not differ between the 2 groups.

Survival Analysis

Median follow up was 431 days. During follow-up, 54 patients (23.3%) died, 18 in the group with low ScvO₂ CV and 36 in the group with high ScvO₂ CV. Cox analysis with spline terms indicated significantly higher risk of death in patients with an ScvO₂ CV >11% (Fig. 2).

Univariate Kaplan-Meier analysis indicated a significantly lower survival probability in patients with higher ScvO₂ CV ($p = 0.043$; log-rank test; Fig. 3). Multivariate Cox analysis with the minimally adjusted model revealed a lower survival in older patients, whereas in the fully adjusted model, older age (years; HR 1.037, $p = 0.0005$), higher ScvO₂ CV (HR 1.16, $p = 0.0005$), higher neutrophil to lymphocyte ratio (HR 1.13, $p = 0.008$), and dialysis vintage (years; HR 1.16, $p = 0.02$) were significantly associated with poorer survival.

Discussion

Our study indicates that in chronic HD patients with CVC as vascular access, a high intradialytic ScvO₂ CV is associated with increased all-cause mortality.

The relative ease with which ScvO₂ can be measured in patients with a CVC in place has made it a preferred hemodynamic monitoring variable in critical care and anesthesiology. In a variety of clinical situations ScvO₂ parallels SmvO₂ and is thus regarded as an indirect indicator of CO [19]. Given this physiological significance, ScvO₂ has been proposed as a marker of intradialytic hemodynamic stress in HD patients [20, 23]. ScvO₂ has been shown to be lower in patients prone to IDH [16]. Recent research has revealed an association between low average ScvO₂ and all-cause mortality in chronic HD patients [21]. Our research adds to the body of evidence by demonstrating an association between intradialytic ScvO₂ variability and all-cause mortality.

To understand potential causes of ScvO₂ variability, it is important to appreciate that ScvO₂ is defined by a complex interplay of numerous factors, which can be summarized in equation (1):

$$\text{ScvO}_2 = \text{SaO}_2 - \frac{100 \times \text{oxygen consumption}}{K \times \text{Hgb} \times \text{UBBF}} \quad (1)$$

with ScvO₂ and SaO₂ in %, upper body oxygen consumption in mL/min, Hgb in g/L, UBBF in L/min, and the constant K being 1.34, the amount of oxygen (in mL) bound per g of hemoglobin.

To review the potential mediators of ScvO₂ variability, we must review the contributions of ScvO₂ [1]. First, any variability in SaO₂ would translate into ScvO₂ variability. Indeed, SaO₂ is not constant throughout HD. On a population level, a bi-phasic SaO₂ dynamic has been observed during dialysis where an SaO₂ decline in the first 40–60 min is followed by an increase to levels above the ones

Table 1. Baseline characteristics in all patients and in groups stratified by median baseline CV ScvO₂

Variables	All patients	CV of ScvO ₂ >5.3%	CV of ScvO ₂ ≤5.3%	Difference mean (95% CI)
Patients, <i>n</i>	232	116	116	
Eligible HD treatments during baseline (number per patient), mean ± SD	26.0±13.3	25.1±12.7	26.9±13.9	-1.8 (-5.2 to 1.6)
Demographics				
Age, years, mean ± SD	62.7±15.7	64.3±13.7	61.1±17.5	3.2 (-0.9 to 7.2)
Race (white), %	56	55.1	56.9	-1.8 (-14.6 to 11.2)
Gender, male, %	48.3	49.1	47.4	1.7 (-11.2 to 14.6)
Vintage, years, mean ± SD	2.9±4.6	3.4±5.3	2.3±3.8	1.1 (-0.1 to 2.3)
BMI, kg/m ² , mean ± SD	28.1±6.9	28.5±7.4	27.7±6.3	0.8 (-1.0 to 2.6)
ScvO ₂ , mean ± SD				
Mean ScvO ₂	58.7±7.3	55±6.8	62.4±5.8	-7.5 (-9.1 to -5.8)
Median ScvO ₂	59.1±7.3	55.4±6.8	62.7±5.9	-7.3 (-8.9 to -5.6)
Minimum ScvO ₂	48.4±9.7	42.5±9.4	54.4±5.6	-11.9 (-13.9 to -9.9)
Maximum ScvO ₂	65.2±6.2	62.8±6.1	67.7±5.3	-4.9 (-6.4 to -3.4)
SD ScvO ₂	3.4±1.1	4.2±1	2.6±0.5	1.6 (1.36 to 1.76)
CV ScvO ₂	6.1±2.7	8±2.7	4.3±0.8	3.7 (3.2 to 4.3)
Comorbidities, %				
Diabetes	59.1	60.3	57.8	2.5 (-10.3 to 15.6)
CHF	22	21.6	22.4	-0.8 (-11.2 to 9.4)
COPD	10.3	10.4	10.3	0.1 (-7.7 to 7.7)
Treatment data, mean ± SD				
Pre-dialysis SBP, mm,Hg	146.4±22.0	143.1±22.9	149.8±20.6	-6.7 (-12.4 to -1.1)
Post-dialysis SBP, mm,Hg	140.3±20.1	135.7±19.1	144.9±20.1	-9.2 (-14.3 to -4.1)
IDWG, kg	2.0±0.8	2.1±0.7	1.9±0.8	0.1 (-0.1 to 0.4)
IDWG relative to post-dialysis weight, %	2.6±0.9	2.7±0.9	2.5±1	0.2 (-0.1 to 0.4)
UFR, mL/kg/h	7.1±2.6	7.4±2.4	6.9±2.8	0.5 (-0.2 to 1.1)
UFV, L	1.9±0.8	2±0.8	1.8±0.8	0.1 (-0.1 to 0.3)
Post-dialysis weight, kg	77.4±20.4	78.3±21.7	76.6±19.1	1.7 (-3.6 to 7.0)
Treatment time, min	219.0±23	218.3±23.2	219.7±22.8	-1.4 (-7.4 to 4.6)
Equilibrated Kt/V	1.5±0.3	1.5±0.3	1.5±0.3	0
Laboratory data, mean ± SD				
Serum albumin, g/dL	3.8±0.4	3.8±0.4	3.8±0.5	-0.01 (-0.1 to 0.1)
Hgb, g/dL	10.6±0.9	10.7±0.9	10.5±1	0.18 (-0.06 to 0.42)
Serum sodium, mmol/L	138.6±3.1	138.7±3	138.6±3.2	0.03 (-0.8 to 0.8)
Serum potassium, mmol/L	4.7±0.6	4.7±0.6	4.7±0.5	0.02 (-0.12 to 0.16)
Intact PTH, pg/mL	518.3±481.1	543.5±553.5	492.6±394.9	50.9 (-73.9 to 175.8)
Serum bicarbonate, mmol/L	23.4±2.2	23.4±2.1	23.4±2.4	0.03 (-0.56 to 0.61)
WBC, 1,000/μL	7.0±2.0	7.2±2.1	6.9±2	0.32 (-0.2 to 0.84)
Platelets, 1,000/μL	212.9±63.9	221.2±61.8	205.3±65.2	15.8 (-1.45 to 33.2)
NLR	4.4±2.6	4.7±2.8	4.1±2.3	0.6 (-0.06 to 1.3)
Ferritin, ng/mL	780.5±510.2	822±442.3	737.6±570.9	84.3 (-48.7 to 217.3)
Transferrin saturation	30.7±9.5	29.8±8.4	31.7±10.4	-1.85 (-4.3 to 0.6)
Erythropoietin, units/treatment ¹	2,357 (1,355–4,591)	2,244 (1,282–4,143)	2,686 (1,440–5,145)	-422 (-1,520 to 375)
Iron dose, mg/treatment ¹	23.1 (13.3–35.4)	21.9 (12–33.4)	27.4 (14.9–35.8)	-5.5 (-11.5 to 3.2)

¹ Median (25th, 75th percentile).CV, coefficient of variation; ScvO₂, Central venous oxygen saturation; HD, hemodialysis; BMI, body mass index; SBP, systolic blood pressure; CHF, Congestive heart failure; COPD, chronic obstructive pulmonary disease; IDWG, interdialytic weight gain; UFR, ultrafiltration rate; UFV, ultrafiltration volume.

Fig. 1. Scatter plot of average ScvO₂ versus ScvO₂ variability (expressed here as SD of ScvO₂).

Fig. 2. Spline analysis of hazard ratio (HR) for all-cause mortality as a function of central venous oxygen saturation (ScvO₂) variability. The solid line represents mean HR; the dotted lines represent 95% confidence limits.

Fig. 3. Kaplan-Meier analysis of survival rates comparing patients with the coefficient of variation (CV) central venous oxygen saturation (ScvO₂) above and below the population median of 5.3%, respectively.

observed at the start of dialysis [18]. Several explanations have been put forward to elucidate this dynamic. One postulates that the initial SaO₂ decline can be attributed to membrane-blood bioincompatibility that results in leucocyte activation and migration into the pulmonary capillary bed causing impaired oxygen uptake [24]. Another potential explanation points toward a reduced re-

spiratory drive in the face of bicarbonate diffusion from the dialysate into the patient and carbon dioxide loss into the dialysate [25]. While plausible, we are not aware of studies that corroborate these hypothesized mechanisms. Fluid removal later into dialysis may improve oxygen diffusion in the lungs and thus improve blood oxygenation, a hypothesis that is supported by circumstantial clinical

Fig. 4. Simulation of the relationship between upper body blood flow (UBBF) and central venous oxygen saturation (ScvO₂). The curve was computed based on equation (1) and assuming a SaO₂ of 92%, a hemoglobin level of 10 g/dL, and an upper body oxygen consumption of 65 mL/min. The lower the UBBF the larger are the effects of UBBF changes on ScvO₂ levels.

Fig. 5. Dynamics of intradialytic estimated upper body blood flow (eUBBF) in a maintenance hemodialysis (HD) patient. The x-axis and y-axis show the 1× per minute measured hemoglobin concentration and ScvO₂, respectively. The family of eUBBF curves is calculated based on equation (1) and assuming a SaO₂ of 92% and an upper body oxygen consumption of 65 mL/min.

evidence [18]. Low intradialytic SaO₂ has been linked to peridialytic hypertension [26], a factor implicated in excess mortality [27, 28]. Recently, prolonged intradialytic hypoxemia (defined as SaO₂ <90% for more than 1/3 of the treatment time) has been associated with an inflammatory phenotype, hospitalization, and all-cause mortality [29]. Against this background, it is conceivable that low SaO₂ may play a causal role in the development of low and unstable ScvO₂.

Second, variations in upper body oxygen consumption during dialysis could result in ScvO₂ variability. Given its high metabolic rate and organ mass, the brain is in absolute and relative terms the main consumer of oxygen in the upper body with an oxygen consumption rate of 2–3 mL/min/100 g tissue in healthy subjects [3] compared to ~0.1 mL/min/100 g by the resting muscle [30–32]. While brain oxygen consumption in patients with chronic kidney disease is reduced by ~15% compared to healthy controls [33] and HD induces an acute decline in cerebral blood flow (CBF) in elderly patients [34], there is no evidence that the brain oxygen consumption rate changes during dialysis [35]. The overall evidence shows that an alteration in CO, either acutely or chronically, leads to a concordant change in CBF that is independent of other

CBF-regulating parameters including blood pressure and carbon dioxide [32]. Any reduction in CBF under conditions of constant cerebral oxygen consumption would lead to increased oxygen extraction and result in lower oxygen saturation in the cerebral veins.

Third, during most HD sessions, the Hgb increases because of the ensuing hemoconcentration. Everything else being equal, a rise in hemoglobin levels would result in a concordant increase in ScvO₂. However, this effect of hemoconcentration could be blunted by a decline in CO and UBBF [36]. It follows from equation (1) that – if every other variable remains constant – even slight changes of UBBF translate into pronounced changes in ScvO₂. Modeling of equation (1) shows that the lower the UBBF the larger the effects of UBBF changes on ScvO₂ levels (Fig. 4).

A notable body of literature supports the notion that CO decreases during dialysis. Several mechanisms have been implicated, such as reduction in preload, myocardial stunning, valvular disease, arrhythmia, and autonomic neuropathy [3, 5, 16, 18]. Recent observations have shown that the rate of ScvO₂ decline during dialysis is significantly correlated with the ultrafiltration volume corrected for body weight [20]. The authors hypothesized that this finding is related to a reduced preload and/or

myocardial stunning in the face of ongoing ultrafiltration. Diastolic dysfunction may play a key role in that context. Echocardiography studies in 109 HD patients have shown that left ventricular diastolic function worsens as early as 60 min into the treatment [37]. In addition, valve disease is common in dialysis patients. Cardiac valve calcification was found in 25.5% of patients in a prospective cohort of maintenance HD patients, and the aortic and mitral valves were mainly affected [6]. In a prospective study using echocardiography, stroke volume changes at the end of dialysis were higher in patients with aortic or mitral regurgitation compared with those without valve abnormalities [10]. It is conceivable that changes in stroke volume during dialysis in patients with valve regurgitation could intermittently impact CO and consequently ScvO₂. Permanent and intermittent arrhythmias are frequent in dialysis patients. In a prospective cohort study comprising 1,516 incident HD patients, around 6.5% had atrial fibrillation (AF) at dialysis initiation [14]. Results from a meta-analysis showed an AF prevalence at dialysis initiation of 11.6% and an overall incidence of 2.7/100 patient-years [15]. P-wave dispersion increases significantly during dialysis and may increase the risk of intermittent intradialytic AF episodes. An increased risk of P-wave abnormalities is related to UFR and electrolyte changes [38]. Based on data from a prospective study of implantable defibrillators in HD patients, the prevalence of paroxysmal AF was threefold higher on dialysis days and specifically increased during the dialysis procedure itself [4]. Clearly, cardiac arrhythmia would translate into instability of CO and consequently ScvO₂ variability. Instability of CO may also be aggravated by autonomic neuropathy [12]. Of note, in our study ScvO₂ variability (expressed as SD of ScvO₂) was inversely correlated with ScvO₂ levels (Fig. 1).

Our study has limitations, most prominently the absence of hemodynamic and SaO₂ measurements during dialysis. It is instructive to picture the dynamics of estimated UBBF (eUBBF) based on actual measured hemoglobin and ScvO₂ levels and reasonable assumptions regarding SaO₂ and upper body oxygen consumption rate. Figure 5 shows data of a patient in whom ScvO₂ and Hgb were measured simultaneously once per minute throughout the whole dialysis session. Assuming a constant SaO₂ of 92% and a constant upper body oxygen consumption rate of 65 mL/min, the eUBBF can be calculated on a minute-by-minute basis by applying equation (1). Wide and rapid swings of eUBBF become evident. It is conceivable that rapid excursions of UBBF pose challenges to the CBF autoregulation. While a continuous measurement of up-

per body oxygen consumption during dialysis is elusive, the continuous measurement of SaO₂ is well established in clinical routine and could provide valuable additional information in future studies [16, 18, 19, 23, 26–28, 39–43].

Clinical acumen and research in intensive care have shown that ScvO₂ is an actionable bio-signal. In HD patients, for example, a decline in preload and CO could be mitigated by, for example, adjusting ultrafiltration volume and UFR. It is even conceivable that ScvO₂ (or eUBBF) could serve as an input signal for a controller of the UFR.

Conclusions

Our study indicates that variability of ScvO₂ is associated with all-cause mortality in patients with a CVC as vascular access. We posit that the primary driver of this ScvO₂ variability is the change that occurs in UBBF and CO. The variability of CO during dialysis could be physiological, for example, an adaptation to a declining preload, or pathological, due to compromised cardiac function. Several currently available technologies allow for a quasi-continuous monitoring of ScvO₂ during dialysis. Such measurements could provide valuable diagnostic and actionable bio-signals. Prospective research into the pathophysiology of ScvO₂ dynamics during dialysis, with concurrent hemodynamic measurements is needed to further elucidate the association between ScvO₂ and outcomes.

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