

**EVIDENCE-BASED CASE REPORT**

Title

**Does High Ultrafiltration Volume Correlate to Occurrence of Desaturation in Patients Undergoing Hemodialysis?**

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Editor:

**Pringgodigdo Nugroho***Received 26 October 2018, revised 25 February 2019, accepted 1 March 2019, published 1 April 2019***Abstract**

**Background:** Hemodialysis is a metabolically stressful condition for patients that leads to reduced oxygen saturation and tissue perfusion. One of the identified drivers is a high ultrafiltration volume (UFV). Concurrently, central venous oxygen saturation (ScvO<sub>2</sub>) is a marker for global tissue hypoxia that has been used in cases of sepsis and trauma to guide fluid therapy. In dialysis patients with a central venous catheter (CVC) access ScvO<sub>2</sub> is accessible. Here we intend to delineate the relationship of UFV to desaturation during dialysis through the measurement of ScvO<sub>2</sub>.

**Methods:** PICO was formulated from a clinical case, and a literature search was conducted in Pubmed, Embase, Scopus, and Cochrane. Selected studies were then critically appraised using harm/etiology worksheet from CEBM<sup>1</sup> for validity, importance, and applicability.

**Results:** Studies by Harrison, et al., Zhang, et al. and Rotondi, et al. were chosen for answering our PICO. Harrison, et al. reported a relation of  $r: -0.680$ ,  $p: 0.015$  between UFV and ScvO<sub>2</sub>. While, Zhang, et al. utilized retrospective data of Critline Monitor (CLM) reading of dialysis patients and reported a negative 0.3% slope of ScvO<sub>2</sub> over corrected UFV (cUFV). Whilst, Rotondi, et al. demonstrated that in 20 patients separated equally to exclusively dialysis or ultrafiltration and both caused lowering of ScvO<sub>2</sub>, but only the former was statistically significant.

**Discussion:** The mechanism of relationship may include incapability of plasma refill rate to compensate for the fluid shift during ultrafiltration, resulting in lower cardiac preload and stroke volume which is detrimental in patients who are natively prone to suffer from reflex bradycardia and intradialytic hypotension. Studies have shown that episodes of hypoxemia in dialysis patients translate to worse prognosis. **Conclusion:** ScvO<sub>2</sub> is inversely proportional to UFV. As such, monitoring for ScvO<sub>2</sub> in dialysis patients will be beneficial to prevent end-organ ischemia.

*Keywords: hemodialysis, ultrafiltration, desaturation, central venous oxygen saturation*

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**Case Illustration**

Mr. SW, 47 years old, came to the emergency department with complaints of nausea, vomiting, and hiccups for the past week. He had no other remarkable complains. Since 25 years, he has been suffering from diabetes mellitus type II and hypertension, both of which were poorly controlled, the former with only metformin 500mg bid PO and the latter with amlodipine 10mg mid PO. He had a history of transient ischemic attack (TIA) 14 years prior, diabetic foot 4 years ago and has progressive poor sight on his left eye.

Upon physical examination, his vital signs showed hypertension 190/110 mmHg, tachypnea of 24x/min, tachycardia (heart rate of a 118x/min) and oxygen saturation of 99% (by peripheral pulse oximetry). There was a positive shadow test for his left eye, anemic conjunctiva and minimal pitting edema on both legs, no other abnormalities were found. His blood workup showed hemoglobin 10.3 g/dL, blood glucose 192 mg/dL, urea 268 mg/dL and creatinine 19.5 mg/dL. The patients' diagnosis was hypertensive emergency, chronic kidney disease stage V with uremic syndrome and fluid overload, and diabetes mellitus type

2 (DM type 2) with chronic diabetic complications. He was administered nicardipine 5mg/h which was raised to 10mg after 30 minutes and achieved SBP reduction of 25% by 1-hour, central venous access was procured using catheter double lumen (CDL) for emergency hemodialysis and his blood glucose was controlled. His hemodialysis regimen used bicarbonate dialysate, polyaryl etherosulfone (PAES) membrane with an ultrafiltration volume of 3,000 mL (cUFV: 44.1 mL/kgBW, 4.6% of interdialytic weight gain (IDWG)) and an ultrafiltration rate of 11mL/kg BW/h. During the initial dialysis session he complained of tiredness and shortness of breath, and his saturation fell to 92% with room air, which was alleviated by oxygen therapy of 3 liters/min. There was no co-occurrence of intradialytic hypotension (IDH) during continuous intradialytic blood pressure monitoring.

Subsequently, he underwent strict volume control and adjusted routine hemodialysis with CDL access for another two months before changing to an arteriovenous fistula. For his DM type 2, the regimen given was insulin aspart 4 unit tid and insulin glargine qDay 8 unit, and his hypertension was controlled by valsartan 40 mg bid PO and verapamil 80 mg tid PO. Additionally, his hemoglobin was sustained at above 10 g/dL without EPO or iron supplementation.

## Background

Hemodialysis in chronic kidney disease (CKD) patients has been understood to introduce hemodynamic stress to the patient. It has been demonstrated since 3 decades ago that during hemodialysis, oxygen saturation decreased and could occur as early as 15 minutes into the dialysis.<sup>2-5</sup> This phenomenon had been ascribed due to types of dialysate (acetate or bicarbonate), dialyzer membranes or respiratory pathologies; though none have been conclusive.<sup>2,6-9</sup> Identified inducers of organ ischemia had been ultrafiltration volume (UFV) and intradialytic hypotension (IDH);<sup>10</sup> UF causes non-physiological fluid shifts and IDH may be related to ensuing peripheral vasodilation and hypovolemia. Qualitatively, high UFV is defined as a volume exceeding the plasma refill volume; whilst there are no standard quantitative definitions of a high UFV, some assign the value to be  $\geq 10$ ml/kgBW/h or above 3 liters in 4 hours for average 70 kg

man.<sup>11,12</sup> A well-described composite marker for oxygen saturation and global tissue oxygen extraction and delivery is central venous oxygen saturation (ScvO<sub>2</sub>); it has been used in the prognosis of trauma, post-surgical, acute coronary syndrome and sepsis.<sup>13-15</sup> In dialysis patients with catheter double lumen (CDL) access, ScvO<sub>2</sub> is an accessible and simple parameter to monitor cardiac output and tissue oxygen delivery and extraction.<sup>17</sup> so that other technologies are emerging. Central venous oxygen saturation measurement (ScvO<sub>2</sub>) To date, the relationship between UFV and oxygen saturation in dialysis patients has not been clearly outlined. Here we aim to assess the best available evidence and try to elucidate this relationship, which may impact hemodialysis treatment in individuals.

## Clinical Questions

Does high ultrafiltration volume correlate to the occurrence of desaturation in patients undergoing hemodialysis?

## Methods

Clinical queries were performed on 23rd August 2018, through PubMed/Medline, SCOPUS, Embase and Cochrane. The terminologies utilized, and search results are listed in Table 1 and Figure 1.

Table 1. Results of Article Search

Database	Search Terms	Hits
Pubmed	(ultrafiltration) and ((oxygen and saturation)	28
SCOPUS	or desaturation or hypoxemia or hypoxia) and	80
Embase	(dialysis or hemodialysis))	160
Cochrane		10

## Results

Search results can be seen in table 2-6.

## Discussion

We summarized three studies based on our systematic article search. Of the three studies, Harrison, et al.<sup>18</sup> and Zhang, et al.<sup>19</sup> agreed that UFV or cUFV is inversely proportionate to decrease in ScvO<sub>2</sub>, while Rotondi, et al.

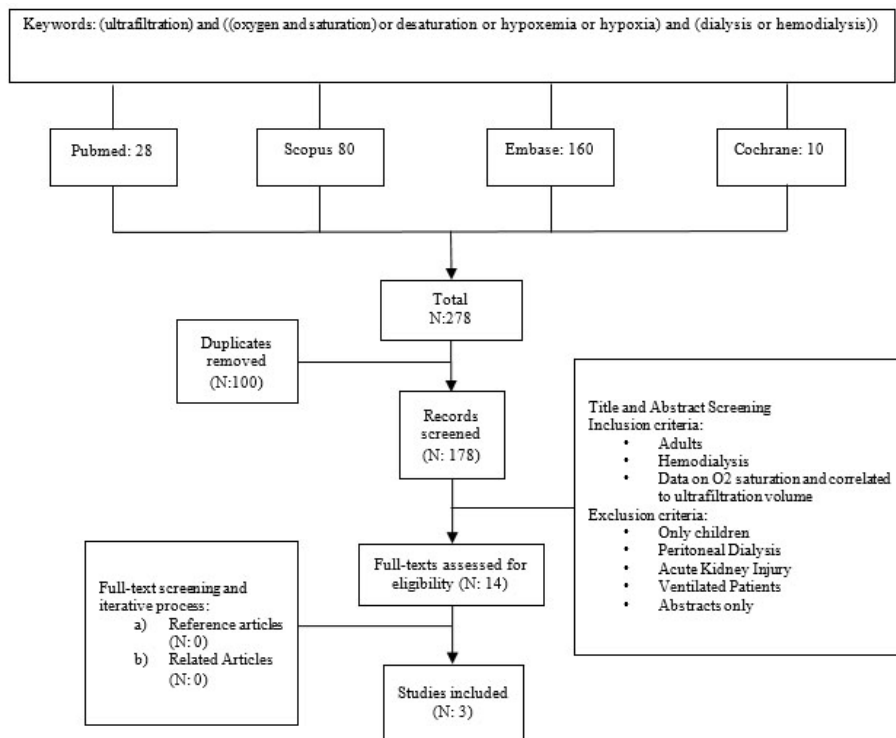


Figure 1. Schematics of article selection.

Table 2. Characteristic of selected studies

	Access	Hemodialysis Regimen (Dialysate/Membrane)	Measured Sessions	No. of Patients	Control	Mean Age (years)	Mean Hemoglobin (g/dl)	Oxygen Saturation Measurement	Findings
Harrison et al. (2014) <sup>16</sup> Central Venous Oxygen Saturation as Potential New Marker for Circulatory Stress in Hemodialysis Patients	CVC	NR	1	18	Pre-post	67±16	NR	BGA (ScvO2)	Inversely Proportional Scvo2 to UFV r: -0.68, to cUEM r: -0.769 (both P<0.01)
Zhang et al. (2017) <sup>17</sup> Association between intradialytic central venous oxygen saturation and ultrafiltration volume in chronic hemodialysis patients	CVC	Bicarb/PAES	25±13.3	232	Pre-post	62.7±15.7	10.6±0.6	CLM (ScvO2)	80% of patients Scvo2 inversely Proportional to UFV, LMM-FE R <sup>2</sup> : -0.03
Rotondi et al. (2018) Oxygen Extraction Ratio (OER) as a Measurement of Hemodialysis Induced Tissue Hypoxia: A Pilot Study <sup>18</sup>	CVC	Bicarb/PAES	10	20	Pre-post and Parallel	77±2.3	10.0±0.4	PPO (SaO2) and BGA (ScvO2)	Scvo2 dropped in isolated UF group Insignificant compared to drop in isolated dialysate group

Abbreviations and Definitions: CVC, Central Venous Catheters; AVF, Arteriovenous Fistula; AVG, Arteriovenous Graft; Bicarb, Bicarbonate; PAES, Polyaryl Ethersulfone; NR, Not Reported; Parallel, control using a separated group; Pre-post, control is pre-hemodialysis value.

Table 3 Critical appraisal of internal validity of the selected studies using CEBM Harm/Etiology Worksheet

Parameter	Harrison, et al. (2014) <sup>16</sup>	Zhang, et al. (2017) <sup>17</sup>	Rotondi, et al. (2018) <sup>18</sup>
Was there a clearly defined question?	Yes, the study aims to display ScvO <sub>2</sub> as a potential marker for hemodynamic stress during hemodialysis	Yes, the study had a question of how intradialytic changes of ScvO <sub>2</sub> changes associate with UFV	Yes, the study examines OER, as a measure of oxygen requirement, during hemodialysis is affected by dialysate or ultrafiltration
Were there clearly-defined, similar groups of patients?	Yes, control was using pre- and post-HD thus the characteristics are inherently the same	Yes, baseline characteristics were displayed, clear inclusion criteria and schematics of patients' selections	Yes, the isolated dialysate (iHD) and isolated ultrafiltration (iUF) groups were derived from the same population of patient selection which has clear and specific inclusion criteria
Were exposures and clinical outcomes measured the same way in both groups?	Yes, all patients had samples collected by CVC and measured by BGA	Yes, all groups used the same dialysis regimen and collection and measurement of ScvO <sub>2</sub> by CLM	Yes, all subjects had peripheral pulse oximeters and BGA with samples from CVC
Was the follow-up complete and long enough?	No, the study only analyzed one session of hemodialysis. Although outcome is acute, more sessions are required to observe reproducibility	Yes, the study, though retrospective, analyzed six months data	Yes, patients were followed up for 6 sessions of hemodialysis, allowing for reproducibility of desaturation
Does the suggested causative link make sense?	Yes, the study suggested the link was due to HD-induced global hypoxia as it has been shown to drive ischemia	Yes, the study argued desaturation occurs due to decline in cardiac preload as there is imbalance in plasma refill rate and cUFV	No, the study suggested significant ScvO <sub>2</sub> drop in iHD and not iUF due to biocompatibility or dialysate, bicarbonate and PAES are associated with lower incidence of desaturation

Table 4 Appraisal of selected studies' importance using CEBM Harm/Etiology Worksheet

Parameters	Harrison, et al. (2014) <sup>16</sup>	Zhang, et al. (2017) <sup>17</sup>	Rotondi, et al. (2018) <sup>18</sup>
What is the magnitude of the association between the exposure and outcome?	Calculation of OR NA, there are no unexposed group	Calculation of OR NA, there are no unexposed group	Calculation of OR NA, ScvO <sub>2</sub> numerical data is not provided, graphical data showed non-difference between ScvO <sub>2</sub> drop in iHD and iUF groups
What is the precision of the estimate of the association between exposure and outcome?	ScvO <sub>2</sub> relation to UFV is - 0.680 95% CI - 0.871 to -0.323	ScvO <sub>2</sub> to UFV decline is 0.3%/h per 10 ml/kg (P<0.001)	ScvO <sub>2</sub> numerical data not provided, mean SaO <sub>2</sub> and mean OER

Table 5 Studies' Critical Appraisal of their applicability using CEBM Harm/Etiology Worksheet

Parameters	Harrison, et al. (2014) <sup>16</sup>	Zhang, et al. (2017) <sup>17</sup>	Rotondi, et al. (2018) <sup>18</sup>
Were the patients similar to the patient under consideration in my practice?	Yes, albeit on average patients are geriatric (mean age of 67), they are hemodialysis-dependent and access was by CVC	Yes, patients are adults (mean age 62 years old), hemodialysis dependent, access by CVC, use bicarbonate/PAES, and 60% are diabetic	Yes, although patients are aged mean 75 years old, they are hemodialysis-dependent, do not have AVF/AVG, CVC access, use bicarbonate/PAES and 35% are diabetic
What are our patient's risks of the adverse event?	High, as he had episode of desaturation previously, with CV comorbidity of TIA and risks such as hypertension and DM		
What are our patient's preferences, concerns and expectations from this treatment?	Expect to be able to have high quality of life, concerned with aspect of long-life treatment, prefer hemodialysis than peritoneal dialysis.		
What alternative treatments are available?	Peritoneal dialysis, which eliminates non-physiological rapid fluid shift, and kidney transplant		

Table 6 Summary of VIA Critical Appraisal of the Selected Studies

Author (Year)	Validity, Importance and Applicability												
	Study design	Number of patients	Patient selection	Measurement of exposure	Measurement of outcome	Follow up	Randomization	Blind	Exposure preceded outcome	Dose-response gradient	Consistency to other studies	Biological plausibility	Level of Evidence*
Harrison et al. (2014) <sup>18</sup>	Prospective Cohort	18	+	+	+	-	-	-	+	+	+	+	3
Zhang et al. (2017) <sup>19</sup>	Retrospective Cohort	232	+	+	+	+	-	-	+	+	+	+	3
Rotondi et al. (2018) <sup>20</sup>	Prospective Cohort	20	+	+	+	+	-	-	+	+	-	+	3

reported non-significant ScvO2 hypoxemia with UFV. In the study by Harrison, et al., 18 patients on hemodialysis were recruited and assessed their ScvO2 by means of blood gas analysis, they showed that pre-HD ScvO2 was 62.5±13% and post-HD 56.4±18%, with correlation ScvO2 decline to UFV was r: -0.680 (p: 0.015) and even stronger for corrected UFV to weight (cUFV), r: -0.769 (p: 0.003). They also validated the ScvO2 to venous pO2 pre- and post-HD with r: 0.78 and 0.92 respectively; both p<0.005). 18 The study by Zhang, et al., by the time this article was written, was

the largest study to date that compared ScvO2 to cUFV, albeit being a retrospective study. They reported that of the 232 patients and 6,042 sessions analyzed, about 80% of the patients had a negative trend of ScvO2; compared to those with positive trend, the cUFV was lower by 0.3L 95% CI 0.04-0.5.19 Zhang, et al. used a Crit Line Monitor (CLM) allowing for minute-to-minute recording of ScvO2; they were able to show that, on a population level the fixed-effect by linear mixed model, ScvO2 decreased by 0.3% per hour for every 10mL/kg of volume filtrated.

This trend was evident in their sample population when the cUFV exceeded a cut-off point of 5mL/kg body weight. They also pointed out that, a small subset of positive ScvO<sub>2</sub> trend patients had a high cUFV and suggested that there was a possibility the cUFV, although high when compared to other samples, was actually too low compared to the interdialytic weight gain (IDWG) of the patients. This, in turn, reduced their UF-driven stress and allowed for the plasma refill rate to compensate and inhibited the occurrence of desaturation.<sup>19</sup>

Rotondi, et al. assessed hypoxemia by measuring oxygen extraction ratio (OER), which was calculated from SaO<sub>2</sub> and ScvO<sub>2</sub>.<sup>20</sup> They reported a stable SaO<sub>2</sub> in their patients throughout the session, though the OER increased due to the drop in ScvO<sub>2</sub>.<sup>20</sup> They measured 20 patients for 4 sessions and found no significant OER changes to UFV, UFR, relative body volume (RBV) or blood pressure (BP); their UFR was kept below 10ml/kg BW/hr. Then, they divided the samples into iHD and iUF groups during the 5th and the 6th session of HD and reported a statistically significant ScvO<sub>2</sub> decline in iHD group but not iUF. Analyzing the report along with supplemental data, the iUF arm also experienced ScvO<sub>2</sub> decrease along with evidently incrementing OER and they reported non-difference of the ScvO<sub>2</sub> decrease between iHD and iUF arms; it is more likely that the statistically insignificant decrease of venous oxygenation in iUF group was due to the small sample size of 10 patients. The authors suggested that the venous hypoxemia was more correlated with membrane biocompatibility or dialysate, of note the study used bicarbonate-buffered dialysate and PAES membrane.<sup>20</sup> Although some suspected acetate dialysate induced hypoxemia, studies showed there were statistically and clinically insignificant difference between acetate and bicarbonate dialysate.<sup>6</sup>

Assessing peripheral oxygen mismatch can be easily obtained by blood samples from the CVC which originates from the superior vena cava or right atrium, where the tip usually resides, thus reflecting ScvO<sub>2</sub>.<sup>16</sup> In turn, ScvO<sub>2</sub> demonstrate cardiac output and upper body blood flow (UBBF), as it is determined by cardiac output, SaO<sub>2</sub>, organs that drain into superior vena cava and hemoglobin (Hb) levels. SaO<sub>2</sub> has been reported to be stable or transiently decline but returning to normal by end of HD<sup>21</sup> and 10

Hb is elevated relatively during HD compared to pre-HD state, thus both unlikely to be the relative cause of decline. Interdialytic weight gain is typically  $\geq 3L$ , with circulating blood volume of 5-6L and 2L of which is plasma water, the volume removed during dialysis equate plasma volume. Thus, as there is an imbalance of ultrafiltration and plasma refill rate there would be a decrease in cardiac preload and circulating volume. Dialysis patients suffer from a phenomenon termed Bezold-Jarisch reflex, upregulation of parasympathetic and inhibition of sympathetic pathways due to activation in inhibitory cardiac receptors within the left ventricle causing, of importance, reflex bradycardia.<sup>22</sup> Paired with decreased preload and stroke volume, this results in the decline of cardiac output. These findings are reinforced by an intradialytic cardiac MRI study that displayed a negative relationship between UFV to cardiac index and stroke volume.<sup>23,24</sup>

The other possible driver of ischemia is IDH, defined as a decrease of SBP <100 mmHg post-HD or an abrupt decline of 20 mmHg from pre- to post-HD SBP; although, new evidence suggest that instead, it occurred later than the decline in oxygen saturation. The study by Harrison, et al. and Zhang, et al. showed that their samples did not suffer from IDH yet still experienced desaturation, with a mean difference of pre- and post-HD SBP of  $9 \pm 20$  mmHg and  $6 \pm 21$  mmHg respectively. Subsequently,  $\Delta$ ScvO<sub>2</sub> was not correlated to  $\Delta$ SBP, pre-SBP or post-SBP, and neither to other confounding factors such as diabetes, chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF). UF, in hemodialysis, drives a rapid shift in the blood volume transiently, leading to lower peripheral perfusion. This decrease in intravascular volume and a defective reflex mechanism may cause not only ischemia but also IDH. Newer reports also suggest that the occurrence of tissue hypoxia, at least in the liver, occurred earlier than IDH<sup>25</sup>, with observed drop in ScvO<sub>2</sub> occurring as early as 15 minutes into dialysis.<sup>3,20</sup> Macini, et al. and Delattre, et al. have also demonstrated that ScvO<sub>2</sub> and SO<sub>2</sub> have good predictive power of IDH (with AUC varying from 0.62 to 0.78) and IDH occurred from 60 to 120 minutes into the HD session.<sup>26,27</sup> Zhang, et al. also reported ScvO<sub>2</sub> negative trend correlated to decrease in SBP (-0.1% per hour per 10 mmHg drop)<sup>19</sup> and the ScvO<sub>2</sub> decrease in IDH-prone pa-

tients have been reported to be greater<sup>28</sup>. IDH may be a later signal towards progressively worsening tissue perfusion. UF-driven circulatory stress and hypoxemia in the long-term have been shown to elicit end-organ dysfunction, such as cardiac stunning, worsening cardiac failure and cognitive deficits. Intradialytic hypoxemia has also been proposed to be associated with all-cause hospitalization, mortality and increased obstructive sleep apnea (OSA)<sup>10,24,29–31</sup>

These studies are admittedly not optimal as they are of small sample sizes or retrospective. There needs to be a large prospective cohort or randomized controlled trial (RCT) study to analyze continuous ScvO<sub>2</sub> and UFV relationship. Study design by Rotondi, et al. allowed for a parallel control group with iHD group unexposed to ultrafiltration and iUF to ultrafiltration only.<sup>20</sup> Possibly, there would also be a need to assess ultrafiltration rate (UFR), as it has a negative circulatory effect and has a strong correlation with the incidence of hypoxemia as well.<sup>16,30</sup>

### Conclusion and Recommendation

These initial results show that UFV tends to be inversely proportionate to ScvO<sub>2</sub>, with ScvO<sub>2</sub> starting to decline when cUFV is higher than 5ml/kgBW or more than 0.5% of IDWG. Further conclusive studies, such as RCTs, should be performed to provide a better quality of evidence. Additionally, ScvO<sub>2</sub> decline is predictive of IDH and associated with long-term organ ischemia, hospitalization, and mortality. ScvO<sub>2</sub> is a relatively simple and accessible method of monitoring in dialysis patients and should be used if possible, in high-risk patients.

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