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Article

Intradialytic Hypoxemia and Clinical Outcomes in Patients on Hemodialysis

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Abstract

Background and objectives Intradialytic hypoxemia has been recognized for decades, but its associations with outcomes have not yet been assessed in a large patient cohort.

Design, setting, participants, & measurements Our retrospective cohort study was conducted between January of 2012 and January of 2015. We recorded blood oxygen saturation every minute during hemodialysis in patients with arteriovenous access. A 6-month baseline period with at least 10 treatments with oxygen saturation measurements preceded a 12-month follow-up. Patients were stratified by the presence or absence of prolonged intradialytic hypoxemia defined as oxygen saturation <90% for at least one third of the treatment time. Demographic, laboratory, and treatment data and hospitalization and mortality rates were compared between the groups. Multivariate Cox regression analysis was used to assess baseline predictors of all-cause mortality during follow-up.

Results In total, 100 (10%) of 983 patients had prolonged intradialytic hypoxemia. These patients were older (+3.6 years; 95% confidence interval, 0.8 to 6.3), had longer dialysis vintage (+1.2 years; 95% confidence interval, 0.3 to 2.1), and had higher prevalence of congestive heart failure (+10.8%; 95% confidence interval, 1.6 to 20.7) and chronic obstructive pulmonary disease (+13%; 95% confidence interval, 5 to 21.2). They also resembled an inflammatory phenotype, with lower serum albumin levels (−0.1 g/dl; 95% confidence interval, −0.2 to 0) and higher neutrophil-to-lymphocyte ratios (+1; 95% confidence interval, 0.5 to 1.6). They had lower hemoglobin levels (−0.2 g/dl; 95% confidence interval, −0.4 to 0) and required more erythropoietin (+1374 U per hemodialysis treatment; 95% confidence interval, 343 to 2405). During follow-up, all-cause hospitalization (1113 hospitalizations; univariate hazard ratio, 1.46; 95% confidence interval, 1.22 to 1.73) and mortality (89 deaths; adjusted hazard ratio, 1.98; 95% confidence interval, 1.14 to 3.43) were higher in patients with prolonged intradialytic hypoxemia.

Conclusions Prolonged intradialytic hypoxemia was associated with laboratory indicators of inflammation, higher erythropoietin requirements, and higher all–cause hospitalization and mortality.

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Introduction

Although intradialytic hypoxemia has been well recognized since the early days of hemodialysis (1–3), epidemiologic data from large populations are missing. Consequently, clinical correlates of intradialytic hypoxemia are ill defined, and associations with hard clinical outcomes have not yet been assessed.

In individuals dwelling at <1000-m altitude, an arterial oxygen saturation (SaO_2) between 96% and 99% is considered normal (4). Although there is no universally agreed on definition of hypoxemia, most references consider $SaO_2 \leq 90\%$ as indicative of hypoxemia (5–7). Of note, oxygen supply to tissues depends on not only SaO_2 but also, the hemoglobin content of the blood, tissue perfusion, and oxygen release from hemoglobin in the tissues.

Although hypoxemia is the common terminal pathway of multiple pathologies, congestive heart failure (CHF) and sleep apnea are particularly prevalent in patients on hemodialysis (8–10). Additionally, there is growing literature about the prevalence of chronic obstructive pulmonary disease (COPD) in patients with CKD (11,12). Notwithstanding etiology, hypoxemia and hypoxia are associated with a host of acute and chronic sequelae affecting multiple organ systems (13–15), including the cardiovascular system (16,17), wound healing (18), proinflammatory pathways (19), and the central nervous system (20). Some of these pathologies are highly prevalent in patients on hemodialysis (for example, inflammation and changes in vascular smooth muscles and endothelium, processes that accelerate arteriosclerosis) (21,22). Hypoxemia also impairs resilience against reactive oxygen species (ROS) and may increase erythrocyte apoptosis (eryptosis) (23). Noteworthy, in patients with CHF and sleep apnea, it was observed

that not only the frequency but also, the time spent with SaO_2<90%, the hypoxic burden, is a predictor for hemodynamic stress (24).

Technologic advances have made routine continuous measurement of blood oxygen saturation during hemodialysis feasible (25). Depending on the type of vascular access, the Crit-Line Monitor (CLM) can determine central venous oxygen saturation or SaO_2.

Recent deployment of the CLM in a large population of United States patients on hemodialysis allowed us to conduct research on associations between intradialytic SaO_2 and clinical outcomes. The goals of this study were to (*1*) assess the epidemiology of intradialytic SaO_2 and (*2*) explore associations between SaO_2 and clinical outcomes.

Materials and Methods

This study is registered at cliniclatrials.gov (NCT02501044).

Population and Study Design

This observational, retrospective, multicenter database study was conducted in a cohort of patients on chronic hemodialysis from 17 facilities of the Renal Research Institute (RRI) between January of 2012 and January of 2015. These clinics were located in North Carolina (six clinics; 108–205 m above sea level), California (three clinics; 8–31 m above sea level), Connecticut (three clinics; 20–70 m above sea level), New York City (three clinics; 28 m above sea level), Michigan (one clinic; 220 m above sea level), and Illinois (one clinic; 180 m above sea level). In these clinics, CLM use is standard care, albeit with some utilization variability related to the phased device rollout. Patients were treated with bicarbonate dialysate and polysulfone membranes. A 6-month baseline period and a 12-month follow-up period were defined on a patient level. The baseline period started on the date of a patient's first SaO_2 measurement between January of 2012 and September of 2014. Patients were censored in the event of transplantation, treatment modality change, transfer, recovery of kidney function, or end of the study period (January 31, 2015). Only patients with ≥10 eligible SaO_2 measurements during baseline and 6 months of data were included in the analysis. The study was approved by the New England Institutional Review Board (14–446), which waived the need for informed consent.

Measurement of Oxygen Saturation

Intradialytic SaO_2 was measured by the CLM (Fresenius Medical Care North America, Waltham, MA), a device approved by the US Food and Drug Administration for the measurement of hematocrit and oxygen saturation in the extracorporeal circuit. It reports oxygen saturation one time per minute. The manufacturer-reported accuracy of SaO_2 measurement is 2%. CLM data were transferred to the RRI data warehouse and subsequently, the study database.

Clinical and Laboratory Data

Laboratory measurements (Spectra Laboratories, New Jersey, NJ) were downloaded to the RRI data warehouse and extracted to the study database.

Data Eligibility

CLM values with the following characteristics were deemed implausible or unreliable and hence, excluded: relative blood volume >102%, SaO_2>100%, hematocrit levels ≤15% or >55%, and data points collected after the end of the prescribed treatment time. In the absence of acceptable data during >50% of the treatment time, the entire treatment was excluded. Likewise, treatments were excluded if the rate of change of relative blood volume was >5% points compared with values 10 and 5 minutes earlier on one or more occasions, SaO_2 of 50% was recorded >40 times, or the mean intradialytic SaO_2 was ≤80%, a level indicative of venous rather than arterial blood.

Comorbidities

CHF, diabetes, and COPD were defined using International Classification of Diseases, Ninth Revision codes.

Statistical Analyses

Descriptive statistics comprised means (±SDs) for continuous variables and percentages for categorical variables. Non–normally distributed variables were expressed as medians (25th, 75th percentiles). Statistics of SaO_2 variables were calculated first per hemodialysis treatment and then, per patient and per group. Start SaO_2 was defined as the mean SaO_2 between treatment minutes 5 and 20, and end SaO_2 was defined as the mean SaO_2 between the final 20 and 5 minutes; these time intervals were selected to avoid potential interference with priming and rinsing procedures.

Patients were stratified into two groups on the basis of an *a priori* definition of prolonged intradialytic hypoxemia (PIH). Diagnosis of PIH required the presence of hypoxemia, defined as SaO_2≤90%, during, on average, more than one third of the recorded treatment time. Patients not fulfilling this definition served as controls. We also conducted investigations using mean SaO_2 and the percentage of treatment time spent with SaO_2≤90% as continuous variables. Group comparisons used chi-squared, Fisher exact, and two–sample *t* tests; mean group differences with 95% confidence intervals (95% CIs) are presented.

Hospitalization rates during follow-up were calculated as hospitalizations per patient-year, and 95% CIs were computed by bootstrapping. Kaplan–Meier plots and Cox proportional hazards models were constructed to explore survival characteristics.

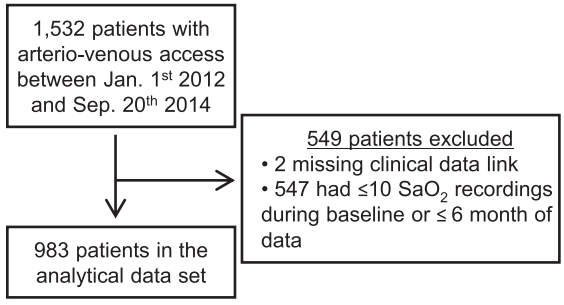

Figure 1. | **Study flow chart.** SaO_2, arterial oxygen saturation.

Table 1. Baseline characteristics of the entire study population and after stratification into groups with and without prolonged intradialytic hypoxemia

Variables	All Patients, Mean±SD	Prolonged Intradialytic Hypoxemia			*P* Value
		Present, Mean±SD	Absent, Mean±SD	Difference between Groups, Mean (95% CI)	
Patients, *N*	983	100	883		
Treatments with SaO_2 measurements, no. per patient	30.5±12.5	29.6±11.4	30.6±12.7	−1 (−3.6 to 1.6)	0.44[a]
Demographics					
Men, %	59.0	53.0	59.6	−6.6 (−17.0 to 3.7)	0.20[b]
Race, % white	52.6	51.0	52.7	−1.7 (−12.4 to 8.4)	0.74[b]
Age, yr	62.1±15.2	65.3±13.0	61.7±15.4	3.6 (0.8 to 6.3)	0.01[a]
BMI, kg/m^2	28.7±7.7	29.5±7.6	28.6±7.8	0.9 (−0.8 to 2.5)	0.30[a]
Obese,[c] %	35.1	41.3	34.3	6.9 (−3.5 to 17.8)	0.21[b]
Oxygen saturation, %					
Mean SaO_2	92.8±1.8	89.1±1.6	93.2±1.3	−4.1 (−4.4 to −3.8)	<0.001[a]
Median SaO_2	92.9±1.8	89.3±1.6	93.3±1.3	−4.0 (−4.4 to −3.7)	<0.001[a]
Minimum SaO_2	90.4±2.8	85.2±2.8	91.0±2.2	−5.8 (−6.4 to −5.2)	<0.001[a]
Maximum SaO_2	94.5±1.4	92.1±1.2	94.8±1.1	−2.7 (−2.9 to −2.5)	<0.001[a]
SD SaO_2	0.8±0.4	1.4±0.5	0.7±0.3	0.7 (0.6 to 0.8)	<0.001[a]
Time spent <90% SaO_2	10.3±18.5	57.6±18.2	4.9±7.8	52.7 (49.1 to 56.3)	<0.001[a]
Time spent <87% SaO_2	2.6±8.7	19.2±20.0	0.7±2.1	18.5 (14.6 to 22.5)	<0.001[a]
Start SaO_2	92.6±1.9	88.8±1.9	93.1±1.4	−4.3 (−4.7 to −3.9)	<0.001[a]
End SaO_2	93.2±1.8	89.7±1.6	93.6±1.3	−3.9 (−4.2 to −3.5)	<0.001[a]
Comorbidities, %					
Diabetes	52.3	56.0	51.9	4.1 (−6.1 to 14.1)	0.43[b]
CHF	23.3	33.0	22.2	10.8 (1.6 to 20.7)	0.02[b]
COPD	8.4	20.0	7.1	12.9 (5.0 to 21.2)	<0.001[b]
Treatment-related parameters					
Vintage, yr	3.9±4.1	5.0±4.3	3.8±4.1	1.2 (0.3 to 2.1)	<0.01[a]
Predialysis SBP, mmHg	146.9±19.4	147.2±19.5	146.9±19.4	0.3 (−3.7 to 4.4)	0.87[a]
Postdialysis SBP, mmHg	137.2±18.2	139.2±19.7	136.9±18.0	2.3 (−1.5 to 6.0)	0.24[a]
IDWG, kg	2.3±0.8	2.5±0.8	2.3±0.8	0.2 (0.0 to 0.4)	0.03[a]
IDWG, % of post-HD weight	2.9±1.0	3.0±1.0	2.8±1.0	0.2 (0.0 to 0.4)	0.06[a]
Treatment time, min	215.9±25.0	215.6±24.3	216.0±25.1	−0.4 (−5.6 to 4.8)	0.89[a]
Ultrafiltration rate, ml/h per kilogram	8.1±3.0	8.6±2.9	8.0±3.0	0.6 (−0.1 to 1.2)	0.07[a]
Ultrafiltration volume, L	2.3±0.8	2.4±0.8	2.2±0.9	0.2 (0.0 to 0.3)	0.05[a]
Equilibrated Kt/V	1.5±0.3	1.5±0.2	1.5±0.3	0.0 (0.0 to 0.0)	0.28[a]
Dialysate sodium, mmol/L	137.2±0.5	137.2±0.4	137.2±0.5	0.0 (−0.1 to 0.1)	0.41[a]
Laboratory parameters					
Serum albumin, g/dl	4.0±0.3	3.9±0.3	4.0±0.3	−0.1 (−0.2 to 0.0)	<0.001[a]
Hb, g/dl	10.9±0.9	10.7±0.9	10.9±0.9	−0.2 (−0.4 to 0.0)	0.02[a]
Serum sodium, mmol/L	138.8±2.6	138.4±3.0	138.9±2.5	−0.5 (−1.1 to 0.1)	0.13[a]

Table 1. (Continued)

Variables	All Patients, Mean±SD	Prolonged Intradialytic Hypoxemia			*P* Value
		Present, Mean±SD	Absent, Mean±SD	Difference between Groups, Mean (95% CI)	
Serum potassium, mmol/L	4.8±0.5	4.9±0.5	4.8±0.5	0.1 (0.0 to 0.2)	0.06[a]
PTH, pg/ml	549±500	543±665	550±478	−6 (−142 to 129)	0.93[a]
Serum calcium, mg/dl	8.9±0.6	8.8±0.7	9.0±0.6	−0.2 (−0.3 to 0.0)	0.01[a]
Serum phosphorous, mg/dl	5.3±1.2	5.2±1.2	5.3±1.2	−0.1 (−0.3 to 0.2)	0.68[a]
Serum bicarbonate, mmol/L	23.2±2.0	23.5±2.1	23.2±2.0	0.3 (−0.1 to 0.7)	0.15[a]
WBC, 1000/μl	6.6±3.1	6.7±2.0	6.6±3.2	0.1 (−0.3 to 0.6)	0.49[a]
Platelets, 1000/μl	205.0±62.9	197.2±64.8	205.9±62.7	−8.7 (−22.1 to 4.7)	0.20[a]
NLR	3.7±2.1	4.6±2.6	3.6±2.0	1.0 (0.5 to 1.6)	<0.001[a]
Ferritin, ng/ml	923±460	884±389	927±467	−43 (−126 to 40)	0.31[a]
Transferrin saturation, %	33.7±8.7	29.5±8.0	34.2±8.7	−4.7 (−6.5 to −2.9)	<0.001[a]
Serum iron, μg/dl	77.7±22.4	67.5±21.3	78.9±22.2	−11.4 (−16.0 to −6.8)	<0.001[a]
Medication					
EPO, U per treatment, median (25th, 75th percentile)	1584 (610, 3240)	2173 (900, 4471)	1531 (603, 3156)	642 (213 to 976)	<0.01[d]
Iron, mg per treatment, median (25th, 75th percentile)	15.1 (7.1, 23.3)	16.8 (7.5, 24.3)	14.7 (7.1, 23.3)	2.1 (−0.9 to 4.2)	0.41[d]
Patients receiving supplemental oxygen, % (*n*)	1.6 (16)	1 (1)	1.7 (15)	−0.7 (−2.3 to 1.9)	>0.99[e]
Treatments with supplemental oxygen, % (*n*)	0.3 (96)	0.3 (8)	0.3 (88)	0 (−0.2 to 0.2)	0.61[e]

95% CI, 95% confidence interval; SaO_2, arterial oxygen saturation; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; SBP, systolic BP; IDWG, interdialytic weight gain; HD, hemodialysis; Hb, hemoglobin; PTH, parathyroid hormone; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; EPO, epoetin alfa.

[a]*t* Test.

[b]Chi-squared test.

[c]BMI≥30 kg/m^2.

[d]Wilcoxon test.

[e]Fisher exact test.

To adjust for potential confounders, minimally and fully adjusted Cox models complemented the crude hazard ratio (HR) analysis. Confounders were selected on the basis of their documented or hypothesized association with exposure and outcome. We used an incremental modeling strategy to assess the stability and spectrum of HR point estimates. Confounders in the minimally adjusted model were age, sex, and presence of COPD and CHF. In addition, the fully adjusted model included levels of serum albumin and hemoglobin, epoetin alfa (EPO) dose, neutrophil-to-lymphocyte ratio, interdialytic weight gain (IDWG; in kilograms), posthemodialysis systolic BP, ultrafiltration rate normalized to treatment time and posthemodialysis weight, presence of diabetes, race, and vintage. In a variant of the fully adjusted model, we added body mass index (BMI) or obesity (defined as BMI>30 kg/m^2).

Statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC) and R i386 3.0.2 (libraries: ggplot2, splines, survival, pspline, mgcv, and assist; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Of 1532 patients with SaO_2 measurements, 547 patients (36%) were excluded, because they had <10 treatments with eligible CLM recordings during baseline or <6 months of data (Figure 1).

The final cohort comprised 983 patients on hemodialysis, with a total of 29,986 treatments with eligible SaO_2 recordings (30.5±12.5 per patient). Age was 62.1±15.2 years old, 59% were men, and 52.6% were white. Dialysis vintage was 3.9±4.1 years, 52.3% were diabetic, 23.3% had CHF, and 8.4% had COPD. Chart review indicated that 16 patients received supplemental oxygen during, in total, 96 treatments. Supplemental oxygen flow rates were documented in 11 patients (range =1.5–3 L/min).

Compared with the excluded patients, those in the analytical dataset were more likely to be white and suffer from diabetes, CHF, and COPD. In addition, they had significantly lower IDWG, serum bicarbonate, and inflammatory markers; received less EPO; and spent less time at <90% SaO_2 (Supplemental Tables 1 and 2).

Baseline SaO_2

Across all patients, mean intradialytic SaO_2 was 92.8% ±1.8%. On average, patients spent 10% and 3% of their treatment time at SaO_2≤90% and ≤87%, respectively (Table 1). SaO_2 increased from 92.6%±1.9% at treatment start to 93.2%±1.8% at the end.

One hundred patients (10.2%) experienced PIH. Patients with PIH had significantly lower means, medians, minimums, maximums, and starting and ending SaO_2 values and spent, on average, 58% and 20% of their treatment time at SaO_2≤90% and ≤87%, respectively. The variability of SaO_2 levels was significantly higher in patients with PIH (SD=1.4% versus 0.7%).

SaO_2 declined after dialysis start in both patients with PIH and patients without PIH, with nadir SaO_2 after around 40 minutes (Figure 2). SaO_2 declined by 0.3% points in controls and 0.5% points in patients with PIH.

Associations between PIH and Baseline Clinical Characteristics

PIH was associated with older age, longer dialysis vintage, slightly higher IDWG, and higher prevalence of CHF and COPD. Patients with PIH had higher neutrophil-to-lymphocyte

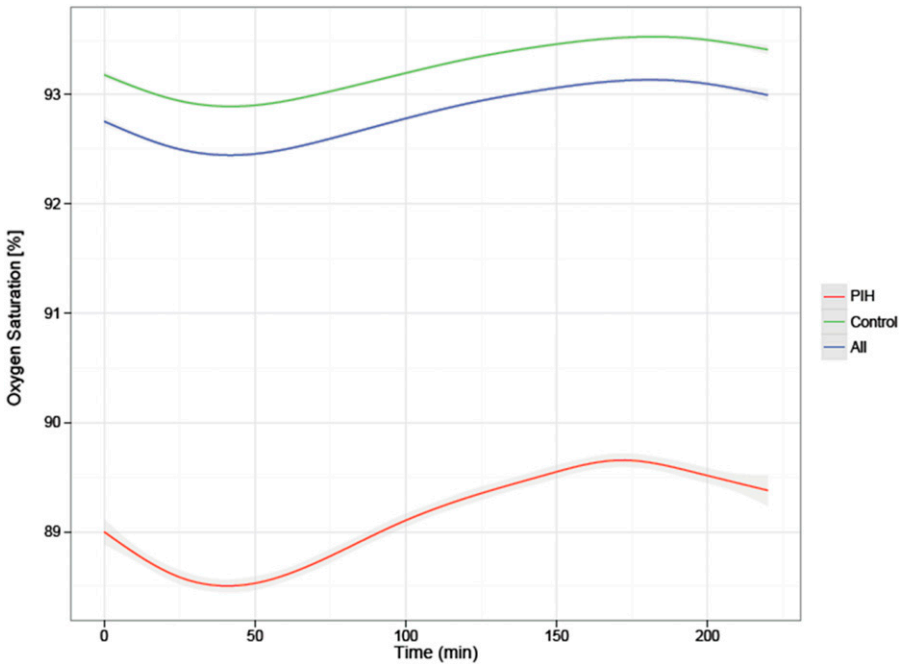

Figure 2. | **Time course of mean arterial oxygen saturation and 95% confidence interval in patients on chronic hemodialysis.** PIH, prolonged intradialytic hypoxemia.

ratio and lower levels of albumin, hemoglobin, serum iron, and transferrin saturation. They received, on average, 1374 U EPO more per treatment (PIH: mean =3823 U; non-PIH: mean =2449 U; P=0.01). Groups did not differ with respect to sex, race, BMI, pre- and postdialytic systolic BP, ultrafiltration volume, ultrafiltration rate, treatment time, serum bicarbonate, white blood cells, platelet counts, ferritin, and iron dose.

PIH and Outcomes during Follow-Up

All-Cause Hospitalization. We recorded 1113 hospitalizations: 150 in patients with PIH and 963 in the controls, resulting in 2.21 (95% CI, 0 to 3.4) and 1.55 (95% CI, 0 to 2.04) hospitalizations per patient-year, respectively. Thus, PIH was associated with 0.66 additional hospitalizations per patient-year ($P<0.01$). The univariate HR of hospitalization of PIH was 1.46 (95% CI, 1.22 to 1.73; $P<0.01$).

All-Cause Mortality. Eighty-nine patients died during follow-up: 18 in the PIH group and 71 controls. The mortality rate per 100 patient-years was 24.1 in the PIH group and 10.2 in the controls. Univariate Kaplan–Meier analysis indicated a significantly higher mortality in patients with PIH ($P<0.001$; log-rank test) (Figure 3); 69 patients with PIH and 668 controls were censored because of end of study (PIH: n=62; controls: n=610) or transfer to another facility (PIH: n=7; controls: n=58).

Analysis treating SaO_2 and percentage of treatment time spent at <90% SaO_2 as continuous variables indicated an almost linear association with all-cause mortality for both (Figure 4, Supplemental Table 3). Multivariate analysis corroborated the higher all–cause mortality in patients with PIH in unadjusted, minimally, and fully adjusted Cox proportional hazards models (Supplemental Figure 1, Table 2). Including BMI or obesity to the fully adjusted model gave results that were materially identical (data not shown).

Sensitivity Analyses. To explore the influence of CHF and COPD on outcomes, we performed a sensitivity analysis. First, the hospitalization rates were computed in both groups with and without patients with COPD or CHF. Although the hospitalization rate in controls was unaffected by excluding patients with COPD or CHF, it decreased in the PIH group (Supplemental Table 4). Second, we calculated the HR of death without patients with COPD or CHF; interestingly, the HR increased from 1.98 (95% CI, 1.14 to 3.43) to 2.21 (95% CI, 1.00 to 4.90) (Supplemental Table 5).

Discussion

Our research in a large cohort of patients on chronic hemodialysis indicates a high rate of intradialytic hypoxemia, with 10% experiencing PIH, a condition characterized by hypoxemia lasting for more than one third of the dialysis treatment time. Our main finding is a significant association between PIH and clinical outcomes, most notably all-cause hospitalization and mortality. Moreover, patients with PIH showed a laboratory profile compatible with an inflammatory phenotype and significantly higher EPO use. CHF and COPD were more prevalent in patients with PIH.

Hypoxemia during hemodialysis has been recognized since the early days of dialysis (26–32). Over the years, several mechanistic explanations have been put forward.

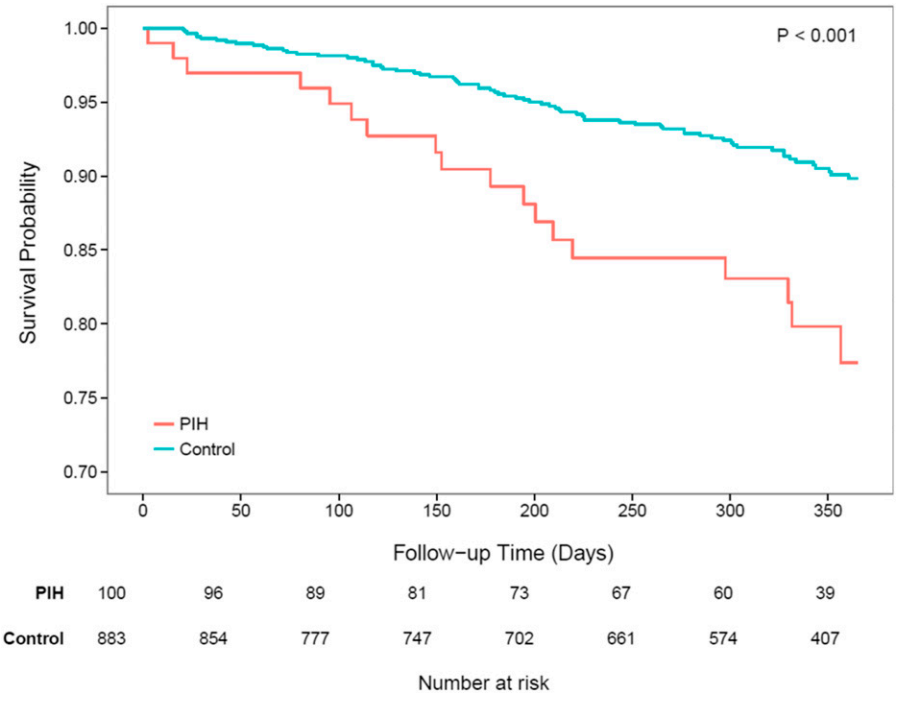

Figure 3. | **Kaplan–Meier estimates of survival probabilities.** Patients were stratified by the presence or absence (control) of prolonged intradialytic hypoxemia (PIH). The number of patients at risk is indicated in the table below the graph. The time to death differs significantly between the two groups ($P<0.001$ by log-rank test).

Sleep apnea is highly prevalent in patients on dialysis, and hypoxemia has been observed in patients while sleeping on dialysis (33,34). Reduced respiratory drive has been incriminated, because CO_2 may diffuse from the blood into the dialysate, resulting in decreased partial pressure of CO_2. Because breathing is tightly controlled by chemoreceptors, which respond to the partial pressure of CO_2 as well as the pH in the blood and cerebrospinal fluid, a reduction in CO_2 tension may result in hypoventilation and hypoxemia (35). Fluid overload, pulmonary congestion, and pulmonary calcification may affect oxygen diffusion, resulting in reduced blood oxygenation; therefore, approaching dry weight should improve SaO_2. Indeed, Anand *et al.* (36) found a positive relationship between the slope of the relative blood volume curve, an indirect marker of volume status, and change in SaO_2, indicating a contribution of volume overload to hypoxemia. In our study, SaO_2 at the end of dialysis was above starting levels, and patients with PIH had a slightly higher IDWG, pointing toward fluid status as a factor affecting SaO_2. Age-related changes of the respiratory system, such as a reduced neuromechanic link between chemosensors, brain stem, and respiratory muscles, may affect blood gases (37). In that context, it is noteworthy that patients with PIH were older, had a longer hemodialysis vintage, and had a higher SaO_2 variability, possibly reflecting

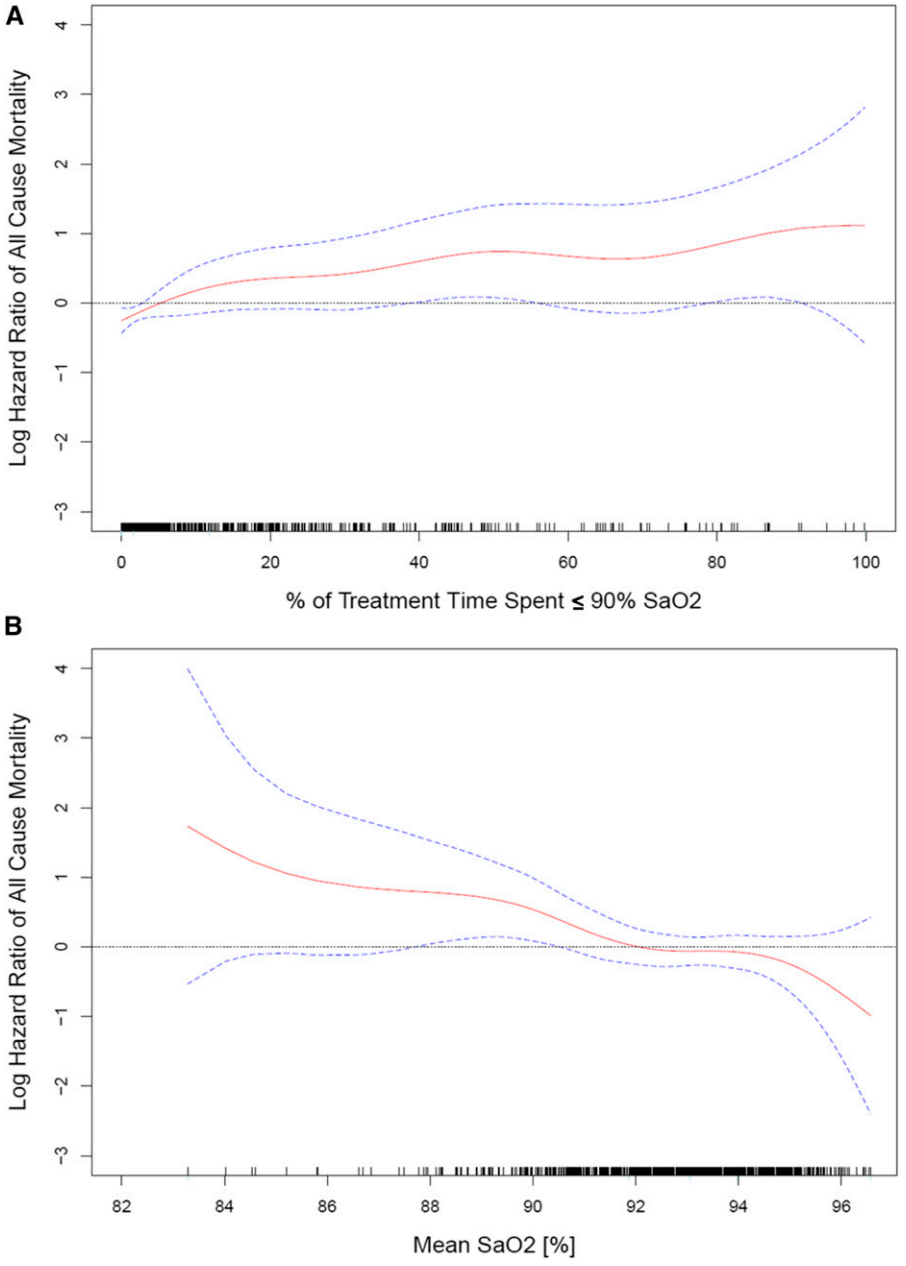

Figure 4. | **Association between intradialytic arterial oxygen saturation and all-cause mortality.** Hazard ratios for (A) average percentage of time spent at <90% oxygen saturation during treatments and (B) mean arterial oxygen saturation (SaO_2).

Table 2. Crude and adjusted hazard ratios for all-cause mortality

Outcome	Events	Crude[a]		Minimally Adjusted[b]		Fully Adjusted[c]	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause mortality	89	2.37 (1.41 to 3.97)	0.001	2.07 (1.22 to 3.51)	<0.01	1.98 (1.14 to 3.43)	0.02

Because of partially incomplete data, six censored patients were not considered in the fully adjusted Cox model. HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Unadjusted model.
[b]Adjusted for age, sex, chronic obstructive pulmonary disease, and congestive heart failure.
[c]Adjusted for age, sex, race, vintage, chronic obstructive pulmonary disease, congestive heart failure, diabetes, albumin, hemoglobin, epoetin alfa dose, neutrophil-to-lymphocyte ratio, interdialytic weight gain, postdialysis systolic BP, and ultrafiltration rate.

respiratory control instability. Previous studies related a high variability and decrease of SaO_2 during dialysis to intradialytic hypotension (38,39). Unfortunately, we can neither corroborate nor refute this observation, because hypotensive episodes were not uniformly documented. Of note, we did not observe a difference in BP between the two groups. Although a contribution of intradialytic hypoxemia to the morbidity and mortality of patients on hemodialysis has been hypothesized (26,40,41), this study shows for the first time, to the best of our knowledge, an association between adverse clinical outcomes and intradialytic hypoxemia. The decision to perform a dichotomous analysis and take one third of treatment time <90% as the threshold was on the basis of the hypoxic burden concept described in patients with CHF. The notion of PIH was developed in appreciation of this concept (24). Because CLM use is standard care in the participating clinics, bias by indication is highly unlikely.

Intermittent hypoxemia has been subject of considerable research. Although modest and acute intermittent hypoxemia may have beneficial effects, severe and chronic intermittent hypoxemia seem to be pathogenic (42). Chronic intermittent hypoxia results in impaired baroreceptor function, vasodilation, high BP, and increased production of ROS (43). Although ROS activate protective transcription factors, like hypoxia–inducible factor-1α and NF (erythroid–derived 2) –like 2, they also stimulate proinflammatory transcription factors, like NFκB and activator protein 1. At low or moderate ROS concentrations, pathways essential for repair and survival predominate, and high ROS levels promote inflammation and injury (20). Although we have no data on ROS in our population, it is tempting to speculate that the inflammatory laboratory phenotype observed in patients with PIH may be related to oxidative stress. Of note, oxidative stress also impairs erythrocyte function; in particular, it may result in reduced cell deformability and thus, contribute to increased erythrocyte removal from the circulation and reduced lifespan (44,45).

Given the fact that hypoxia is the primary stimulus for EPO production, showing higher EPO utilization in patients with PIH seems counterintuitive. Patients with PIH had not only a higher EPO use but also, lower hemoglobin levels, indicating some degree of EPO resistance. An obvious link may exist between the EPO hyporesponsiveness and the aforementioned inflammatory phenotype of patients with PIH, which may result in limited iron availability, a reduced number of EPO receptors, and impaired EPO receptor signaling (46). Recent evidence suggests that hypoxemia may affect erythrocyte resilience against oxidative stress. The erythrocyte ROS resilience depends on the availability of GSH, which is recycled from glutathione disulfide through the action of glutathione reductase and NADPH as a substrate. Glucose entering the erythrocytes is subject to metabolism in two pathways: the Embden–Meyerhof pathway, the source of ATP, and the hexose monophosphate pathway, the sole source of NADPH in erythrocytes. Deoxygenized hemoglobin favors Embden–Meyerhof pathway substrate fluxes over the hexose monophosphate pathway, resulting in reduced NADPH synthesis and eventually, less resilience to oxidative stress (47). Against this physiologic background, we hypothesize that hypoxemia–induced impaired erythrocyte ROS resilience may result in shortened erythrocyte lifespan, a recognized cause of EPO resistance (48). Testing this hypothesis will require carefully designed *in vitro* and clinical studies.

Our study has limitations. First and foremost is its observational nature, which prevents conclusions concerning causality. Second, longer follow-up periods are desirable. Third, we have no data that would allow us to address the hypotheses formulated above in greater detail. Fourth, we have no information on baseline SaO_2 and scarce records of supplemental oxygen use during dialysis, an intervention that clearly affects SaO_2. Carefully conducted prospective trials are necessary to address these limitations.

From a clinical standpoint, it will be essential to develop care pathways for patients with PIH. Given the plethora of pathologies resulting in hypoxemia, a multidisciplinary approach including pulmonologists will be critical to translate these findings into improved patient care.

One potential intervention could be the administration of oxygen during dialysis. Although large and comprehensive trials are missing, a few small studies showed a positive effect of intradialytic oxygen administration. Diroll (38) reported that intranasal oxygen (2 L/min) normalized SaO_2 and BP in a hypoxemic hemodialysis patient. In a

study of eight patients on hemodialysis, intranasal oxygen (2 L/min) improved SaO_2 and vascular refill (49). Yap *et al.* (50) showed in seven patients on chronic hemodialysis that intranasal oxygen (4 L/min) protected against an intradialytic SaO_2 decline. Taken together, limited data indicate some desirable effects of supplemental oxygen, but firm conclusions are currently elusive.

PIH is associated with an inflammatory phenotype, hyporesponsiveness to EPO, higher hospitalization, and mortality. A better understanding of its pathophysiology, clinical consequences, and medical management requires future carefully designed *in vitro* and clinical studies.

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Disclosures

P.K. holds stock in Fresenius Medical Care North America (Waltham, MA). The remaining authors declared no competing interest.

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