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## ORIGINAL ARTICLE

# Hypoxia during maintenance hemodialysis—the critical role of pH

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## ABSTRACT

**Background.** The impact and management of subclinical hypoxia during hemodialysis is a significant medical challenge. As key determinants of O<sub>2</sub> availability and delivery, proposed mechanisms contributing to hypoxia include ischemia, alkalemia and pulmonary leukocyte sequestration. However, no study has comprehensively investigated and compared these interrelated mechanisms throughout a typical hemodialysis treatment week. This study aimed to comprehensively assess the physiological mechanisms that contribute to hypoxia during hemodialysis.

**Methods.** In 76 patients, we measured arterial blood gases and pH at four time-points during hemodialysis (start, 15 min, 60 min, end) over the course of a standard treatment week. For the mid-week hemodialysis session, we additionally measured central hemodynamics (non-invasive cardiac output monitoring) and white blood cell count.

**Results.** Linear regression modelling identified changes in pH, but not central hemodynamics or white blood cell count, to be predictive of changes in PaO<sub>2</sub> throughout hemodialysis (e.g. at 60 min,  $\beta$  standardized coefficient pH = 0.45, model R<sup>2</sup> = 0.25,  $P < .001$ ). Alkalemia, hypokalemia, decreased calcium and increased hemoglobin–O<sub>2</sub> affinity (leftward shift in the oxyhemoglobin dissociation curve) were evident at the end of hemodialysis. pH and hemoglobin–O<sub>2</sub> affinity at the start of hemodialysis increased incrementally over the course of a standard treatment week.

**Conclusion.** These data highlight the important role of pH in regulating O<sub>2</sub> availability and delivery during hemodialysis. Findings support routine pH monitoring and personalized dialysate bicarbonate prescription to mitigate the significant risk of alkalemia and subclinical hypoxia.

## LAY SUMMARY

Low blood oxygen levels are common during hemodialysis and can cause unpleasant symptoms. There are many things that can contribute to low blood oxygen levels, such as low blood pressure, but this area has not been fully investigated. We measured oxygen levels during hemodialysis over the course of a normal treatment week. We also measured blood flow, blood pressure, blood acidity (pH) and white blood cell count. Changes in pH were found to be the best predictor of blood oxygen levels. pH changes mostly due to the use of bicarbonate to reduce acidity during hemodialysis. The findings suggest that people undergoing hemodialysis may benefit from regular pH measurement

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during treatment, and that bicarbonate should be individually prescribed rather than a standard dose being given to everyone.

**Keywords:** bicarbonate, cardiac output, hypoxia, pH, white blood cell count

## INTRODUCTION

Reduced oxygen availability ( $\text{PaO}_2$ ) and delivery ( $\text{p50}$ ), often collectively defined as hypoxia, are common complications of hemodialysis, associated with increased morbidity and mortality [1]. During hemodialysis, hypoxia is likely the result of numerous contributing mechanisms including multi-organ ischemia [1–3], alkalosis [4] and pulmonary leukocyte sequestration [5]. Current consensus proposes ischemia to be the predominant catalyst, resultant from rapid fluid volume removal and hemodynamic instability [6]. However, in addition to the removal of excess fluid, hemodialysis aims to correct acidosis, typically with an acid buffer such as bicarbonate. Maintenance of optimal serum bicarbonate concentration can reduce mortality [7], thus accurate dialysate bicarbonate prescription is pivotal in the maintenance of homeostasis.

Despite therapeutic benefit, the use of bicarbonate during hemodialysis can also be associated with adverse clinical outcomes. Analysis of 17 031 in-center hemodialysis patients from 11 countries identified an increased all-cause mortality attributed to higher dialysate bicarbonate [8]. Overcompensation of acidemia, inadvertently leading to alkalemia during hemodialysis and the interdialytic period, may contribute to hypoxia and other medical sequelae. For example, cardiac arrhythmias may result from alkalosis caused by decreased potassium and reduced ionized calcium, potentially explaining the high prevalence of sudden cardiac death during hemodialysis [9]. There is also a considerable risk that alkalosis further precipitates intradialytic hypoxia via a leftward shift in the oxyhemoglobin dissociation curve [10].

The role of alkalosis in hemodialysis-induced hypoxia has not been fully investigated. In clinical practice, few hemodialysis units mitigate this risk; individualized bicarbonate prescription and pH assessment prior to treatment are not always routine [8]. An assumption of consistent pre-hemodialysis pH and acidemia may risk sub-therapeutic or toxic serum bicarbonate levels resulting in subclinical hypoxia during hemodialysis and the interdialytic period. In the existing literature, small study populations, and lack of serial pH and  $\text{PaO}_2$  measurements, limit the understanding of this mechanism which prevents effective medical management.

The aim of this study was to comprehensively assess and compare causes of hypoxia during hemodialysis with a view to better understanding the physiological mechanisms contributing to this phenomenon over the course of a typical treatment week.

## MATERIALS AND METHODS

Participants were recruited from University Hospital Coventry and Warwickshire NHS Trust between April and August 2021. During all weekly hemodialysis sessions (HD session 1, Monday/Tuesday; HD session 2, Wednesday/Thursday; HD session 3, Friday/Saturday), blood samples were collected via the arterial-venous fistula/graft at the start of hemodialysis (start-HD), af-

ter 60 min (typical nadir in  $\text{PaO}_2$  during hemodialysis) (60 min-HD) and at the end (end-HD), for assessment of blood gases (Fig. 1). Accordingly, over the course of a standard treatment week, arterial blood gas profiles were compared during and between hemodialysis sessions. To comprehensively assess the predictors of hypoxia during hemodialysis, additional measures were completed during HD session 2, chosen to avoid any effect of higher filtration rates and volumes commonly associated with the first hemodialysis session of the week. Specifically, a blood sample was collected after 15 min (typical nadir in leukocyte count during hemodialysis, thus indirectly indicative of pulmonary leukocyte sequestration) (15 min-HD), and cardiac output (CO) and mean arterial pressure (MAP) were monitored throughout.

## Participants

Adults (>18 years) undergoing three times weekly maintenance hemodialysis, using an arterial-venous fistula or graft, with a minimum hemodialysis vintage of 3 months, were included in the study. Exclusion criteria included use of a central venous catheter, or a planned kidney transplant during the study period. Exclusion criteria were purposely minimal to ensure a study sample representative of the maintenance hemodialysis population. The study abided by the Declaration of Helsinki and was approved by the Health Research Ethics Committee (20/NE/0227) and prospectively registered with ClinicalTrials.gov (NCT04501159). Written informed consent was obtained for all participants.

## Hemodialysis

All participants dialyzed using a synthetic hollow fiber polynephron membrane three times weekly for 3–5 h via an arterial-venous fistula or graft. A standard bicarbonate and acetate dialysate solution was used for all treatments. Filtration rates and volumes were determined by the clinical team depending on fluid status and target weight.

## Blood sampling and analysis

For the assessment of arterial blood gases, whole blood samples were collected from the arterial line diaphragm of the extracorporeal circuit using heparinized syringes (safe Pico aspirator, Radiometer, UK). Arterial blood pH, partial pressure of  $\text{CO}_2$  ( $\text{PaCO}_2$ ),  $\text{O}_2$  availability [ $\text{PaO}_2$  (partial pressure of  $\text{O}_2$ )],  $\text{O}_2$  delivery [ $\text{p50}$  (partial pressure of  $\text{O}_2$  when hemoglobin is 50% saturated)],  $\text{O}_2$  saturation ( $\text{SaO}_2$ ), bicarbonate ( $\text{HCO}_3^-$ ) and electrolytes ( $\text{K}^+$  and  $\text{Ca}^{2+}$ ) were determined immediately using an arterial blood gas analyser (ABL90 Flex blood gas analyzer; Radiometer, UK). The arterial line provided a convenient means of repeated blood sampling. Studies have supported this approach, reporting minimal difference in blood gas measurements between direct arterial and arterial line samples [11–13]. Samples for white blood cell count (WBC) were collected into EDTA tubes.

HD Session 1			HD Session 2				HD Session 3		
Start-HD	60 min-HD	End-HD	Start-HD	15 min-HD	60 min-HD	End-HD	Start-HD	60 min-HD	End-HD
ABG	ABG	ABG	ABG	ABG	ABG	ABG	ABG	ABG	ABG
pH	pH	pH	pH	pH	pH	pH	pH	pH	pH
			CO	CO	CO	CO			
			MAP	MAP	MAP	MAP			
			WBC	WBC	WBC	WBC			

Figure 1: Measurement time-points and parameters during HD sessions 1, 2 and 3. ABG, arterial blood gas.

White blood cell count was determined using a point of care device (HemoCue WBC Total Analyzer, Radiometer, UK). A droplet of whole blood was pipetted onto a hydrophobic surface and suspended in a pre-prepared methylene blue microvette slide. Samples were analyzed after a processing time of 5 min.

### Non-invasive cardiac output monitor

Cardiac output was assessed with bioreactance, using a non-invasive cardiac output monitor (NICOM) device (Starling SV, Baxter, USA). Four dual sensor electrodes were placed on the right and left subclavicular region and superior iliac crest. Each electrode emitted a high-frequency current across the thorax for 30 s. With the returning signal, the processing unit determined the relative phase shift ( $\Delta\phi$ ) of the input signal, relative to the output signal.  $\Delta\phi$  was calculated relative to changes in blood flow through the aorta. This allowed estimation of stroke volume with the equation:  $SV = C \cdot VET \cdot \Delta\phi / \Delta t_{max}$ , where C was a constant of proportionality and VET was the ventricular ejection time determined with electrocardiogramas the time between aortic valve opening and closure.  $\Delta\phi / \Delta t_{max}$  indicated the relative bioreactance phase shift from the injected and returning current after traversing the thorax. CO was subsequently calculated as the product of heart rate and stroke volume. The device has shown acceptable accuracy compared with thermodilution methods [14, 15].

### Sample size

Sample size was determined with G-power using a conventional large multivariate linear regression effect size of 0.35, an alpha of 0.05 and  $\beta$  of 0.95, giving a sample size of  $n = 59$  as sufficient to detect changes in the dependent variable ( $PaO_2$ ) with respect to four predictor variables (pH, CO, WBC, MAP).

### Statistical analysis

All data were assessed for normality using the Shapiro-Wilk test and histogram plots, and expressed in tables, figures and text as mean  $\pm$  standard error (SE) for parametric data, or median and interquartile range for nonparametric data.

Multivariate linear regression was used to compare the dependent ( $PaO_2$ ) and independent variables (pH, CO, WBC, MAP). For comparison of relative changes between participants, the change (delta,  $\Delta$ ) between start-HD and the 15 min-HD, 60 min-HD and end-HD timepoints was calculated for all variables. Correlation coefficients were determined using Pearson's  $r$  or Spearman's  $Rho$  as appropriate. Correlations showing  $P < .25$  were included in each regression model [16]. Collinearity greater than 0.7 warranted exclusion from the model.

Homoscedasticity was assessed by plotting the standardized residuals against the standardized predicted values.  $R^2$  was derived for each model and the standardized  $\beta$  coefficients presented.

Changes in  $PaO_2$ , p50, pH, CO, WBC and MAP during a single hemodialysis session (start-HD, 15 min-HD, 60 min-HD, end-HD) were evaluated using a one-way ANOVA or Friedman test, dependent on normality of distribution. To account for violations of sphericity, degrees of freedom were corrected using the Greenhouse-Geisser ( $<0.75$ ) or Huynh-Feldt ( $>0.75$ ) tests as appropriate. Changes over the course of one week (HD sessions 1, 2, 3), and during each hemodialysis session (start-HD, 60 min-HD, end-HD) were evaluated using a two-way within subjects ANOVA or Friedman test. Post hoc analysis was carried out using a one-way ANOVA or Wilcoxon test after a main effect for group and/or time was identified.  $P < .05$  indicated statistical significance.  $P$ -values were corrected with Bonferroni adjustment for multiple comparisons, and values showing  $P = .000$  were reported as  $P < .001$ . Data were analyzed using SPSS (IBM, version 26).

## RESULTS

Of 149 hemodialysis patients screened, 98 were eligible and 76 agreed to take part in the study. Mean age was  $66 \pm 13$  years, and 24/76 (32%) participants were female (Table 1). Mean hemodialysis vintage was  $82 \pm 84$  months, and the most common primary diagnosis was diabetic nephropathy (20/76, 26%). Filtration volume and rate, and pre- and post-hemodialysis weight, were higher on HD session 1 compared with HD sessions 2 and 3 (Table 2). All other hemodialysis parameters were consistent between HD sessions.

### Predictors of $\Delta PaO_2$

In univariate analysis,  $\Delta pH$  (start-HD to 15 min-HD =  $0.007 \pm 0.003$ ; to 60 min-HD =  $0.02 \pm 0.004$ ; to end-HD =  $0.06 \pm 0.01$ ) was associated with  $\Delta PaO_2$  (start-HD to 15 min-HD =  $-2.45 \pm 0.85$ ; to 60 min-HD =  $-2.74 \pm 1.18$ ; to end-HD =  $0.3 \pm 1.05$  mmHg; Table 3). In the linear regression model,  $\Delta pH$  significantly predicted  $\Delta PaO_2$ , contributing a higher  $\beta$  standardized coefficient than  $\Delta WBC$  count and  $\Delta CO$  at each time point (Table 4).  $\Delta WBC$  count (start-HD to 60 min-HD =  $-0.35 \pm 0.15$ ; to end-HD  $0.15 \pm 0.16 \times 10^9/L$ ) was associated with  $\Delta PaO_2$  at both 60 min-HD and end-HD in the univariate analysis. Despite these associations, WBC count did not significantly contribute to the linear regression model at 60 min-HD or end-HD.  $\Delta CO$  (start-HD to end-HD =  $0.050 \pm 0.2$  L/min) was associated with  $\Delta PaO_2$  from start-HD to end-HD in the univariate analysis but did not significantly contribute to the linear regression model. At 15 min-HD,  $\Delta pH$  accounted for 18.5% of the variation in  $\Delta PaO_2$ .

Table 1: Participant characteristics.

	(n = 76)
Age (years)	66 ± 13
Weight (kg)	81 ± 18
Height (cm)	179 ± 27
BMI (kg/m <sup>2</sup> )	26.8 ± 7.2
Sex (n, male/female)	52/24
Smoking status (n, never/former/current)	41/28/7
Ethnicity (n)	
Black	5
Caucasian	54
Asian	17
Hemodialysis vintage (months)	82 ± 84
Arterio-venous fistula/graft (n)	72/4
Primary diagnosis (n, %)	
Diabetic nephropathy	20 (26)
Glomerulonephritis	16 (21)
Renovascular disease	11 (14)
Hypertensive nephropathy	4 (5)
Pyelonephritis	2 (3)
Hereditary nephropathy	11 (14)
Other	4 (5)
Idiopathic	8 (10)
Comorbidities (n, %)	
Diabetes	20 (26)
Hypertension	34 (45)
Stroke	4 (4)
Coronary artery disease	18 (24)
Peripheral artery disease	6 (8)
Heart failure	3 (4)
Carcinoma	7 (9)
Asthma	3 (4)
COPD	7 (9)
Ulcerative colitis	2 (3)
Medication (n, %)	
Anti-arrhythmic	2 (3)
Anti-hypertensive	62 (82)
Anti-diabetic	25 (33)
Anti-lipid	41 (54)
Corticosteroids	15 (20)
Iron treatment	14 (18)
Erythropoietin	31 (41)
Folic acid	4 (5)
Phosphate binder	41 (54)
Vitamin D	46 (61)
Calcium	28 (37)
Antiplatelet	32 (42)
Anticoagulants	11 (14)
Proton pump inhibitor	39 (51)

Data are presented as mean ± SD or n (%) as appropriate. BMI, body mass index; COPD, chronic obstructive pulmonary disease.

At 60 min-HD,  $\Delta$ pH and  $\Delta$ WBC accounted for 25.0% of the variation in  $\Delta$ PaO<sub>2</sub>. At end-HD,  $\Delta$ pH,  $\Delta$ CO and  $\Delta$ WBC accounted for 14.5% of the variation in  $\Delta$ PaO<sub>2</sub>.

### Hemodynamic and arterial blood gas profile during a single hemodialysis session

Hemodynamics and arterial blood gases fluctuated during HD session 2 (Fig. 2). PaO<sub>2</sub> (O<sub>2</sub> availability) decreased from start-HD to 15 min-HD ( $P = .007$ ), and was lower at 60 min-HD than end-HD ( $P = .042$ ). pH increased incrementally at each time point throughout the session ( $P < .001$ ). White blood cell count was

lower at 15 min-HD compared with start-HD and 60 min-HD but was greater at 60 min-HD than end-HD (all  $P < .001$ ). MAP was lower at 15 min-HD, 60 min-HD and end-HD compared with start-HD (all  $P < .01$ ).

### Arterial blood gas and electrolyte profile over a full treatment week (HD sessions 1, 2 and 3)

Arterial blood gases and electrolytes differed between hemodialysis sessions both in terms of absolute values at each timepoint, and the intradialytic profile (Figs 3 and 4). A total of 17, 25 and 20 participants experienced hypoxemic events (PaO<sub>2</sub> <80 mmHg) during sessions 1, 2 and 3, respectively. Further, the number of participants with SaO<sub>2</sub> <95% was 10, 14 and 8 for sessions 1, 2 and 3, respectively.

During HD session 1, PaO<sub>2</sub> (O<sub>2</sub> availability) decreased from start-HD to 60 min-HD ( $P = .024$ ) (Fig. 3). PaO<sub>2</sub> at end-HD was greater than at 60 min-HD for HD sessions 2 ( $P = .021$ ) and 3 ( $P = .005$ ). However, there was no overall difference in PaO<sub>2</sub> between HD sessions ( $P = .109$ ). At start-HD and 60 min-HD, PaCO<sub>2</sub> was greater during HD sessions 2 and 3 compared with HD session 1 (both  $P < .001$ ). PaCO<sub>2</sub> increased from start-HD to 60 min-HD during all three sessions ( $P < .001$ ). However, only during HD session 3 did PaCO<sub>2</sub> increase from start-HD to end-HD ( $P < .001$ ). During HD session 2, SaO<sub>2</sub> was lower at 60 min-HD and higher at end-HD compared with start-HD ( $P < .001$ ). p50 (O<sub>2</sub> delivery) at start-HD was higher for HD sessions 2 and 3 compared with HD session 1 (both  $P < .001$ ).

Starting pH was greater for HD sessions 2 and 3 compared with HD session 1 ( $P < .001$ ) (Fig. 4). During all sessions, pH at end-HD was greater than at start-HD and 60 min-HD (both  $P < .001$ ). Serum bicarbonate levels at start-HD and 60 min-HD were greater during HD sessions 2 and 3 compared with HD session 1 ( $P < .001$ ). During all sessions, bicarbonate levels increased from start-HD to end-HD ( $P < .001$ ). Potassium levels at start-HD were lower for HD sessions 2 and 3 compared with HD session 1 ( $P < 0.001$ ). Further, at 60 min-HD, potassium was lower in HD session 3 than HD session 1 ( $P = .013$ ). During all sessions, potassium decreased from start-HD to end-HD ( $P < .001$ ). Calcium was greater at 60 min-HD during HD sessions 2 and 3 compared with HD session 1 ( $P = .008$ ). Calcium levels decreased from start-HD to end-HD during HD sessions 2 and 3 ( $P = .008$ ).

## DISCUSSION

This prospective study, investigating the determinants of hypoxia during hemodialysis over the course of a typical treatment week, reports a number of important findings. Firstly, we demonstrated that pH was a stronger predictor of O<sub>2</sub> availability (PaO<sub>2</sub>) than cardiovascular hemodynamics and leukocyte sequestration. Secondly, we observed widespread alkalemia and increasing hemoglobin-O<sub>2</sub> affinity (p50) throughout hemodialysis, in addition to hypokalaemia and decreasing ionized calcium. It is likely that these findings indicate a critical relationship between pH and hemodialysis induced subclinical hypoxia.

Our data are suggestive of extensive alkalemia throughout hemodialysis when dialyzing using a bicarbonate prescription of 36 mmol/L, and highlight the significant role of pH in alterations in PaO<sub>2</sub>, gas exchange and electrolyte concentration. PaO<sub>2</sub> was better predicted by changes in pH compared with CO, WBC and MAP. This association may be explained by alkalemia-induced hypoventilation and altered cellular gas exchange during hemodialysis. In relation to hypoxia, these mechanisms have been described previously [1], although somewhat



Table 2: Hemodialysis parameters.

	HD session 1	HD session 2	HD session 3	P-value
Time (h)	4 (0.25)	4 (0.25)	4 (0.5)	.174
Volume (L)	2.58 ± 0.13	2.30 ± 0.13*	2.26 ± 0.13*	<.001
Filtration rate (mL/h)	714 (391)	669 (464)*	550 (501)*	<.001
Pre weight (kg)	84.0 (27.9)	83.5 (28.0)*	83.4 (27.9)*	<.001
Post weight (kg)	82.0 (27.2)	81.6 (26.8)*	81.2 (27.7)*	<.001
Pump speed (ml/min)	350 (50)	350 (50)	350 (57.5)	.641
Dialysate temp (°C)	35.98 ± 0.02	35.96 ± 0.03	35.89 ± 0.03	.819
NaHCO <sub>3</sub> prescription (mmol/L)	35.97 ± 0.07	35.97 ± 0.06	35.87 ± 0.06	.223
Dialysate fluid composition				
Na <sup>+</sup> (mmol/L)	138 ± 0	138 ± 0	138 ± 0	N/a
K <sup>+</sup> (mmol/L)	1.95 ± 0.06	1.97 ± 0.06	1.95 ± 0.06	.368
Ca <sup>2+</sup> (mmol/L)	1.27 ± 0.02	1.27 ± 0.02	1.27 ± 0.02	N/a
Mg (mmol/L)	0.5 ± 0	0.5 ± 0	0.5 ± 0	N/a
Cl <sup>-</sup> (mmol/L)	108.5 ± 0.07	108.5 ± 0.07	108.5 ± 0.07	.223
HCO <sub>3</sub> (mmol/L)	32 ± 0	32 ± 0	32 ± 0	N/a
Acetate (mmol/L)	3 ± 0	3 ± 0	3 ± 0	N/a
Glucose (g/L)	1.76 ± 0.05	1.77 ± 0.05	1.76 ± 0.05	.368
Osmolarity (mosm/L)	286.3 ± 3.4	292.8 ± 1.6	286.3 ± 3.4	.041

Data are presented as mean ± SE, or median and interquartile range as appropriate; N/a, not applicable.

\*Significant difference compared with HD session 1.

Table 3: Univariate analysis for  $\Delta$ PaO<sub>2</sub> during HD session 2.

$\Delta$ PaO <sub>2</sub>	Correlation coefficient	P-value
15 mins-HD		
$\Delta$ pH	0.430*	<.001
$\Delta$ CO	0.043	.726
$\Delta$ WBC	-0.070	.579
$\Delta$ MAP	-0.018	.885
60 min-HD		
$\Delta$ pH	0.440*	<.001
$\Delta$ CO	-0.010	.934
$\Delta$ WBC	0.266*	.030
$\Delta$ MAP	0.066	0.588
End-HD		
$\Delta$ pH	0.254*	.028
$\Delta$ CO	-0.158*	.180
$\Delta$ WBC	0.168*	.175
$\Delta$ MAP	-0.046	.705

$\Delta$ , change.

\*P < .25.

Table 4: Multivariate regression analysis for  $\Delta$ PaO<sub>2</sub> during HD session 2.

$\Delta$ PaO <sub>2</sub>		P-value
15 min-HD		
Model R <sup>2</sup>	0.185*	<.001
$\Delta$ pH $\beta$	0.430*	<.001
60 min-HD		
Model R <sup>2</sup>	0.250*	<.001
$\Delta$ pH $\beta$	0.448*	<.001
$\Delta$ WBC $\beta$	0.164	.143
End-HD		
Model R <sup>2</sup>	0.145*	.021
$\Delta$ pH $\beta$	0.314*	.011
$\Delta$ CO $\beta$	-0.145	.225
$\Delta$ WBC $\beta$	0.119	.323

$\Delta$ , change;  $\beta$ ,  $\beta$  standardized coefficient.

\*P < .05.

neglected in comparison with the ischemic hypothesis. Many studies have demonstrated impaired CO and tissue perfusion during hemodialysis, most notably that of hypoxia to the myocardium induced by high filtration rates and volumes [6, 17–21]. However, we did not observe a significant decrease in CO during HD session 2. Despite a strong rationale for hypoperfusion as a cause of hemodialysis-induced hypoxia, our data suggest that pH plays a more significant role. Determinants of hemodialysis-induced hypoxia will most likely differ throughout the treatment week, but our data confirm a strong relationship between pH and hypoxia during HD session 2. As a consequence of larger filtration rates and volumes during HD session 1, it is possible that CO and MAP may have a greater influence on PaO<sub>2</sub>; however, we did not collect these data.

Although our data by no means discredit the influence of altered hemodynamics during treatment, supported by decreasing MAP in our study, they do highlight the significant influence of pH changes during hemodialysis. Interestingly, during HD session 2, we found WBC to be better associated with PaO<sub>2</sub>, compared with CO or MAP. Decreasing WBC early in hemodialysis has been shown to indicate leukocyte sequestration in pulmonary tissue resultant from hemodialysis membrane complement activation and subsequent inflammation [5]. Despite the use of biocompatible membranes, our data confirm the occurrence of this phenomenon as indicated by decreased WBC at 15 min-HD. It is likely that a combination of these mechanisms increase susceptibility to hemodialysis induced hypoxia. Nevertheless, our data strongly support prioritizing better pH regulation to mitigate the risks of hemodialysis-induced hypoxia.

The data from our study infer that a bicarbonate prescription  $\geq 36$  mmol/L may be unnecessary for the majority of patients and may even be detrimental due to dysregulated O<sub>2</sub> availability and electrolyte imbalances. It was apparent throughout the treatment week that hemodialysis consistently induced alkalemia and a corresponding decrease in p50 (O<sub>2</sub> delivery). These data indicate a leftward shift in the oxyhemoglobin dissociation curve resulting from increased hemoglobin–O<sub>2</sub> affinity and decreasing 2,3-diphosphoglycerate, these mechanisms being described from early investigations into acid/base changes during

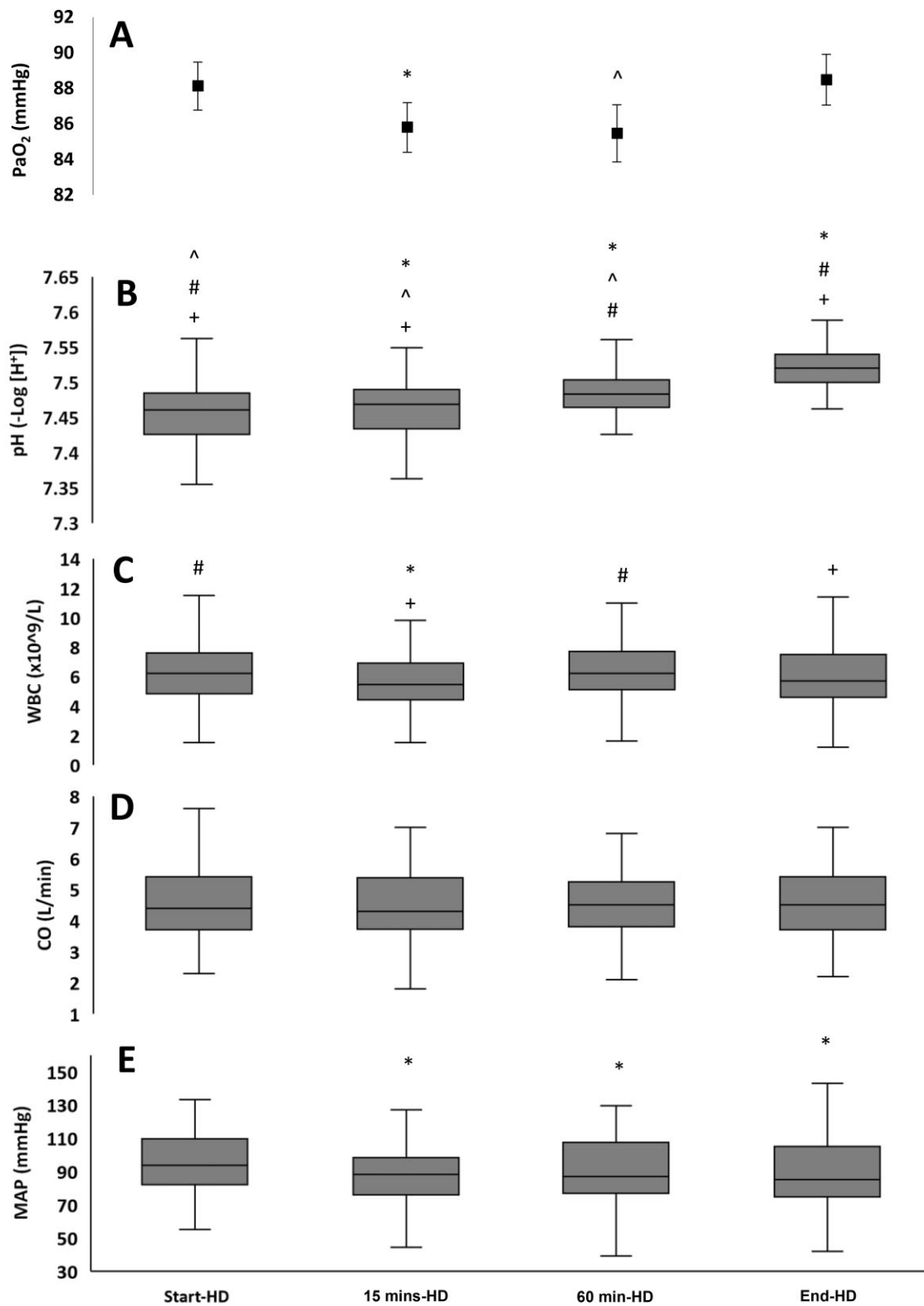
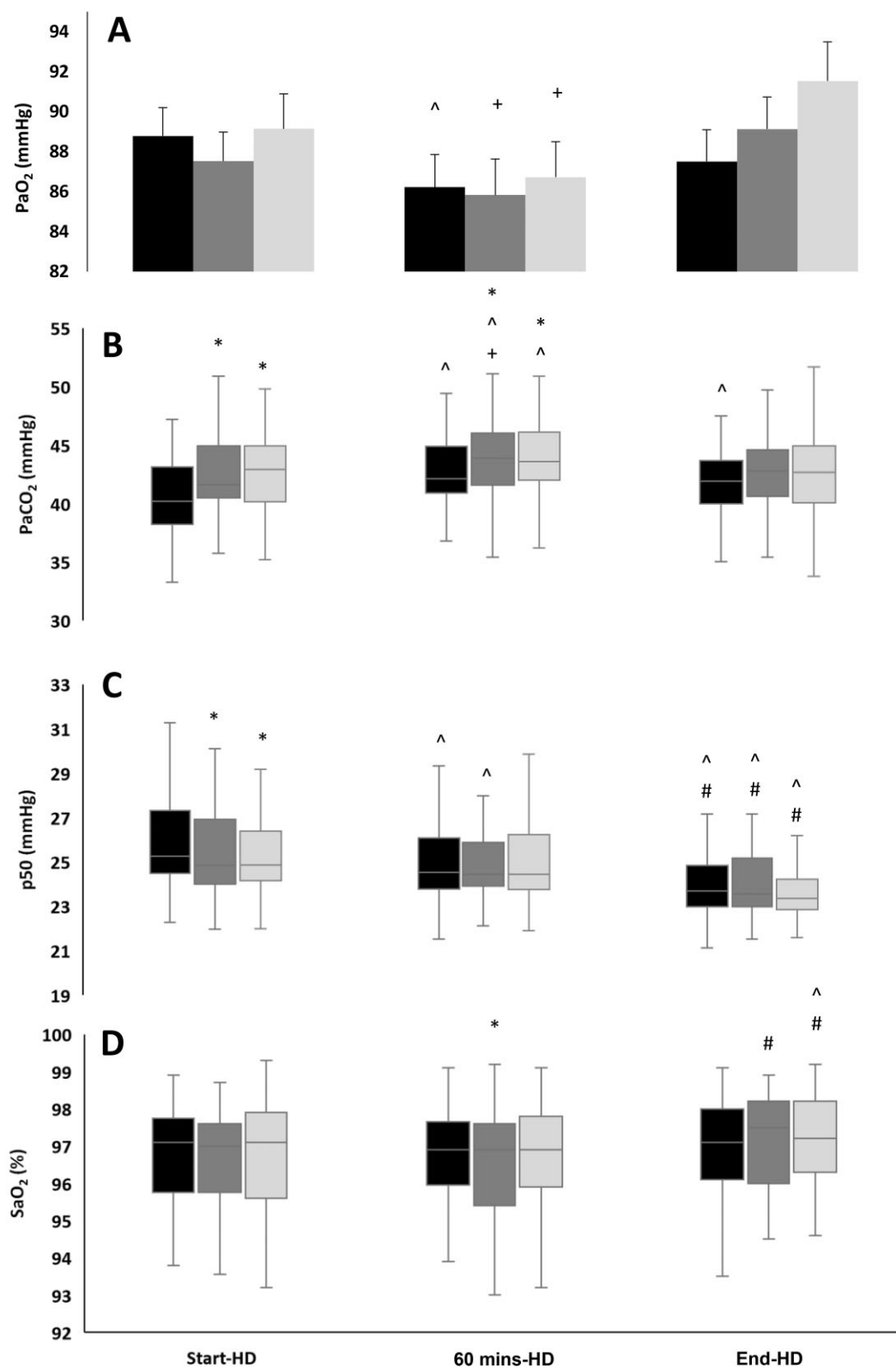


Figure 2: Hemodynamic and arterial blood gas profile during a single hemodialysis session. PaO<sub>2</sub> (A), pH (B), WBC (C), CO (D) and MAP (E), at four time-points during HD session 2 (start-HD, 15 min-HD, 60 min-HD, end-HD). Bar chart data (normally distributed), are mean  $\pm$  SE (A). Box plot data (not normally distributed) are median and interquartile range (B-E). Significant difference to: \*start-HD, #15 min-HD, +60 min-HD, ^end-HD.



**Figure 3:** Arterial blood gas profile over a full treatment week. PaO<sub>2</sub> (A), PaCO<sub>2</sub> (B), p50 (C) and SaO<sub>2</sub> (D) at three time-points (start-HD, 60 min-HD, end-HD) during HD session 1 (black), session 2 (gray) and session 3 (white). Bar chart data (normally distributed), are mean  $\pm$  SE (A). Box plot data (not normally distributed) are median and interquartile range (B–D). Significant difference to: ^ session 1, # start-HD, \* 60 min-HD, + end-HD.



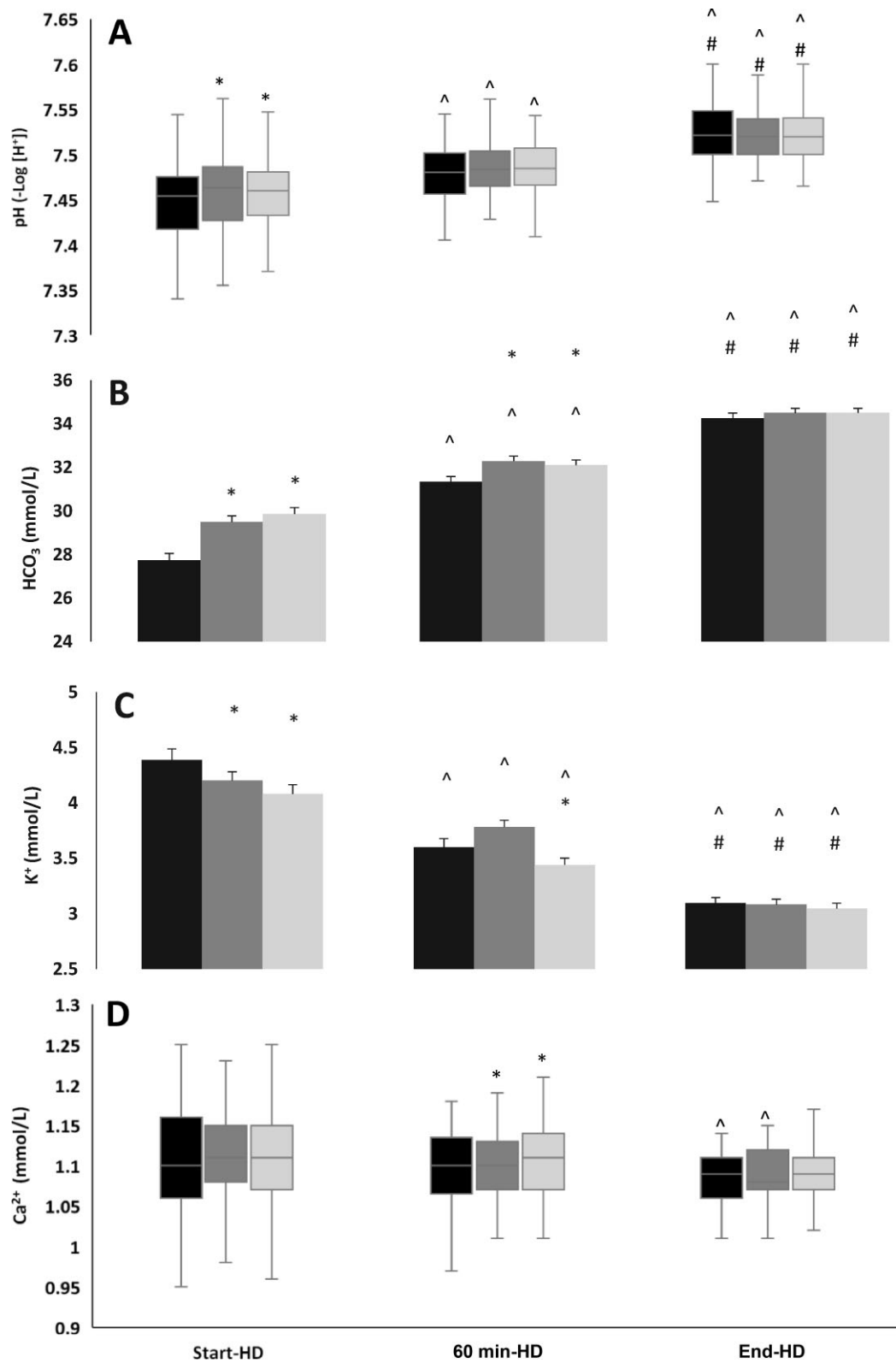


Figure 4: Arterial blood gas profile over a full treatment week. pH (A), HCO<sub>3</sub><sup>-</sup> (B), K<sup>+</sup> (C) and Ca<sup>2+</sup> (D) at three time-points (start-HD, 60 min-HD, end-HD) during HD session 1 (black), session 2 (gray) and session 3 (white). Bar chart data (normally distributed), are mean  $\pm$  SE (B, C). Box plot data (not normally distributed) are median and interquartile range (A, D). Significant difference to: \*session 1, ^start-HD, #60 min-HD.

hemodialysis [4]. We observed an initial reduction in O<sub>2</sub> availability and delivery within the first hour of hemodialysis, potentially contributing to hypoxemia. Mechanisms responsible may include dysregulated ventilation, impaired cellular gas exchange, decreasing MAP and pulmonary leukocyte sequestration [1, 4, 5]. This may help explain previous data demonstrating that hypoxemia during hemodialysis predicts hospitalization and mortality [1].

A key oversight in the literature is that for some individuals the absence of hypoxemia, in response to alkalosis later in hemodialysis, does not necessarily indicate normalized O<sub>2</sub> availability (PaO<sub>2</sub>) and delivery (p50). Cells may still be hypoxic due to decreased O<sub>2</sub> delivery to tissue resultant from augmented hemoglobin–O<sub>2</sub> affinity, somewhat similar to histotoxic hypoxia [1, 4]. This mechanism may obscure impaired O<sub>2</sub> utilization later into treatment, as PaO<sub>2</sub> and SaO<sub>2</sub> will appear to be within normal range. Therefore, the distinction between hypoxemia and alternative mechanisms of hypoxia, such as impaired cellular gas exchange due to alkalosis, is key when assessing the clinical status of the patient. It is likely that the primary cause of hypoxia may change throughout each hemodialysis session and also over the course of a typical treatment week, thus highlighting the complexity of hemodialysis-induced hypoxia. It should be acknowledged that numerous comorbidities may also contribute to hemodialysis-induced hypoxia, such as anaemia, cardiovascular and respiratory disease, and transient phenomena such as osmotic shifts, intradialytic hypotension, hypovolemia and bio-incompatibility [9]. However, our data indicate that shifting acid/base balance during hemodialysis is likely a strong influencing factor on O<sub>2</sub> availability and delivery, and should be considered critical to the maintenance of homeostasis.

Both potassium and calcium levels decreased throughout hemodialysis. Alkalemia during hemodialysis can partially explain these electrolyte shifts and provides a rationale for the prevalence of arrhythmias during and post treatment, these shifts being associated with QTc interval prolongation [8, 22]. Interestingly, decreasing ionized calcium in response to alkalosis may even explain hemodynamic instability, with previous studies showing that higher bicarbonate dialysate corresponded to larger drops in MAP [23]. Additionally, higher bicarbonate prescription has been linked to intradialytic hypotension [8]. Cerebral atrophy and cognitive impairment due to cerebral vascular vasoconstriction and decreasing perfusion may also be linked to alkalemia. Therefore, apparently unrelated complications of treatment may be partially attributed to alkalemia, potentially explaining multiple hemodialysis complications, ranging from headaches and fatigue to cerebral hypoxia, cognitive impairment and fatal arrhythmias [9, 23].

Our data may support numerous mechanisms that contribute to hypoxia during hemodialysis-induced alkalemia and explain multiple complications with treatment. These mechanisms may explain higher bicarbonate prescription predicting hospitalization and mortality in end-stage renal disease, as shown in the Dialysis Outcomes And Practice Patterns Study (DOPPS). For every 4 mEq/L (95% confidence interval 1.01–1.15) higher dialysate bicarbonate, an increased mortality hazard ratio of 1.08 was observed [8]. These data, in combination with our current findings, highlight the importance of averting excessive alkalemia. However, a fine balance is required to maintain serum bicarbonate levels between 18 and 26 mmol/L, thus avoiding similar risks associated with acidemia [7]. This recommendation may be achieved by in-

dividualized bicarbonate prescription, direct monitoring of pH and targeted interventions of acid/base disorders in the interdialytic phase. Our data challenge the understanding of hemodialysis induced hypoxia and emphasize the prognostic importance of avoiding alkalemia for hemodialysis patients.

## Limitations

There are a number of limitations to our study. First, we used the extracorporeal arterial line circuit to measure arterial blood gases. Whilst this may be considered a surrogate of direct arterial blood gas measurement, this approach has been advocated previously as a convenient and accurate measure of oxygen status during hemodialysis [11, 13]. Furthermore, changes in blood gases are likely to present similarly, irrespective of the sampling method. Second, our comparison of the main predictors of hypoxia was restricted to HD session 2, based on this being the most 'stable' session of the week. However, this does mean our data regarding the predictors of hypoxia relate only to this session. Indeed, CO and MAP may contribute more to hypoxia during HD session 1 due to higher filtration rates and volumes. Regardless, our observations during HD session 2 are highly informative in relation to the potential for alkalemia-induced subclinical hypoxia. Finally, we did not include patients using a central venous catheter. However, we suspect that the current data would apply to these patients due to similar dialysate fluid composition and bicarbonate prescription.

## CONCLUSION

In conclusion, pH during hemodialysis was a better predictor of PaO<sub>2</sub> when compared with cardiovascular hemodynamics and WBC count. Our data may highlight the critical role of individualized pH monitoring and personalized dialysate bicarbonate prescription for the mitigation of intra- and interdialytic alkalemia, subclinical hypoxia and many of the complications associated with hemodialysis. Interventional randomized control trials are required to assess whether monitoring pH is efficient in preventing hemodialysis-induced hypoxia, and whether morbidity and mortality can be reduced in these patients.

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## AUTHORS' CONTRIBUTIONS

S.M., G.M., D.J., E.H. and N.K. developed the study; S.M., A.W., S.L.R., F.D. and S.E. were responsible for data collection; S.M. performed the data analysis; S.M. and G.M. prepared the manuscript; D.J., E.H., N.K., A.W., S.L.R., F.D., A.R.M. and S.E. reviewed and approved the final version.

## DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

## CONFLICT OF INTEREST STATEMENT

None declared.

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