






Temporal Changes in Electrolytes, Acid-Base, QTc Duration, and Point-of-Care Ultrasound during Inpatient Hemodialysis Sessions

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Key Points

- Serum chemistry levels, sonographic metrics of extra-vascular volume, and QTc durations are dynamic during HD.
- This research provides comprehensive data on the dynamic changes in physiology during the course of contemporary HD sessions.
- This research illustrates methods for performing point-of-care ultrasound which may enhance volume management for HD patients in the future.

Abstract

Background Of the more than 550,000 patients receiving maintenance hemodialysis (HD) in the United States, each has an average of 1.6 admissions annually (>880,000 inpatient HD sessions). Little is known about the temporal changes in laboratory values, ECGs, and intravascular and extravascular volume during inpatient HD sessions.

Methods In this prospective cohort study of hospitalized HD patients, we assessed intradialytic laboratory values (metabolic panels, blood gases, ionized calcium levels), ECGs, and sonographic measures of volume status.

Results Among 30 participants undergoing HD (mean age 62 years; 53% men, 43% Black) laboratory values had the largest changes in the first hour of HD. There was no significant change in ionized calcium levels pre- to post-HD (change: -0.01 ± 0.07 , $P=0.24$); 12 of 30 and 17 of 30 patients had levels below the lower reference limit at the beginning and end of HD, respectively. The mean pH increased pre- to post-HD (change: 0.06 ± 0.04 , $P<0.001$); 21 of 30 had a pH above the upper reference limit post-HD. There was a trend toward longer median QTc duration from pre- to post-HD (change: 7.5 msec [-5 msec, 19 msec], $P=0.07$). The sum of B lines on lung ultrasound decreased from pre- to post-HD (median decrease: 3 [1, 7], $P<0.01$). The collapsibility index of the inferior vena cava increased pre- to post-HD (median increase: 4.8% [1.5%, 13.4%], $P=0.01$), whereas internal jugular vein diameter did not change ($P=0.24$).

Conclusions Among hospitalized patients undergoing HD, we found dynamic changes in laboratory values, QTc duration, and volume status. Further research is required to assess whether HD prescriptions can be tailored to alter these variations to potentially improve patient outcomes.

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Introduction

Of the more than 550,000 patients receiving maintenance hemodialysis (HD) in the United States (1), each has an average of 1.6 admissions per year (>880,000 inpatient HD sessions) (2). Despite in-hospital monitoring, little is known about the temporal changes in laboratory values, electrocardiograms (ECGs), and intravascular and extravascular volume status during inpatient HD sessions. The risk of complications during HD may be increased in the hospital setting,

where patients often face acute illness that may compromise their hemodynamic stability. Understanding expected changes in electrolytes, pH, cardiac rhythms, and volume status may help the clinician respond more readily when complications such as intradialytic hypotension and arrhythmia occur during HD sessions. For example, both lower serum calcium and potassium levels are associated with longer QTc durations (3). Further, alkalemia promotes intracellular shift of serum potassium (4) and also leads to a

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change in the electrical charge of proteins, which promotes protein-to-calcium complex formation and results in lower ionized calcium concentrations (5); thus, alkalemia may also contribute to QTc prolongation. QTc prolongation represents an important biomarker because it is associated with ventricular arrhythmia (6) and bradyarrhythmia in patients with CKD (7) and is an independent predictor of sudden cardiac death (8) and mortality (9) in patients with ESKD.

Intradialytic hypotension affects 15%–50% of outpatient HD sessions and may be even more prevalent in the inpatient setting where acute illness may affect hemodynamic stability (10, 11). Point-of-care ultrasound provides a unique approach to assess volume shifts in both the extravascular and intravascular spaces. Knowledge of the timing of these shifts in the setting of dialysis may provide the clinician with improved understanding of the etiology of intradialytic hypotension when it occurs in their patients so that they may more readily respond. In the present study, lung ultrasound to assess for pulmonary congestion is used as a proxy for extravascular volume, and the internal jugular vein and inferior vena cava are used as markers of intravascular volume.

The aim of this work is to provide a comprehensive investigation of intradialytic changes with respect to laboratory markers, ECG findings, and point-of-care ultrasound measures of volume status in a cohort of maintenance HD inpatients.

Materials and Methods

Study Population

Patients admitted to Brigham and Women's Hospital in Boston, Massachusetts, from September 2019 through February 2021 were screened for inclusion. Thirty ESKD maintenance HD patients were included. There was a 6-month pause in recruitment after 10 patients were enrolled due to the coronavirus disease 2019 pandemic. Patients were on floor level of care, had been on HD for >90 days, were ≥ 18 years of age, were on thrice-weekly HD with sessions at least 3 hours long, and had capacity to provide informed consent. Patients requiring vasopressor therapy other than midodrine were excluded. Patients with atrial fibrillation, supraventricular tachycardia, and left bundle branch block were excluded because these rhythm abnormalities may compromise the ability to quantify QTc durations. To prevent complications from potential anemia caused by blood draws, patients with acute coronary syndrome or stroke, or the possibility of these complications in the preceding 7 days were excluded, as were patients with hematocrit levels <24% and patients with active bleeding. Given the associated changes in hemodynamics, pregnant patients were also excluded. Patients with active coronavirus disease 2019 infection were excluded. In addition, patients with lung transplant ($n=2$) were excluded from the lung ultrasound image analysis because prior lung surgery could have affected lung ultrasound findings irrespective of volume status. As pneumonia and interstitial lung disease could affect B-line number (12), we performed a sensitivity analysis that additionally excluded patients ($n=1$) with these conditions to assess whether removing this subgroup affected B-line changes during HD.

Study Design

In this prospective cohort study, blood laboratory testing (electrolytes, blood gases, and ionized calcium levels) and ECGs were obtained pre, 1 hour into, and post-HD in a single HD session per participant. Patients underwent point-of-care ultrasound examinations for the assessment of volume status at several time points: lung and inferior vena cava ultrasound were obtained pre, post, and 1 hour post-HD, and internal jugular vein imaging was obtained pre and post-HD. HD prescriptions and ultrafiltration volumes were collected from the medical records. Dialysate prescriptions were not dictated by protocol but rather as deemed clinically indicated by the patient's inpatient nephrology team.

Laboratory Analyses

Blood gas samples were transported on ice immediately to the hospital's central laboratory for processing. As blood was collected *via* the HD machine, blood gas samples were considered central venous when HD was performed through internal jugular access (13) and arterial when arteriovenous access was used (14). At each time point, 6 ml of blood was collected in a lithium heparin tube with gel separator for complete metabolic panels, and 3 ml of blood was collected in a Luer lock syringe for blood gas samples. The lithium heparin tubes were placed on ice and processed at the completion of HD sessions. Blood was centrifuged at 1700g for 15 minutes at 4°C. Plasma supernatant was extracted and pipetted into 0.5 ml aliquots. Samples were stored immediately in a -80°C freezer. At the end of the study, all electrolytes and laboratory measurements, aside from blood gases and ionized calcium levels, which were immediately processed onsite, were batch-processed at Quest Diagnostics using standard techniques.

ECG Analyses

QTc durations were adjudicated by two board-certified cardiologists. Reviewers were blinded to clinical information and imaging time point.

Ultrasound Image Acquisition and Analyses

Images were obtained using a Philips Lumify Ultrasound and were analyzed offline by a core imaging laboratory. Six-second clips were obtained for all images. All ultrasound videos were analyzed offline by a single investigator blinded to clinical data and measurement time point.

Lung ultrasound. Images were acquired in eight chest zones with patients in the supine position, using a phased array transducer (4–1 MHz) in sagittal orientation as described previously (12). For B-line quantification, the highest number of B lines seen at any time during the clip in a single intercostal space was the number of B lines assigned to the image (12). As B-line count quantified in eight lung zones are highly related to 28 zones (Spearman's $\rho=0.93$, $P<0.001$) and are equivalently predictive of cardiovascular events and mortality in HD patients (15), this more feasible method was used in our hospitalized population, consistent with other studies by our group and others (16–18). Zones 1, 2, 5, and 6 captured anterior lung fields, and zones 3, 4, 7, and 8 captured lateral lung fields. The sum of B lines in eight lung zones was used as the B-line count for each patient.

Pleural effusions. The presence of pleural effusions was assessed with patients in the supine position, using the same transducer as for lung ultrasound images. Pleural effusions were assessed laterally on each hemithorax as described previously (19). For the semiquantitative assessment of pleural effusion size, a score was applied to each ultrasound clip (0, no pleural effusion visible; 1, pleural effusion visible in the costophrenic angle only; 2, pleural effusion extends over the costophrenic angle, no clear separation of the lung base from the diaphragm; 3, clear separation between the diaphragm and lung base at all points during the respiratory cycle; and 4, pleural effusion encompasses >50% of the basal pleural cavity) as described previously (19). Pleural effusion fluid burden was estimated for each person at each time point using the sum of pleural effusion scores from bilateral hemithoraces (score range: 0–8).

Inferior vena cava ultrasound. The inferior vena cava was imaged with patients in the supine position, using the transthoracic echocardiographic subcostal view. It was visualized in the sagittal plane just proximal to the junction of the hepatic veins that lie 0.5–3 cm proximal to the ostium of the right atrium. Maximum and minimum diameters were measured from inner-to-inner edge at nonforced end-expiratory and end-inspiratory phases. The collapsibility index was calculated as (end-expiratory diameter–end-inspiratory diameter)/end-expiratory diameter \times 100 (20, 21).

Internal jugular vein ultrasound. Images were acquired with a linear transducer (12–4 MHz) with patients sitting at 45° breathing normally. The right internal jugular vein diameter and area were assessed with the transducer held in transverse orientation and measured with the patient's head turned to the left at two points: just below the jaw and at the level of the clavicle. The largest diameter in the anterior-to-posterior direction from inner-to-inner edge and largest cross-sectional area with the contour traced along the luminal side of the vessel during the clip were measured as the measurements corresponding to end expiration during normal respiration. Similar methods have been described previously (22–25).

Statistical Analyses

Summary statistics were performed using standard approaches according to data distribution. Changes in parameters were estimated by subtracting pre-HD values from post-HD values. Estimates of significant change between time points were performed using the paired *t* test for normally

distributed outcomes and using the Wilcoxon signed-rank test for non-normally distributed outcomes. The intrareader agreement for the total number of B lines across all eight lung zones was tested in 15 patients using Bland–Altman analysis. Similarly, the intrareader agreement for the area and diameter of the internal jugular vein under the jaw and at the level of the clavicle during normal respiration was tested in 15 patients using Bland–Altman analysis. Two-tailed *P* values <0.05 were considered statistically significant without consideration of multiple testing. Missing data were not imputed. Analyses were completed using Stata v16.1 (StataCorp, College Station, TX).

Ethics

The study protocol was reviewed and approved by the Mass General Brigham Institutional Review Board (approval number: 2019P000727), which oversaw all study procedures. All participants provided written informed consent.

Results

Baseline Characteristics

During the recruitment period, 63 patients on the floor level of care HD inpatient list did not meet the inclusion criteria. Thirty-four patients were approached, and 30 of these consented and ultimately participated in this study (see enrollment flow chart shown in Figure 1). The mean age of participants was 62 \pm 12 years; 53% were men; 43% were Black, and 13% were Hispanic. A total of 53% of participants had diabetes mellitus, 60% had history of heart failure, 53% had history of ischemic heart disease, and 53% had obstructive lung disease (chronic obstructive pulmonary disease, asthma, or obstructive sleep apnea; Table 1).

HD Treatment Characteristics

The median duration of HD was 3.75 hours [3.5 hours, 4 hours] with a mean single-pool Kt/V of 1.7 \pm 0.3 and net ultrafiltration volume of 2.1 \pm 1.1 L. Thirteen patients were dialyzed against a 2 mEq/L potassium bath, 13 were dialyzed against a 3 mEq/L potassium bath, and four were dialyzed against a 4 mEq/L potassium bath. Twenty-eight were dialyzed on a 2.5 mEq/L calcium bath; one was on a 2 mEq/L calcium bath, and one was on a 3 mEq/L calcium bath. All patients were on a bicarbonate bath of 35 mEq/L (Table 2).

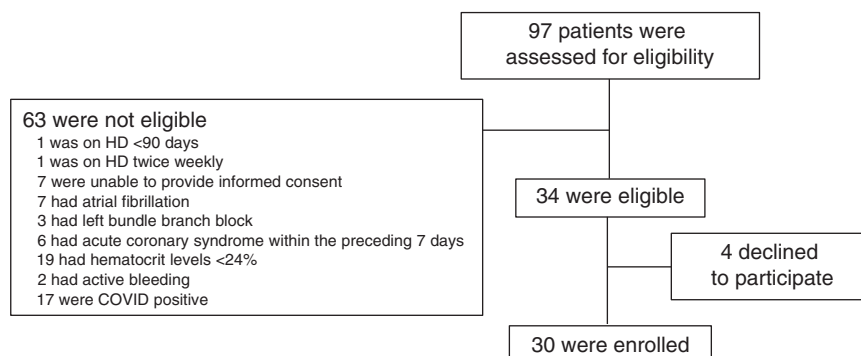


Figure 1. | Enrollment flow chart.

Table 1. Characteristics of the participants

Baseline Characteristics	All subjects (N=30)
Age, yr	62±12
Men, n (%)	16 (53)
Race and ethnicity, n (%)	
White	12 (40)
Black	13 (43)
Other/unknown	5 (17)
Hispanic	4 (13)
Body mass index, kg/m ²	28±7
ESKD vintage, yr	2.6 [1.1, 5.2]
Vascular access, n (%)	
AV fistula	13 (43)
AV graft	7 (23)
Catheter	10 (33)
Comorbid conditions, n (%)	
Diabetes mellitus	16 (53)
Ischemic heart disease	16 (53)
Heart failure	18 (60)
Stroke	2 (7)
Peripheral vascular disease	10 (33)
Obstructive lung disease	16 (53)
Chronic obstructive lung disease	8 (27)
Asthma	6 (20)
Obstructive sleep apnea	9 (30)
Pre-HD systolic blood pressure, mm Hg	137±25
Medication use, n (%)	
Statin	18 (60)
ACEI or ARB	3 (10)
β blockers	17 (57)
Calcium channel blockers	9 (30)
Loop diuretic	0 (0)
Pre-HD QTc, msec	468 [455, 486]
Admission for volume overload, n (%) ^a	6 (2)
Number of Days Admitted on Study Date	4 [3, 6]

Continuous variables are presented as means±SD or median [25th, 75th percentiles]. Obstructive lung disease was classified as any of the following: chronic obstructive lung disease, asthma, or obstructive sleep apnea. AV, arteriovenous; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
^aVolume overload was defined as "fluid overload, pleural effusion, heart failure, or pulmonary edema" as has been defined in a prior validation study (37).

Laboratory Values

Plasma chemistry levels were dynamic, with the most profound changes occurring within the first hour for all biomarkers (shown in Figure 2). Pre-HD, 1 of 30 patients had a pH lower than the reference range (this patient had comorbid chronic obstructive pulmonary disease and obstructive sleep apnea), and 1 of 30 patients had a pH above the reference range (this patient had asthma). One hour into HD, 5 of 29 had a pH above the reference range, and one patient had a pH below the reference range. By the end of HD, 21 of 30 patients had a pH above the reference range, and none had a pH below the reference range. During HD, serum bicarbonate increased (mean increase 4±3 mEq/L, $P<0.001$), whereas pCO₂ levels did not change ($P=0.82$). Nine of 30 patients were hyperkalemic (>5.3 mmol/L) pre-HD, whereas 15 of 30 patients were hypokalemic (<3.5 mmol/L) post-HD. Calcium and

Table 2. Characteristics of the dialysis prescription

Baseline Characteristics	All Subjects (N=66)
Duration of hemodialysis, h	3.75 [3.5, 4]
Session of week, n (%)	
1st	11 (37)
2nd	8 (27)
3rd	11 (37)
spKt/V	1.7±0.3
Predialysis weight, kg	81±21
kg over dry weight target before dialysis	1.6 [0, 3.9]
Net ultrafiltration, L	2.1±1.1
Dialysate flow, ml/min	750 [700, 800]
Blood flow, ml/min	350 [350, 400]
Dialysate potassium, mEq/L, n (%)	
2	13 (43)
3	13 (43)
4	4 (13)
Dialysate calcium, mEq/L, n (%)	
2	1 (3)
2.5	28 (93)
3	1 (3)
Dialysate sodium, mEq/L, n (%)	
140	30 (100)
Dialysate bicarbonate, mEq/L, n (%)	
35	30 (100)

Continuous variables are presented as means±SD or median [25th, 75th percentiles]. One patient was initially on a 3 K bath but was changed to a 4 K bath 60 minutes into her 4-hour-long HD session; this patient was included as a 4 K bath for our analyses. spKt/V, single-pool Kt/V where K=dialyzer clearance of urea, t=dialysis time, and V=volume of distribution of urea.

ionized calcium levels did not change from pre- to post-HD ($P=0.56$ and 0.24 , respectively). Calcium levels also did not change when the two patients on dialysate calcium baths other than 2.5 mEq/L were excluded ($P=0.42$), but there was a drop in ionized calcium levels when patients only on 2.5 mEq/L dialysate calcium baths were assessed (decrease of $0.02±0.05$ mmol/L, $P=0.04$). Full results of laboratory parameters at the pre, 1 hour into, and post-HD time points are shown in Tables 3–5, respectively.

QTc Durations

The median pre-HD QTc was 468 msec [455 msec, 486 msec], the median QTc duration 1 hour into HD was 475 msec [460 msec, 501 msec], and the median post-HD QTc was 480 msec [467 msec, 502 msec]. QTc durations were >500 msec in 6 of 30 patients pre-HD, 8 of 30 patients 1 hour into HD, and 8 of 30 patients post-HD. The median increase in QTc duration on ECG (post-HD QTc minus pre-HD QTc) was 7.5 msec [−5 msec, 19 msec].

Volume Status

The median sum of B lines on lung ultrasound in eight zones was nine [5, 18] pre-HD, five [3, 9] post-HD, and four [2, 9] 1 hour post-HD (Figure 3, Table 6). The sum of B lines in eight zones decreased from pre- to post-HD (median decrease: 3 [1, 7], $P<0.01$) and from pre to 1 hour post-HD (median decrease: 4 [0, 8], $P=0.02$). The sum of B lines in

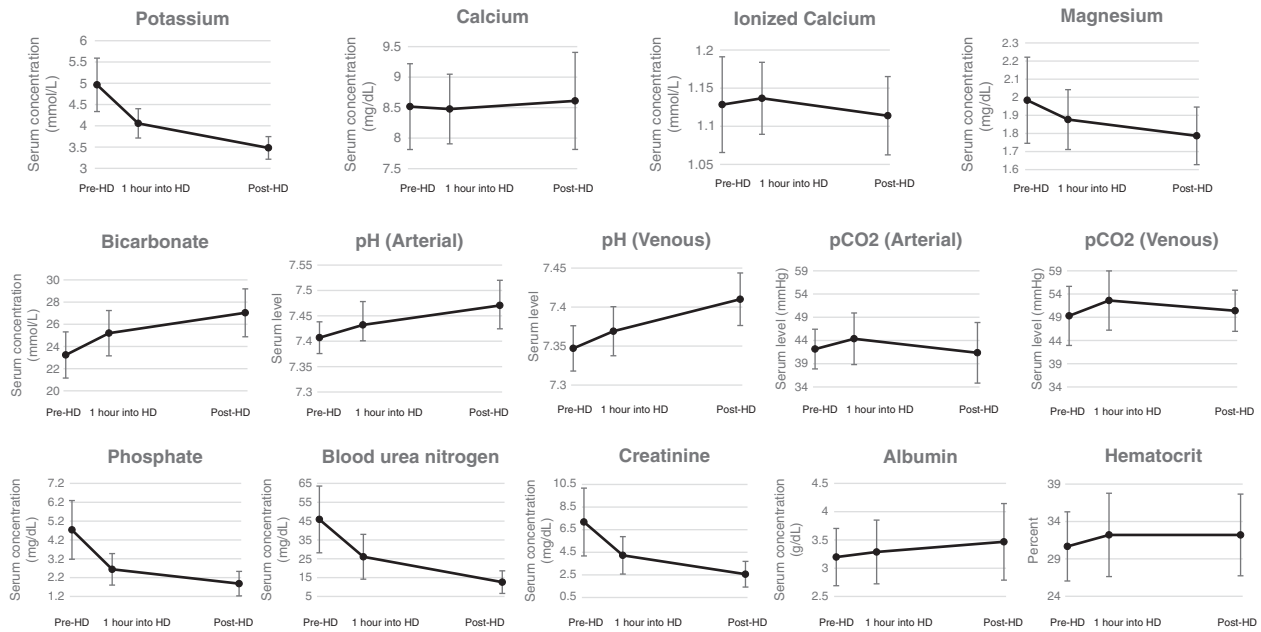


Figure 2. | Intradialytic serum laboratory levels.

eight zones also showed a trend toward continued decrease from post-HD to 1 hour post-HD (median decrease: 2 [0, 3], $P=0.05$). Pre-HD, 17 of 28 individuals had at least one lung zone with three or more B lines. Post-HD, 11 of 24 individuals had at least one lung zone with three or more B lines. One hour post-HD, 7 of 22 individuals had at least one lung zone with three or more B lines (Table 6). In sensitivity analyses in which one patient was excluded for having pneumonia, B lines still decreased from pre- to post-HD (median

decrease: 2 [1, 4], $P=0.01$) and from pre to 1 hour post-HD (median decrease: 4 [0, 8], $P=0.02$).

Pleural effusions were rare at any point during HD (median scores: pre-HD 0 [0, 0], post-HD 0 [0, 0.5], and 1 hour post-HD 0 [0, 0]), and the median pleural effusion score did not change from pre- to post-HD ($P=1$; Table 6).

Although the median end-expiratory inferior vena cava diameter did not change from pre- to post-HD ($n=13$, $P=0.27$), the median end-inspiratory diameter decreased

Table 3. Electrolyte and laboratory values pre-HD

Laboratory Parameter	Pre-HD Value, Mean±SD, n	Lower Limit of Normal	Frequency of Pre-HD Concentrations below the Lower Limit of Normal, n (%)	Upper Limit of Normal	Frequency of Pre-HD Concentrations above the Upper Limit of Normal, n (%)
Potassium, mEq/L	5±0.6, 30	<3.5	0 (0)	>5.3	9 (30)
Bicarbonate, mEq/L	23±2, 30	<20	2 (7)	>32	0 (0)
pH (arterial)	7.41±0.03, 20	<7.35	0 (0)	>7.45	1 (5)
Carbon dioxide (arterial), mm Hg	42±4, 20	<36	1 (5)	>47	4 (20)
pH (central venous)	7.35±0.03, 10	<7.3	1 (10)	>7.4	0 (0)
Carbon dioxide (central venous), mm Hg	49±6, 10	<38	0 (0)	>50	3 (30)
Calcium, mg/dl	8.5±0.7, 30	<8.6	16 (53)	>10.3	0 (0)
Ionized calcium, mmol/L	1.13±0.06, 30	<1.13	12 (40)	>1.32	0 (0)
Magnesium, mg/dl	2±0.2, 30	<1.5	0 (0)	>2.5	1 (3)
Phosphate, mg/dl	4.7±1.6, 30	<2.5	2 (7)	>4.5	16 (53)
BUN, mg/dl	46±18, 30	<7	0 (0)	>25	26 (87)
Creatinine, mg/dl	7.1±3, 30	<0.6	0 (0)	>1.35	30 (100)
Albumin, g/dl	3.2±0.5, 30	<3.6	23 (77)	>5.1	0 (0)
HCT, %	31±5, 30	<36	25 (83)	>48	0 (0)

Percent of sessions with a value above or below the limits of normal are calculated as $N_{\text{measurement outside of limits of normal}} / N_{\text{total measurements}}$. pH and pCO₂ were arterial if drawn from arteriovenous access and central venous if drawn from a central line (13, 14). HCT, hematocrit; HD, hemodialysis.

Table 4. Electrolyte and laboratory values pre- and 1 hour into HD

Laboratory Parameter	Pre-HD Value, Mean±SD, n Subjects	1 Hour into HD Value, mean±SD, n Subjects	Δ (1 Hour into HD minus Pre-HD), Mean±SD, n Subjects	P Value (1 Hour into Pre-HD)	Lower Limit of Normal	Frequency of 1 Hour into HD Concentrations		Frequency of 1 Hour into HD Concentrations above the Upper Limit of Normal, n (%)
						Below the Lower Limit of Normal, n (%)	Upper Limit of Normal	
Potassium, mEq/L	5±0.6, 30	4.1±0.3, 30	-0.9±0.4, 30	<0.001	<3.5	0 (0)	>5.3	0 (0)
Bicarbonate, mEq/L	23±2, 30	25±2, 30	2±3, 30	<0.001	<20	0 (0)	>32	0 (0)
pH (arterial)	7.41±0.03, 20	7.43±0.05, 19	0.02±0.03, 19	<0.01	<7.35	1 (5)	>7.45	5 (26)
Carbon dioxide (arterial), mm Hg	42±4, 20	44±6, 19	2±4, 19	0.03	<36	1 (5)	>47	5 (26)
pH (central venous)	7.35±0.03, 10	7.37±0.03, 10	0.02±0.02, 10	0.01	<7.3	0 (0)	>7.4	0 (0)
Carbon dioxide (central venous), mm Hg	49±6, 10	53±6, 10	3±3, 10	<0.01	<38	0 (0)	>50	6 (60)
Calcium, mg/dl	8.5±0.7, 30	8.5±0.6, 30	0±0.5, 30	0.67	<8.6	15 (50)	>10.3	0 (0)
Ionized calcium, mmol/L	1.13±0.06, 30	1.14±0.05, 30	0.01±0.06, 30	0.43	<1.13	12 (40)	>1.32	0 (0)
Magnesium, mg/dl	2±0.2, 30	1.9±0.2, 30	-0.1±0.1, 30	<0.001	<1.5	0 (0)	>2.5	0 (0)
Phosphate, mg/dl	4.7±1.6, 30	2.6±0.8, 30	-2.1±1, 30	<0.001	<2.5	13 (43)	>4.5	1 (3)
BUN, mg/dl	46±18, 30	26±12, 30	-20±8, 30	<0.001	<7	1 (3)	>25	16 (53)
Creatinine, mg/dl	7.1±3, 30	4.2±1.7, 30	-2.9±1.6, 30	<0.001	<0.6	0 (0)	>1.35	30 (100)
Albumin, g/dl	3.2±0.5, 30	3.3±0.6, 30	0.1±0.2, 30	<0.01	<3.6	21 (70)	>5.1	0 (0)
HCT, %	31±5, 30	32±6, 29	2±6, 29	0.13	<36	22 (76)	>48	0 (0)

Mean differences (Δ) were calculated using data from subjects who had both pre and post measurement for each given value. Percent of sessions with a value above or below the limits of normal are calculated as $N_{\text{measurement outside of limits of normal}}/N_{\text{total measurements}}$. pH and pCO₂ were arterial if drawn from arteriovenous access and central venous if drawn from a central line (13, 14). HCT, hematocrit; HD, hemodialysis.

($n=13$, median decrease: 0.2 cm [0.0 cm, 0.3 cm], $P<0.01$), and the inferior vena cava collapsibility index increased ($n=13$, median increase: 4.8% [1.5%, 13.4%], $P=0.01$). The collapsibility index trended toward being higher post-HD compared with 1 hour post-HD ($n=10$, median decrease: 1 hour post compared with post-HD 10.5% [-2.2%, 20.2%], $P=0.08$). The collapsibility index pre compared with 1 hour post-HD was unchanged ($N=9$, $P=0.5$; Table 6).

The internal jugular vein diameter did not change from pre- to post-HD just below the jaw ($P=0.67$) or at the level of the clavicle ($P=0.24$). Similarly, the area did not change from pre- to post-HD just below the jaw ($P=0.26$) or at the level of the clavicle ($P=0.37$; Table 6; example images shown in Figure 4). Results were unchanged when patients with right internal jugular dialysis catheters were excluded (data not shown).

With regard to the intrareader agreement analysis, the mean B-line difference for the total number of B lines in 15 patients was 0.67 (95% CI, -3.63 to 4.96; Spearman's $\rho=0.98$; $P<0.001$). Moreover, the mean difference in area and diameter of the internal jugular vein under the jaw during normal respiration in 15 patients was -0.012 cm² (95% CI, -0.18 to 0.20 cm²) and -0.036 cm (95% CI, -0.23 to 0.15 cm), respectively (Spearman's $\rho=0.93$ [$P<0.001$] and 0.92 [$P<0.001$], respectively). The mean difference in area and diameter of the internal jugular vein at the level of the clavicle during normal respiration in 15 patients was -0.008 cm² (95% CI, -0.11 to 0.13 cm²) and -0.006 cm (95% CI, -0.08 to 0.07 cm), respectively (Spearman's $\rho=0.98$ [$P<0.001$] and 1 [$P<0.001$], respectively).

In this comprehensive physiology study of individuals receiving inpatient HD, marked changes in electrolytes, acid-base, electrocardiography, and sonographic measures

of volume status are described. Significant proportions of patients finish HD with electrolyte abnormalities and with evidence of pulmonary congestion, despite having just undergone ultrafiltration.

One of the novel aspects of our study is that it includes data on serum laboratory parameters 1 hour into HD and post-HD. These time points have rarely been studied in research settings, are infrequently obtained in clinical practice, and add to our prior data describing rebound changes in electrolytes in the hours just post-HD (26). Further research is required to determine how changes in laboratory parameters during and just at the end of HD may relate to patient symptoms and outcomes.

The frequency of abnormal acid-base status during HD is noteworthy. One patient presented to HD with acidosis and one with alkalosis, respectively, whereas more than two thirds of participants had alkalosis post-HD. Concomitantly, serum bicarbonate increased during HD, whereas pCO₂ did not change. Predialysis acidosis in HD patients is associated with catabolism of protein consumed as part of a normal diet, whereas relative alkalosis in this population may be a marker of inadequate nutrition (27). Alkalosis (pre-HD pH ≥ 7.40 compared with 7.30-7.34) was associated with higher risk of all-cause and cardiovascular mortality in 15,132 outpatients observed in Japan (28). Especially in the setting of acute illness, poor nutrition and associated alkalosis may be a concern. For hospitalized patients, acid-base physiology is a highly relevant issue affected not only by nutrition, but also by pathologic acid production (e.g., lactic acidosis), HD prescriptions, and other factors in the setting of acute illness. Patients in the inpatient setting may have a greater tendency to be undernourished, with less acid generation between HD sessions

Table 5. Electrolyte and laboratory values pre and immediately post-HD

Laboratory Parameter	Pre-HD Value, Mean±SD, n Subjects	Post-HD Value, Mean±SD, N Subjects	Δ (Post-HD minus Pre-HD), Mean±SD, n Subjects	P Value (Post-versus Pre-HD)	Lower Limit of Normal	Frequency of Post-HD Concentrations	
						below the Lower Limit of Normal, n Subjects	above the Upper Limit of Normal, n Subjects
Potassium, mEq/L	5±0.6, 30	3.5±0.3, 30	-1.5±0.7, 30	<0.001	<3.5	15 (50)	>5.3 0 (0)
Bicarbonate, mEq/L	23±2, 30	27±2, 30	4±3, 30	<0.001	<20	0 (0)	>32 0 (0)
pH (arterial)	7.41±0.03, 20	7.47±0.05, 20	0.06±0.04, 20	<0.001	<7.35	0 (0)	>7.45 14 (70)
Carbon dioxide (arterial), mm Hg	42±4, 20	41±7, 20	-1±4, 20	0.38	<36	3 (15)	>47 4 (20)
pH (central venous)	7.35±0.03, 10	7.41±0.03, 10	0.06±0.03, 10	<0.001	<7.3	0 (0)	>7.4 7 (70)
Carbon dioxide (central venous), mm Hg	49±6, 10	50±4, 10	1±3, 10	0.34	<38	0 (0)	>50 4 (40)
Calcium, mg/dl	8.5±0.7, 30	8.6±0.8, 30	0.1±0.9, 30	0.56	<8.6	12 (40)	>10.3 0 (0)
Ionized calcium, mmol/L	1.13±0.06, 30	1.11±0.05, 29	-0.01±0.07, 29	0.24	<1.13	17 (59)	>1.32 0 (0)
Magnesium, mg/dl	2±0.2, 30	1.8±0.2, 30	-0.2±0.2, 30	<0.001	<1.5	1 (3)	>2.5 0 (0)
Phosphate, mg/dl	4.7±1.6, 30	1.9±0.6, 30	-2.9±1.2, 30	<0.001	<2.5	26 (87)	>4.5 0 (0)
BUN, mg/dl	46±18, 30	13±6, 30	-33±14, 30	<0.001	<7	6 (20)	>25 1 (3)
Creatinine, mg/dl	7.1±3, 30	2.5±1.1, 30	-4.6±2.2, 30	<0.001	<0.6	0 (0)	>1.35 24 (80)
Albumin, g/dl	3.2±0.5, 30	3.5±0.7, 30	0.3±0.3, 30	<0.001	<3.6	18 (60)	>5.1 0 (0)
HCT, %	31±5, 30	32±5, 30	2±5, 30	0.1	<36	24 (80)	>48 1 (3)

Mean differences (Δ) were calculated using data from subjects who had both pre and post measurement for each given parameter. Percent of sessions with a value above or below the limits of normal are calculated as $N_{\text{measurement outside of limits of normal}} / N_{\text{total measurements}}$. Two participants had phosphate levels <1 post-HD; for calculation of the intra-HD change and post-HD mean, post-HD phosphate was replaced with 1 mg/dL in these individuals. pH and pCO₂ were arterial if drawn from arteriovenous access and central venous if drawn from a central line (13, 14). HCT, hematocrit; HD, hemodialysis.

and subsequently higher pre-HD serum bicarbonate, compared with stable outpatients. The post-HD alkalosis appears to be mostly driven by the bicarbonate load delivered during HD. Further research is required to determine optimal pH balance, whether dialysate bicarbonate prescriptions can be personalized to reach this optimal balance, and whether these manipulations can improve outcomes in the inpatient setting.

Ionized calcium concentrations, which provide information about free calcium levels available to cardiac myocytes that facilitate normal cardiac conduction, are rarely measured in clinical practice. Rather, serum calcium, which includes calcium bound to protein, is typically measured. In the present study, it appears that calcium, measured as total

or ionized serum calcium levels, remains relatively stable during HD, and is low in about half of these patients throughout the HD session. Due to concerns for vascular calcification, dialysate calcium prescriptions have decreased in recent years (29). Prior research suggests that a dialysate calcium of 2.75 mEq/L may lead to a net zero intradialytic calcium balance (29), and the lower dialysate calcium prescriptions seen in this study could be contributing to the low ionized calcium levels observed in these patients. The long-term risks for vascular calcification may be decreased by lower calcium baths; however, given that the mortality rate of ESKD patients is very high at about 15%–20% per year (30), further studies should assess whether this long-term benefit outweighs the short-term risk for increased arrhythmia and hypotension associated with lower dialysate calcium concentrations in the maintenance HD patient population (31, 32). Although changing dialysate concentrations appropriately may be limited in the inpatient setting by short times between morning blood draws and HD sessions, research on this is especially indicated in the hospital setting where patients may face compromise to their hemodynamics and cardiac electrophysiology in the setting of acute illness that may place them at even higher risk for arrhythmia.

In our cohort, QTc durations were >500 msec in a substantial proportion of patients. QTc prolongation is associated with arrhythmia in patients with CKD (6, 7) and is an independent predictor of sudden cardiac death (8) and mortality (9) in patients with ESKD. Lower serum calcium and potassium levels are associated with longer QTc durations (3). Further, alkalosis, which we noted occurred frequently, drives potassium intracellularly and increases

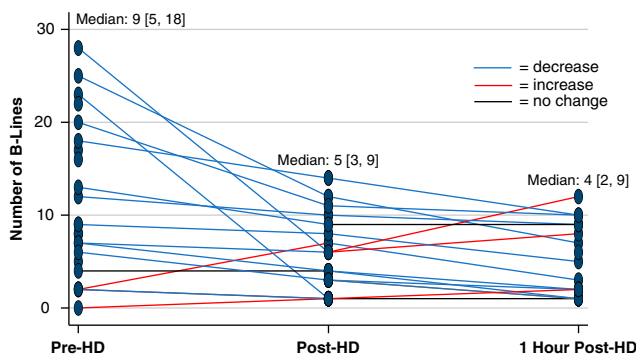


Figure 3. | Spaghetti plot demonstrating individual changes in B lines over the course of hemodialysis.

Table 6. Trajectory of ultrasound measures during the course of HD

Ultrasound Category	Pre-HD Median [25th, 75th Percentiles], <i>n</i> Subjects	Post-HD Median [25th, 75th Percentiles], <i>n</i> Subjects	1 Hour Post-HD Median [25th, 75th percentiles], <i>n</i> Subjects	<i>P</i> Value Difference Pre- to Post-HD
Lung				
B-line count in eight lung zones	9 [5, 18], 23	5 [3, 9], 18	4 [2, 9], 18	<0.01
Pleural effusion score	0 [0, 0], 18	0 [0, 0.5], 16	0 [0, 0], 17	1
Inferior vena cava				
Diameter at end-expiration, cm	2 [1.5, 2.3], 21	1.8 [1.4, 2], 15	2.1 [1.8, 2.2], 14	0.27
Diameter at end inspiration, cm	1.6 [1, 1.8], 20	1.4 [0.8, 1.6], 15	1.5 [1.1, 1.8], 12	<0.01
Inferior vena cava collapsibility index, %	24.7 [15.6, 32.5], 20	26.2 [16.6, 38.5], 15	23.1 [16.3, 33.3], 12	0.01
Internal jugular vein				
Diameter level of clavicle, cm	1 [0.7, 1.3], 27	0.9 [0.8, 1.3], 23		0.24
Diameter below jaw, cm	0.7 [0.4, 1], 26	0.7 [0.4, 0.9], 21		0.67
Area level of clavicle, cm ²	1 [0.6, 1.4], 26	0.9 [0.6, 1.5], 23		0.37
Area below jaw, cm ²	0.6 [0.2, 1], 25	0.4 [0.3, 0.8], 21		0.26

calcium-to-protein binding, thus also decreasing these electrolyte levels (4, 5). This may partially explain prior observations of QTc prolongation during HD with higher dialysate bicarbonate levels (33). Although dialysate potassium prescriptions were commonly adjusted in response to pre-HD serum concentrations in this study, dialysate bicarbonate and calcium baths had little variation. Given that changing dialysate concentrations is simple and cost neutral and that higher dialysate bicarbonate and lower dialysate calcium are associated with greater intra-HD QTc prolongation (as are lower potassium baths) (33), robust clinical trials are urgently needed to delineate how HD prescriptions may contribute to QTc prolongation and dysrhythmia in the peri-HD setting and whether dialysate prescriptions with personalized bicarbonate and calcium baths may prevent dysrhythmia from occurring.

As expected, volume status was also dynamic during HD sessions. Many patients had sonographic evidence of pulmonary congestion and continued to have evidence of this post-HD. There was a decrease in the sum of pulmonary B lines in eight lung zones in post compared with pre-HD, suggesting that extravascular volume in the lungs is removed during HD, as described previously (34). However, many patients continued to demonstrate at least three B lines in one or more lung zone—a finding that is associated with higher risk of rehospitalization for hypervolemia in patients with chronic heart failure (35). Our data show that the internal jugular vein diameter did not change during HD. This is consistent with prior findings that showed the internal jugular vein aspect ratio (anteroposterior diameter/lateral diameter) did not change significantly from pre- to post-HD (36). Given the observed decrease in B lines, without change in internal jugular vein diameter, it is possible that plasma refilling occurred quickly during HD in our

cohort. However, our findings also demonstrate increased inferior vena cava collapsibility post compared with pre-HD. Interestingly, this collapsibility decreased back to pre-HD levels 1-hour post-HD. The trend toward continued decrease in B lines 1 hour post compared with post-HD with the simultaneous rebound decrease in collapsibility of the inferior vena cava may suggest continued mobilization of volume from the extra- to intravascular space in the hour after HD. Further studies to measure intracardiac filling pressures invasively would be helpful in assessing intravascular volume during HD and whether internal jugular vein and inferior vena cava ultrasound can be used as accurate surrogates of intravascular volume status.

There are several strengths to the present study. It is novel for its comprehensive and serial collection of laboratory tests during HD, including blood gases and ionized calcium levels. Further, it provides not only pre- and post-HD electrolyte data, but also an assessment during HD at the 1-hour mark. Additionally, ultrasound techniques to assess both intra- and extravascular volume during HD sessions in the inpatient setting were applied with the reader blinded to intradialytic time point. Further, we demonstrate the feasibility of the simplified eight lung zone method employed by a nephrologist to identify volume changes that occur during HD sessions. Despite these strengths, some limitations deserve consideration. First, guidelines in relation to HD prescriptions were not specified because the present study aimed to observe real-world changes. In addition, obtaining inferior vena cava data was only feasible in 12 patients at all time points. These data should therefore be interpreted with caution. Although this marker provided useful information regarding intravascular volume for our study, difficulty positioning the inpatient dialysis patient during HD compromised optimal

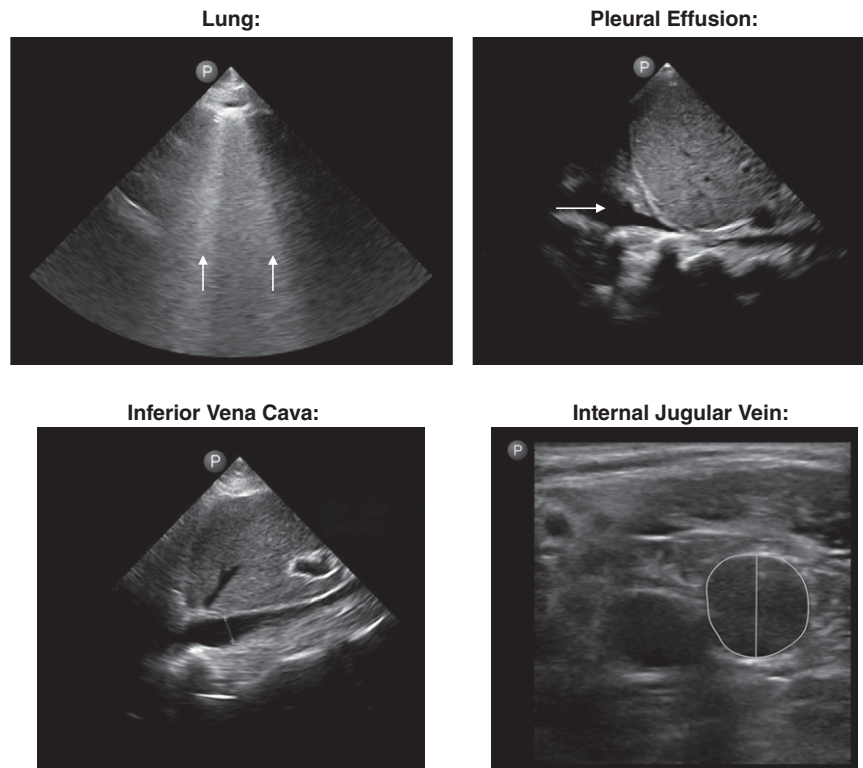


Figure 4. | Example lung, diaphragm, inferior vena cava, and internal jugular vein images obtained by the nephrologist investigator for this study. Arrows indicate B lines on the lung image and a pleural effusion on the pleural effusion image. The diameter is labeled on the image of the inferior vena cava, and the diameter and area are labeled on the image of the internal jugular vein.

imaging. To save the patient from additional study time, images were obtained during HD. In an ideal clinical setting, these images should be obtained with the patient off the HD machine for optimal positioning. It should also be noted that we do not have data regarding the degree of tricuspid regurgitation in this cohort, which could affect internal jugular vein measurements. Further, with regard to lung ultrasound, our analysis of B lines in anterior and lateral lung fields may have missed B lines in posterior lung fields, which may be particularly relevant in inpatients who spent most hours before their lung ultrasound exams in bed. Additionally, given concerns that contributing to anemia with additional blood draws might contribute to ischemia, patients with recent acute coronary syndrome or stroke were excluded from this study, which may compromise generalizability to the larger maintenance HD inpatient population. A final concern is that as this was a single-center study on 30 patients, the results may not be generalizable to the wider hospitalized maintenance HD population.

In conclusion, among hospitalized patients undergoing HD, dynamic changes in blood chemistry parameters, QTc durations, and volume status occur during their HD sessions. These data describe the time course of changes in important clinical parameters during an inpatient HD session that may be useful for clinicians evaluating adverse patient symptoms or events related to HD. Further research is required to assess how variations in these changes during HD are associated with clinical outcomes and whether HD prescriptions can be tailored to optimize patient care.

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Author Contributions

K.A. Curtis and K.S. Ravi were responsible for project administration; F.R. McCausland and E. Platz were responsible for supervision; K.S. Ravi was responsible for funding acquisition; all

authors were responsible for conceptualization, data curation, formal analysis, investigation, and methodology, wrote the original draft of the manuscript and reviewed and edited the manuscript; and all authors agree to be accountable for ensuring that all questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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