Title

Ultrafiltration during intermittent hemodialysis in dogs with acute kidney injury

Journal

Journal of Veterinary Internal Medicine, 37(3)

ISSN

0891-6640

Authors

Kopecny, Lucy
Palm, Carrie A
Segev, Gilad
et al.

Publication Date

2023-05-01

DOI

10.1111/jvim.16649

Peer reviewed

Received: 3 April 2022 | Accepted: 1 February 2023

DOI: 10.1111/jvim.16649

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Ultrafiltration during intermittent hemodialysis in dogs with acute kidney injury

Lucy Kopecny[1] | Carrie A. Palm[1] | Gilad Segev[2] | Larry D. Cowgill[1]

[1]Department of Veterinary Medicine and Epidemiology, University of California, Davis, Davis, California, USA

[2]Koret School of Veterinary Medicine, The Robert H. Smith Faculty of Agriculture, Food and Environment, Hebrew University of Jerusalem, Jerusalem, Israel

Correspondence
Lucy Kopecny, Small Animal Specialist Hospital, 1 Richardson Place, North Ryde, NSW 2113, Australia.
Email: lucy.kopecny@gmail.com

Abstract

Background: Ultrafiltration is performed to alleviate fluid overload in dogs with acute kidney injury (AKI) undergoing intermittent hemodialysis (IHD).

Objectives: To describe prescription patterns for ultrafiltration in dogs receiving IHD for AKI and risk factors for ultrafiltration-related complications.

Animals: Seventy-seven dogs undergoing 144 IHD treatments between 2009 and 2019.

Methods: Medical records of dogs receiving IHD for AKI were reviewed. The initial 3 IHD treatments in which ultrafiltration was prescribed were included. Ultrafiltration-related complications were defined as those requiring an intervention such as transient or permanent discontinuation of ultrafiltration.

Results: Mean fluid removal rate per treatment was 8.1 ± 4.5 mL/kg/h. Ultrafiltration-related complications occurred in 37/144 (25.7%) of treatments. Hypotension was rare (6/144, 4.2% of treatments). No ultrafiltration-related complications resulted in deaths. The mean prescribed fluid removal rate per treatment was higher in dogs with ultrafiltration-related complications than without (10.8 ± 4.9 mL/kg/h vs 8.8 ± 5.1 mL/kg/h, respectively; $P = .03$). The mean delivered fluid removal rate per treatment was significantly lower in dogs with UF-related complications compared to those without complications (6.8 ± 4.0 mL/kg/h vs 8.6 ± 4.6 mL/kg/h, respectively; $P = .04$). Variables associated with ultrafiltration-related complications ($P < .05$) included central venous oxygen saturation, body temperature before IHD treatment, total extracorporeal circuit volume and BUN at the end of IHD treatment.

Conclusions and Clinical Importance: Ultrafiltration during IHD in dogs with AKI is overall safe. Higher prescribed ultrafiltration rates were associated with increased risk of complications. Decrease in central venous oxygen saturation is associated with ultrafiltration-related complications, emphasizing the utility of in-line blood monitoring.

Abbreviations: AKI, acute kidney injury; bpm, beats per minute; BUN, blood urea nitrogen; IHD, intermittent hemodialysis; IQR, interquartile range; OR, odds ratio; PCV, packed cell volume; RI, reference interval; ROC, receiver operated curve; RRT, renal replacement therapy; TP, total protein; UF, ultrafiltration.

KEYWORDS
canine, extracorporeal therapy, hypotension, kidney disease

1 | INTRODUCTION

Acute kidney injury (AKI) is common in dogs and the associated abrupt decline in kidney function leads to retention of uremic toxins, fluid, electrolyte, and acid-base disturbances.[1] As such, IV fluid therapy is 1 of the cornerstones of medical management of AKI, however, iatrogenic fluid overload is a common complication. Of dogs admitted to secondary and tertiary referral hospitals, 42% present with fluid overload at admission or develop fluid overload during hospitalization.[2]

Renal replacement therapy (RRT) is initiated when medical management fails to control the uremic syndrome.[3] The survival rates for both dogs managed medically and with RRT is approximately 50%[4-8]; however, the latter likely have more severe kidney dysfunction. Fluid overload unresponsive to medical management with cessation of fluid administration or diuretic initiation is 1 of the major indications for RRT in dogs with AKI.[3] In humans, fluid overload in AKI patients is associated with worse outcomes, even when illness severity and hemodynamic instability are considered.[9] Excess fluid accumulates throughout body organs and tissues, resulting in life-threatening conditions such as pulmonary edema and systemic hypertension. Intrarenal edema expands the interstitial space, causes cell damage and increases venous, interstitial and subcapsular pressure, which results in decreased renal blood flow and glomerular filtration rate and development or worsening of oliguria. This in turn contributes to maintenance and progression of AKI.[9]

Ultrafiltration (UF) is the process of convective fluid transfer across the semipermeable membrane of a hemodialyzer or hemofilter due to the hydrostatic pressure gradient across the membrane. Ultrafiltration is prescribed during RRT such as intermittent hemodialysis (IHD) to restore euhydration, alleviating the clinical consequences of fluid overload, and facilitate fluid intensive treatments. Ultrafiltered fluid derives from plasma water in the intravascular compartment and UF can therefore be associated with hemodynamic instability if the fluid removal rate exceeds the refill rate of the intravascular compartment from other body compartments.[10] Clinical signs of UF-induced hemodynamic instability during RRT include abdominal discomfort, nausea, vomiting, muscle cramps, restlessness, anxiety and syncope in humans.[11] Hemodynamic instability has been associated with higher in-hospital mortality and possibly, impairs recovery of kidney function, likely secondary to hypovolemia-induced decreases in renal perfusion in already compromised kidneys.[10]

Patient-related risk factors associated with intradialytic hemodynamic instability in humans include age, sex, comorbid diseases such as diabetes mellitus and cardiac dysfunction, lower predialysis blood pressure, antihypertensive medications, and lower serum albumin concentration.[12] Higher UF rates and lower dialysate sodium concentrations are dialysis prescription-related factors that are associated with intradialytic hypotension.[12] In dogs, UF is prescribed empirically based on estimated degree of overhydration; data on prescribed UF rates, complications, and risk factors for complications are not available in the veterinary literature.

This study aimed to describe practice patterns for UF prescription in dogs receiving IHD for AKI including total UF goals, UF rates and risk factors for complications.

2 | MATERIALS AND METHODS

Medical records of dogs receiving IHD for AKI or acute on chronic kidney disease at the University of California, Davis Veterinary Medical Teaching Hospital between January 2009 and December 2019 were reviewed. Dogs were considered if UF was prescribed and ≥100 mL of fluid was removed by UF over the course of a treatment. Only the initial 3 IHD treatments for each dog were considered for inclusion. Dogs starting planned chronic IHD for International Renal Interest Society (IRIS) Stage IV chronic kidney disease[13] were excluded as they were considered to have different characteristics to dogs with any component of AKI. Dogs where no data on UF or complications during IHD treatments were available were also excluded.

Intermittent hemodialysis was performed using the Gambro Phoenix IHD platform (Baxter International Inc, Deerfield, Illinois) in all dogs. When possible, the volume of the extracorporeal circuit was selected to be ≤20% of total blood volume. Where the extracorporeal circuit volume was >20%, the use of synthetic colloids (eg, 6% Hetastarch) in the priming solution (final concentration of 1.0%-3.0%) was often prescribed to reduce the risk of intradialytic hypotension. The UF rate was prescribed by the attending clinician based on the degree of overhydration and its clinical consequences. The UF rates were adjusted throughout the treatment based on the dog's individual tolerance of UF. The remainder of the IHD prescription was individualized to each dog.

During IHD treatments, heart rate, respiratory rate, temperature, and blood pressure were recorded every 15-30 minutes. In-line blood volume monitoring (Crit-line III, Fresenius Medical Care North America, Waltham, Massachusetts), pulse oximetry, and electrocardiography were used as indicated during treatments.

Signalment and cause of AKI were recorded. Administration and timing of antihypertensive drugs were noted. Body weight, blood pressure, heart rate, temperature, packed cell volume (PCV) and total protein (TP), blood urea nitrogen (BUN), serum or plasma creatinine, and sodium concentrations were measured before and after each IHD treatment. An equilibrated sample was collected from the inlet blood line 30 seconds after the end of the treatment with the blood pump set at 50 mL/min, the IHD machine set to bypass mode, and UF discontinued.

Recorded prescription data collected included hemodialyzer and circuit type, volume of the extracorporeal circuit in relation to the dog's weight, use of a colloid in the priming solution, dialysate sodium setting, use of sodium profiling, and target and achieved UF volume. Target and delivered total volume of UF were used to calculate the rate of UF using the dog's weight before the IHD treatment and target and delivered duration of IHD, respectively. Estimate of the dog's overhydration was not included in data analysis as it was not recorded consistently in the medical record.

Total blood volume was calculated as 85 mL/kg[14] and was based on weight before each IHD treatment. Central venous oxygen saturation, hematocrit, and relative blood volume changes were obtained from in-line blood monitoring data performed at 1-minute intervals throughout the treatment. In-line blood monitoring was started within 15 minutes of treatment initiation, once the priming solution had been completely administered. Initial observations were assessed 15 minutes after in-line blood monitoring was initiated, and the final observations were recorded 15 minutes before discontinuation of the IHD treatment, including net changes in blood volume over the course of the treatment. The nadir central venous oxygen saturation was recorded for each treatment. The total UF volume and decreases in blood volume >10% from the initial reading were noted.

Ultrafiltration-related complications were defined as clinical events requiring UF rate reduction or discontinuation of UF, intradialytic IV administration of fluids to treat hemodynamic instability, or both. Ultrafiltration-related complications included 1 or more of the following: hypotension (systolic blood pressure <90 mm Hg or mean arterial pressure <60 mm Hg), development of tachycardia during UF (heart rate > 150 beats per minute), increase in heart rate >50% from baseline, and presence of clinical signs including restlessness or agitation that resolved with decreasing or discontinuation of UF. A decrease in blood volume >10% over 60 minutes was also recorded but not considered as an UF-related complication.

Predicted risk factors for UF-related complications were evaluated within 24 hours before the dialysis start time, and when relevant, after the treatment and included the dog's weight before and after IHD treatment, timing of antihypertensive drugs, blood pressure before and after IHD treatment, PCV and TS before IHD treatment, serum or plasma BUN, creatinine, sodium concentration before and after IHD treatment, difference between the dog's predialysis sodium and prescribed dialysate concentration, sodium profiling prescription, total and relative volume of the extracorporeal circuit in relation to the dog's weight, use of colloids in the priming solution, and in-line blood monitoring variables (hematocrit, central venous oxygen saturation, and relative blood volume change).

2.1 | Statistical analysis

The distribution pattern of continuous variables was assessed using the Shapiro-Wilk's test. Generalized estimating equations (GEE) were used to assess the relationship between variables and UF-related complications. Variables significantly ($P < .05$) associated with UF-related complications were subjected to a multivariable analysis (using GEE) to further examine their association with the outcome. Receiver operator curves (ROC) and area under the curve were calculated for prescribed UF rate and UF-related complications and the sensitivity and specificity of the cut point determined. All tests were 2-tailed and in all, $P < .05$ was considered significant. Analyses were performed using a statistical software package (SPSS 22.0 for Windows, IBM Corp, Armonk, New York).

3 | RESULTS

A total of 77 dogs undergoing 144 IHD treatments with UF were included. Of these, 35/77 were female spayed (45%), 26/77 male castrated (34%), 13/77 male intact (17%) and 3/77 female intact (4%). The most common breeds were mixed breed dogs (18/77, 23%), Labrador retriever (11/77, 14%), golden retriever (6/77, 8%) and pitbull terrier (5/77, 6%). Mean age (±SD) of all dogs was 6.9 ± 3.4 years. Of 77 included dogs, 60 (78%) were diagnosed with AKI and 17 (22%) were diagnosed with an acute on chronic kidney injury. Etiologies causing AKI or acute on chronic kidney injury included leptospirosis (25/77, 32%), immune complex-mediated glomerulopathies (diagnosed based on renal pathology; 7/78, 9%), ethylene glycol toxicity (3/77, 4%) and grape ingestion (3/78, 4%). Etiology was unknown in 29 dogs (37%). Of dogs with immune-complex mediated glomerulopathy, 3 had an acute on chronic kidney injury based on history of increased serum creatinine concentrations, renal changes on abdominal ultrasound examination consistent with chronic kidney disease, renal histopathology or a combination of these.

Of 144 included IHD treatments, 69 (47.9%) were the dog's first IHD treatment, 48 (33.3%) were the second IHD treatment and 27 (18.8%) were the third IHD treatment. Of dogs included, 24 dogs had 1 IHD treatment included, 34 dogs had 2 IHD treatments included and 19 dogs had 3 IHD treatments included. All dogs were assessed to be overhydrated and ultrafiltration was prescribed as part of IHD treatment. The median treatment duration was 300 minutes (interquartile range [IQR], 245-314 minutes). The median prescribed total fluid removal for 144 treatments in 77 dogs was 1000 mL (IQR, 500-2000 mL). The median prescribed fluid removal rate per hour was 9.2 mL/kg/h (IQR, 5.4-12.8 mL/kg/h) in 144 treatments in 77 dogs.

Median extracorporeal circuit volume, including the tubing, dialyzer and where used, Crit-Line blood chamber, was 161 mL (IQR, 117-164 mL), corresponding to a median of 5.9% (IQR, 4.7-7.9%) of the dog's blood volume. Antihypertensive medications were administered within 12 hours of IHD in 25/144 treatment sessions (17.4%).

The median pretreatment body weight of all dogs was 29.8 kg (IQR, 20.8-36.8 kg) and posttreatment body weight was 28.9 kg (IQR, 20.6-36.0 kg). Mean systolic/diastolic (mean) blood pressure pretreatment was 156 ± 25/96 ± 22 (119 ± 22) mm Hg and immediately posttreatment was 158 ± 27/101 ± 22 (122 ± 23) mm Hg. The mean systolic/diastolic (mean) blood pressure within the 30 minutes before the end of IHD treatment was 151 ± 25/100 ± 76 (115 ± 21) mm Hg. The mean heart rate for all dogs before treatment initiation was 116

± 28 beats per minute [bpm] and immediately after treatment was 106 ± 30, respectively. Median pretreatment body temperature was 99.6°F (IQR, 98.3-100.6°F) and posttreatment was 100.6°F (IQR, 99.7-101.3°F).

Median pretreatment BUN concentration for all dogs was 117 mg/dL (reference interval [RI], 11-33 mg/dL; IQR, 79.5-155.0 mg/dL) and at the end of the treatment, median BUN concentration was 22.5 mg/dL (IQR, 6.0-59.3 mg/dL) for all dogs. The median pretreatment serum creatinine concentrations for all dogs was 8.2 mg/dL (RI, 0.8-1.5 mg/dL; IQR, 6.8-10.1 mg/dL) and at the end of the treatment was 2.5 mg/dL (IQR, 1.3-4.8 mg/dL). The mean pretreatment PCV for all dogs was 28.6% (±6.0).

The mean sodium concentration in dogs was 145.7 ± 5.8 mEq/L (RI, 143-151 mEq/L) before treatment and 144.9 ± 4.0 mEq/L after treatment. Mean plasma sodium to dialysate concentration difference was 6.3 ± 7.3 mEq/L at start of IHD. Sodium modeling was prescribed in 49/144 (34.0%) of IHD treatments in 40/77 (51.9%) dogs. Where sodium modeling was prescribed, sodium was modeled up from a lower dialysate sodium concentration to a higher dialysate sodium concentration in 46/49 (93.9%) treatments where it was used. For treatments in which sodium modeling was used, the median initial prescribed dialysate sodium concentration was 150 mEq/L (IQR, 145-150 mEq/L) and median end prescribed dialysate sodium concentration was 150 mEq/L (IQR, 150-155 mEq/L). Colloid was used as part of the priming solution in 20/144 (13.9%) of treatments. In-line blood monitoring was performed in 114/144 (79.2%) treatments (Table 1).

3.1 | Ultrafiltration-related complications and risk factors

Overall, UF-related complications were documented in 37/144 (25.7%) of all treatments and in 26/77 (33.8%) of dogs. Ultrafiltration-related complications occurred in 17/69 (25%) first IHD treatments, 14/48 (29%) of second IHD treatments and 6/27 (22%) of third IHD treatments. Of the 37 treatments where there were UF-related complications, clinical signs were present in 10 treatments (27%). Ultrafiltration was discontinued, either transiently or permanently, in 33/37 instances (89%). Fluids were administered IV to treat UF-induced hemodynamic instability in 16/37 instances (43%) of UF-related complications. No deaths occurred because of UF-related complications.

Of 37 IHD treatments with UF-related complications, hypotension was documented in only 6 of these IHD treatments (16% of treatments with UF-related complications or 4.2% of all included 144 IHD treatments) and tachycardia or increased heart rate from baseline in 7 IHD treatments (19% of treatments with complications or 4.9% of all treatments). A decrease in blood volume > 10% within 60 minutes occurred in 20/37 (54%) treatments with UF-related complications (54%) and in 15/107 (14%) treatments without UF-related complications. In 18 of these 20 treatments where dogs had rapid blood volume changes, increased heart rate from baseline or decreased central venous oxygen saturation was observed, suggesting hypovolemia, and transient or permanent discontinuation of UF was required; in 9 of these IHD treatments with rapid blood volume changes, dogs also required fluid administration IV.

Descriptive statistics for variables by UF-related complications are summarized in Table 2. The variables associated with UF-related complications were body temperature before IHD treatment (odds ratio [OR] 1.35; 95% confidence interval [CI], 1.03-1.77; $P = .03$), PCV before IHD treatment (OR 0.93; 95% CI, 0.87-1.0; $P = .05$), total extracorporeal circuit volume (OR 1.01; 95% CI, 1.00-1.03; $P = .03$), central venous oxygen saturation at 15 minutes after starting IHD (OR 0.95; 95% CI, 0.91-0.98; $P = .002$), nadir central venous oxygen saturation (OR 0.95; 95% CI, 0.92-0.98; $P = .001$), final central venous oxygen saturation (OR 0.96; 95% CI, 0.92-1.0; $P = .05$) and BUN at the end of IHD treatment (OR 0.99; 95% CI, 0.98-1.0; $P = .04$). The remaining variables were not statistically significant. The variables that were associated with UF-related complications in univariable analysis did not remain statistically significant in multivariable analysis.

The mean prescribed fluid removal rate per treatment was higher for dogs with UF-related complications compared to dogs without UF-related complications (10.8 ± 4.9 mL/kg/h vs 8.8 ± 5.1 mL/kg/h, respectively; OR 1.11; 95% CI, 1.01-1.14; $P = .03$; Figure 1). The proportion of IHD treatments where the prescribed UF rate was >10 mL/kg/h was higher in treatments with UF-related complications compared to treatments without UF-related complication (24/36 [67%] vs 38/101 [37.6%], respectively; $P < .001$). Based on ROC, the optimal

TABLE 1 Descriptive statistics for in-line blood monitoring variables in 114 intermittent hemodialysis (IHD) treatments with and without ultrafiltration-related complications.

	All treatments	Treatments with ultrafiltration complications	Treatments without ultrafiltration complications
Central venous oxygen saturation at 15 min after IHD start (%) (median [IQR])	74.8 (67.1-80.1)	73.8 (65.5-78.4)	75.7 (67.5-80.9)
Nadir central venous oxygen saturation (%) (median [IQR])	56.8 (45.7-64.2)	53.5 (37.3-62.4)	57.0 (47.2-64.4)
Central venous oxygen saturation at 15 min before IHD end (%) (median [IQR])	71.3 (63.3-76.4)	71.7 (62.3-77.2)	71.2 (64.4-75.6)
Blood volume change at 15 min after IHD start (%) (median [IQR])	−1.2 (−3.7 to 1.6)	−2.4 (−5.1 to −0.5)	−0.9 (−2.9 to 1.9)
Blood volume at 15 min before IHD end (%) (median [IQR])	−3.5 (−9.1 to 3.1)	−5.2 (−10.6 to 3.0)	−2.8 (−7.2 to 3.0)

Note: Initial variables were those collected within <15 min of initiation of IHD and final variables were those collected <15 min before IHD treatment end.
Abbreviations: IHD, intermittent hemodialysis; IQR, interquartile range.

TABLE 2 Descriptive statistics for 144 intermittent hemodialysis treatments by occurrence of ultrafiltration-related complications.

	Treatments with UF-related complications	Treatments without UF-related complications
Body weight pre-IHD (kg) (median [IQR])	31.6 (25.0-40.0)	28.0 (19.3-36.5)
Body weight post-IHD (kg) (median [IQR])	31.4 (23.8-39.0)	27.4 (19.1-35.4)
Blood pressure pre-IHD (systolic/diastolic [mean], mm Hg) (mean [±SD])	151 ± 24/96 ± 20 (117 ± 21)	157 ± 25/97 ± 23 (120 ± 23)
Blood pressure post-IHD (systolic/diastolic [mean], mm Hg) (mean [±SD])	157 ± 26/102 ± 27 (118 ± 24)	159 ± 27/100 ± 20 (123 ± 23)
Heart rate pre-IHD (beats per minute) (mean [±SD])	117 ± 29	116 ± 28
Heart rate post-IHD (beats per minute) (mean [±SD])	116 ± 33	103 ± 28
Body temperature pre-IHD (°F) (median [IQR])	100.0 (99.2-101.1)	99.4 (98.2-100.3)
Body temperature post-IHD (°F) (median [IQR])	100.8 (99.9-101.6)	100.5 (99.7-101.1)
BUN concentration pre-IHD (mg/dL) (mean [±SD])	110 ± 46	126 ± 57
BUN concentration post-IHD (mg/dL) (median [IQR])	24 (9-51)	23 (6-73)
Serum creatinine concentration pre-IHD (mg/dL) (median [IQR])	8.4 (6.9-9.8)	8.2 (6.8-10.4)
Serum creatinine concentration post-IHD (mg/dL) (median [IQR])	2.6 (1.6-3.9)	2.5 (1.2-5.2)
Sodium concentration pre-IHD (mEq/L) (median [IQR])	148 (144-151)	145 (143-149)
PCV pre-IHD (%) (mean [±SD])	27 ± 6	29 ± 6
Extracorporeal circuit volume (mL) (median [IQR])	163 (150-164)	161 (101-206)
Percentage of patient blood volume in extracorporeal circuit (%) (median [IQR])	5.9 (4.4-6.8)	5.9 (4.8-8.2)
Prescribed dialysate-plasma sodium difference (mEq/L) (mean [±SD])	5.1 ± 5.8	6.8 ± 7.7
Sodium profiling		
Yes (number [%])	12 (8.4)	37 (25.9)
No (number [%])	25 (17.5)	69 (48.3)
Colloid use in priming solution		
Yes (number [%])	2 (1.4)	18 (12.5)
No (number [%])	35 (24.3)	89 (61.8)
Receiving antihypertensive medications		
Yes (number [%])	14 (9.8)	53 (37.1)
No (number [%])	23 (16.1)	53 (37.1)

Abbreviations: BUN, blood urea nitrogen; IHD, intermittent hemodialysis; IQR, interquartile range; PCV, packed cell volume; UF, ultrafiltration.

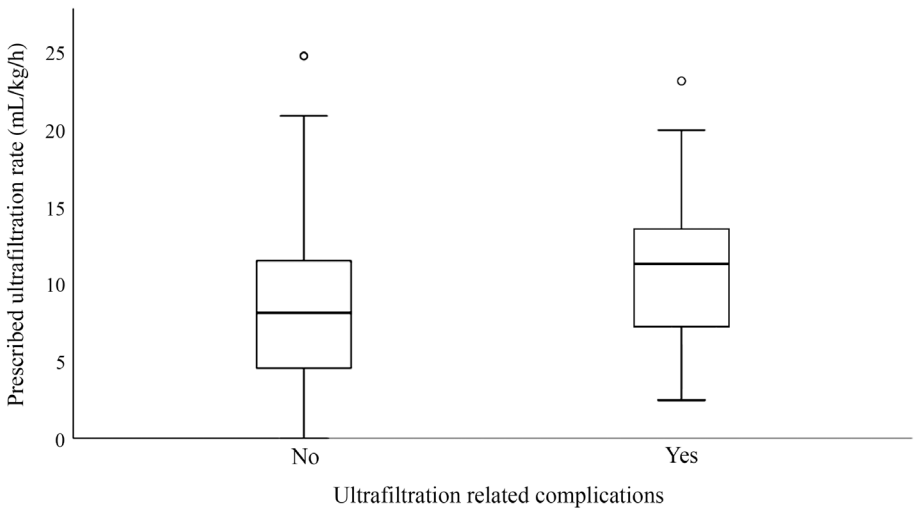

FIGURE 1 The prescribed ultrafiltration rate (mL/kg/h) in dogs with and without ultrafiltration-related complications during intermittent hemodialysis treatments. Ultrafiltration-related complications were considered clinical events requiring UF rate reduction or discontinuation of UF, intradialytic administration of IV fluids to treat hemodynamic instability, or both. The mean ultrafiltration rate was 10.8 ± 4.9 mL/kg/h in dogs with ultrafiltration-related complications and 8.8 ± 5.1 mL/kg/h without ($P = .03$).

cut point for prescribed UF rate to differentiate between dogs with and without UF-related complications was 10 mL/kg/h with sensitivity of 67% and specificity of 63%.

The mean UF rate at the time that UF-related complications were recognized was 10.3 ± 4.7 mL/kg/h. The mean delivered fluid removal rate per treatment for all dogs was 8.1 ± 4.5 mL/kg/h and

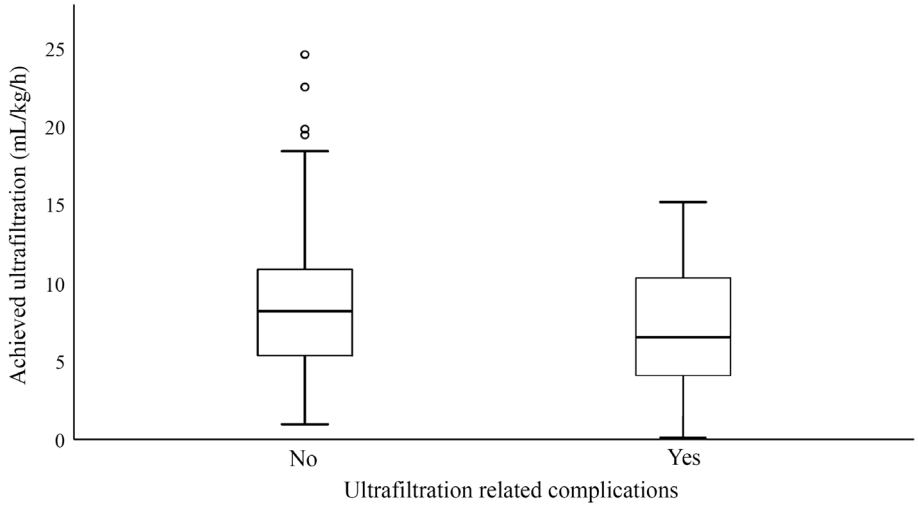

FIGURE 2 The achieved (delivered) ultrafiltration rate (mL/kg/h) in dogs with and without ultrafiltration-related complications during intermittent hemodialysis treatments. The mean ultrafiltration rate was lower in dogs with UF-related complications compared to those without (6.8 ± 4.0 mL/kg/h vs 8.6 ± 4.6 mL/kg/h, respectively; $P = .04$).

was significantly lower in dogs with UF-related complications compared to those without complications (6.8 ± 4.0 mL/kg/h vs 8.6 ± 4.6 mL/kg/h, respectively; OR 0.90; 95% CI, 0.82-0.99; $P = .04$) (Figure 2). Ultrafiltration target (>90% of the prescribed volume) was achieved in 47/140 of all treatments (33.6%). The delivered UF volume was significantly more likely to be <90% of the prescribed UF volume in IHD treatments with UF-related complications (33/37, 89%), as compared to treatments without complications (60/103, 58.3%) ($P < .001$).

4 | DISCUSSION

Ultrafiltration is a critical component of the IHD prescription and is aimed at restoring euvolemia, thereby alleviating the morbidity and higher mortality associated with overhydration.[3] The results of this study demonstrate that UF during IHD in dogs with AKI is generally safe when performed in accordance with recommended guidelines,[2] however, in 26% of IHD treatments, the prescribed UF was not tolerated. In addition, in 89% of IHD treatments where there were UF-related complications, the prescribed UF target could not be delivered and a lower total fluid volume was removed. The majority of UF-related adverse events necessitating a change in UF target were mild, and severe complications such as intradialytic hypotension were rare (4% of treatments). Ultrafiltration-related adverse events were likely diagnosed early, before overt hypovolemia developed, due to careful monitoring and recognition of subtle changes indicative of early hypovolemia, including increase in heart rate from baseline, changes on in-line blood volume monitoring or both. The association between rapid decreases in central venous oxygen saturation and UF-related complications emphasizes the utility of in-line blood monitoring systems during IHD as a means to decrease the risk of severe complications of hypovolemia like intradialytic hypotension.

During UF, fluids are removed from the intravascular space with concurrent refilling of the intravascular space from the overexpanded interstitial and intracellular compartments. When the UF rate exceeds the vascular refilling rate, transient hypovolemia and hemodynamic instability can occur, particularly where vascular compensatory mechanisms are inadequate.[10,15] In humans with AKI undergoing IHD, overall incidence of intradialytic hypotension is approximately 20%,[12] but can range from 5% to 57%. Some of this variation in reported hypotension relates to the definition of intradialytic hypotension used.[10,12,16-19] The low incidence of intradialytic hypotension in the present study is likely multifactorial including the UF rate and total UF volume selected, low occurrence of underlying diseases such as cardiogenic shock and sepsis that contribute to hemodynamic instability in humans receiving hemodialysis,[10] more intense clinical monitoring during IHD, and use of in-line blood monitoring systems. In humans, the duration of IHD is often 3 to 4 hours, in which large volumes of UF might be prescribed, while the median treatment duration in dogs in this study was 5 hours.[10,19] Increased treatment time allows for a lower UF rate to achieve the same prescribed total UF goal, and thereby decreases the risk of hemodynamic instability.[10] The higher heart rate documented posttreatment among dogs with UF-related complications suggests some compensated ongoing hemodynamic instability.

The actual achieved (delivered) UF rate was lower in treatments in dogs with UF-related complications during IHD, reflecting early adjustment of the prescribed UF target or UF rate. The failure to achieve the UF target can be detrimental as fluid overload is not corrected. Safe delivery of the required UF volume necessitates a longer treatment duration, lower UF rate or both. If the initial or residual fluid burden is not life-threatening, fluid removal can be achieved over sequential IHD treatments. The mean prescribed rate of fluid removal in treatments with UF-related complications was 10.8 mL/kg/h, higher than in treatments without complications, where the mean prescribed rate was 8.8 mL/kg/h. Correspondingly, at the time UF-related complications occurred, the mean UF rate was 10.3 mL/kg/h. In humans, UF rates >10 mL/kg/h have been associated with higher risk of death due to hemodynamic instability.[20,21] The findings in the present study suggest that UF rates <10 mL/kg/h are likely to be safer in dogs, similar to humans, though this should also be evaluated in

prospective studies. It is also possible that the higher prescribed rate of UF in dogs with UF-related complications led to complications due to overestimation of the volume of fluid overload.

In-line blood monitoring systems enable prediction of hypotension and intradialytic morbidity and have additionally improved assessment of dry weight, defined as the weight without any excess fluid burden.[22-24] These systems, as used in the present study, continuously measure hematocrit and oxygen saturation in the flowing extracorporeal blood and calculate the relative change in blood volume based on changes in hematocrit.[25] In our practice, the in-line monitoring is routinely started within the first 15 minutes of treatment initiation (after the priming solution has been completely administered to the dog), though there is likely some variation in when this was started, and during this time, there might be some redistribution of the priming solution that could affect blood volume changes early in treatment.

Central venous oxygen saturation early in the treatment was associated with UF-related complications, demonstrated by a lower central venous oxygen saturation at 15 minutes after starting IHD and 15 minutes before stopping IHD and lower central venous oxygen saturation nadir in dogs with UF-related complications. Central venous oxygen saturation is influenced by arterial oxygen saturation, hemoglobin concentration, cardiac output and tissue oxygen consumption and is an indicator of oxygen delivery and consumption.[26] Lower central venous oxygen saturation in dogs with UF-related complications is thought to be linked to decreased cardiac output, resulting in decreased tissue perfusion.[26] In healthy dogs, central venous oxygen saturation is 82.3% (±3.5).[27] In humans having chronic hemodialysis, higher ultrafiltration volumes are associated with greater decreases in central venous oxygen saturation, likely reflecting decreases in blood volume and thus cardiac output negatively affecting tissue and organ perfusion, including already compromised kidneys.[28,29] As changes in central venous oxygen saturation can signal early hemodynamic instability,[23,24] measurement of this variable in dogs included in this study might have helped to decrease the frequency of severe UF-related complications such as intradialytic hypotension.

Hemodynamic instability in humans during hemodialysis is affected by multiple factors, which likely also contribute to hemodynamic instability and UF-related complications in dogs. The prescribed dialysate sodium concentration might influence osmotic shifts of fluid into (or from) the vasculature. A low dialysate sodium concentration relative to plasma sodium might promote a sodium shift from plasma, exacerbating osmotic water shifts associated with reduction in urea concentrations.[30-32] In this study, there was no association between the dialysate-plasma sodium difference and UF related complications. Similarly, there was no association between sodium profiling and UF-related complications. These findings might have been mitigated by considerations of dialysate sodium or other prescription variables in dogs considered to be at higher risk of UF-related complications.

The extracorporeal circuit volume might contribute to hemodynamic instability as it is relatively high in veterinary medicine as IHD in dogs is delivered using human IHD platforms. The prescribed extracorporeal circuit volume was associated with development of UF-related complications in the current study, with dogs with UF-related complications having a higher total extracorporeal circuit volume than dogs without UF-related complications. Consideration should be given to selection of the smallest extracorporeal circuit volume appropriate for the size of the dog where possible. That the percent of the dog's blood volume in the extracorporeal circuit was not statistically significant could reflect intentional strategies in dogs at risk for hemodynamic instability, particularly using colloidal priming solutions to decrease the risk of hypovolemia. In our study, using colloidal priming solutions did not alter risk of UF-related complications, but in human patients, priming the extracorporeal circuit with 17.5% albumin rather than 0.9% NaCl in critically ill septic patients improves hemodynamic tolerance of hemodialysis.[33] Although not represented in this retrospective cohort of dogs, priming the extracorporeal circuit with blood or blood components has been employed more recently in dogs with small blood volumes relative to the size of the extracorporeal circuit volume.

There was evidence of an association between lower posttreatment BUN concentration and increased risk of UF-related complications. In human patients undergoing maintenance hemodialysis, higher calculated plasma osmolality before treatment and more rapid removal of urea have been associated with greater risk of intradialytic hypotension.[34,35] Rapid declines in plasma urea (and osmolarity) during treatment results in delayed solute and osmotic equilibration[34,35] and consequent fluid shifts from the intravascular space (low osmolarity) to the extra- and intracellular compartments (higher osmolarity). Although conservative prescription guidelines are used in veterinary medicine, where gradual decreases in BUN concentration are emphasized in the setting of AKI, this could still be a contributing factor in this group of dogs.[3] The lower posttreatment BUN concentration in treatments with UF-related complications could also be due to IHD being initiated due to fluid overload and resulting solute hemodilution rather than the severity of azotemia alone, resulting in prescription of higher UF rates and associated risk of complications during IHD.

A lower pretreatment PCV was associated with a higher risk of UF-related complications. This could occur through local tissue ischemia from anemia worsening hypotension,[36] however, a lower PCV could also be an indicator of more severe fluid overload leading to dilution of PCV and therefore, higher prescribed UF rates. The risk of UF-related complications was also higher in treatments where dogs had higher pretreatment body temperatures. This could reflect an underlying infectious or inflammatory etiology of the AKI, with resulting increased risk of hemodynamic instability.

Limitations of the present study include its retrospective nature, with the possibility that some data were missing or incomplete. For example, it was not possible to estimate the degree of fluid overload of dogs as this was not recorded consistently in the medical record and therefore, this was not included in the analysis. The target volume of UF was included, however, this might not reflect the total estimated volume of fluid overload as fluid overload might be corrected over >1 treatment. In addition, fluid inputs during IHD were not consistently reported in medical records and thus the recorded UF

represents total rather than net UF (ie, fluids administered either by mouth or IV during the treatment were not considered). Recording of dialysate temperature was inconsistently available and therefore was not included in the analysis. Regardless, dialysate temperature is rarely adjusted in the dialysate prescriptions and is unlikely to be an important limitation to the observations. Determination of UF-related complications was based on thorough medical record review, with strict definitions of UF-related complications; however, it is possible that some UF-related complications were misclassified or missed.

ACKNOWLEDGMENT

No funding was received for this study.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Lucy Kopecny https://orcid.org/0000-0002-6935-9463
Carrie A. Palm https://orcid.org/0000-0003-1445-5113
Gilad Segev https://orcid.org/0000-0003-4714-3159

REFERENCES

1. International Renal Interest Society. *IRIS Guideline Recommendations for Grading of AKI in Dogs and Cats*; 2016. http://www.iris-kidney.com/guidelines/grading.html. Accessed September 28, 2019.
2. Cole LP, Jepson R, Dawson C, Humm K. Hypertension, retinopathy, and acute kidney injury in dogs: a prospective study. *J Vet Intern Med*. 2020;34(5):1940-1947.
3. Cowgill LD, Francey T. Hemodialysis and extracorporeal blood purification. In: DiBartola SP, ed. *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice*. 4th ed. Saint Louis, MO: W.B. Saunders; 2012:680-713.
4. Segev G, Kass PH, Francey T, Cowgill LD. A novel clinical scoring system for outcome prediction in dogs with acute kidney injury managed by hemodialysis. *J Vet Intern Med*. 2008;22(2):301-308.
5. Segev G, Langston C, Takada K, Kass PH, Cowgill LD. Validation of a clinical scoring system for outcome prediction in dogs with acute kidney injury managed by hemodialysis. *J Vet Intern Med*. 2016;30(3):803-807.
6. Eatroff AE, Langston CE, Chalhoub S, Poeppel K, Mitelberg E. Long-term outcome of cats and dogs with acute kidney injury treated with intermittent hemodialysis: 135 cases (1997-2010). *J Am Vet Med Assoc*. 2012;241(11):1471-1478.
7. Vaden SL, Levine J, Breitschwerdt EB. A retrospective case-control of acute renal failure in 99 dogs. *J Vet Intern Med*. 1997;11(2):58-64.
8. Behrend EN, Grauer GF, Mani I, Groman RP, Salman MD, Greco DS. Hospital-acquired acute renal failure in dogs: 29 cases (1983-1992). *J Am Vet Med Assoc*. 1996;208(4):537-541.
9. Prowle JR, Kirwan CJ, Bellomo R. Fluid management for the prevention and attenuation of acute kidney injury. *Nat Rev Nephrol*. 2014;10(1):37-47.
10. Douvris A, Zeid K, Hiremath S, et al. Mechanisms for hemodynamic instability related to renal replacement therapy: a narrative review. *Intens Care Med*. 2019;45(10):1333-1346.
11. Hayes W, Hothi DK. Intradialytic hypotension. *Pediatr Nephrol*. 2011;26(6):867-879.
12. Chou JA, Kalantar-Zadeh K, Mathew AT. A brief review of intradialytic hypotension with a focus on survival. *Semin Dial*. 2017;30(6):473-480.
13. International Renal Interest Society. *IRIS Staging of CKD; Modified*; 2019. http://www.iris-kidney.com/guidelines/staging.html. Accessed November 26, 2022.
14. Jahr JS, Lurie F, Bezdikian V, Driessen B, Gunther RA. Measuring circulating blood volume using infused hemoglobin-based oxygen carrier (Oxyglobin®) as an indicator: verification in a canine hypovolemia model. *Am J Ther*. 2008;15:98-101.
15. Schortgen F. Hypotension during intermittent hemodialysis: new insights into an old problem. *Intens Care Med*. 2003;29(10):1645-1649.
16. Palevsky PM, Zhang JHY, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359(1):7-20.
17. Tonelli M, Astephen P, Andreou P, Beed S, Lundrigan P, Jindal K. Blood volume monitoring in intermittent hemodialysis for acute renal failure. *Kidney Int*. 2002;62(3):1075-1080.
18. Bitker L, Bayle F, Yonis H, et al. Prevalence and risk factors of hypotension associated with preload-dependence during intermittent hemodialysis in critically ill patients. *Crit Care*. 2016;20(44):1-11.
19. Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med*. 2002;346(5):305-310.
20. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int*. 2011;79(2):250-257.
21. Saran R, Bragg-Gresham JL, Levin NW, et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. *Kidney Int*. 2006;69(7):1222-1228.
22. Rodriguez HJ, Domenici R, Diroll A, Goykhman I. Assessment of dry weight by monitoring changes in blood volume during hemodialysis using Crit-Line. *Kidney Int*. 2005;68(2):854-861.
23. Steuer RR, Leypoldt JK, Cheung AK, Harris DH, Conis JM. Hematocrit as an indicator of blood volume and a predictor of intradialytic morbid events. *ASAIO J*. 1994;40(3):691-696.
24. Barth C, Boer W, Garzoni D, et al. Characteristics of hypotension-prone haemodialysis patients: is there a critical relative blood volume? *Nephrol Dial Transpl*. 2003;18(7):1353-1360.
25. Van Buren PN. Relative blood volume monitoring in hemodialysis patients: identifying its appropriate role. *Nephrol Dial Transpl*. 2019;34(8):1251-1253.
26. Walton RAL, Hansen BD. Venous oxygen saturation in critical illness. *J Vet Emerg Crit Care*. 2018;28(5):387-397.
27. Tamura J, Itami T, Ishizuka T, et al. Central venous blood gas and acid-base status in conscious dogs and cats. *J Vet Med Sci*. 2015;77(7):865-869.
28. Zhang HJ, Chan LL, Meyring-Wosten A, et al. Association between intradialytic central venous oxygen saturation and ultrafiltration volume in chronic hemodialysis patients. *Nephrol Dial Transpl*. 2018;33(9):1636-1642.
29. Harrison LE, Selby NM, McIntyre CW. Central venous oxygen saturation: a potential new marker for circulatory stress in haemodialysis patients? *Nephron Clin Pract*. 2014;128(1–2):57-60.
30. Schortgen F, Soubrier N, Delclaux C, et al. Hemodynamic tolerance of intermittent hemodialysis in critically ill patients—usefulness of practice guidelines. *Am J Respir Crit Care Med*. 2000;162(1):197-202.

31. Paganini EP, Sandy D, Moreno L, Kozlowski L, Sakai K. The effect of sodium and ultrafiltration modeling on plasma volume changes and haemodynamic stability in intensive care patients receiving haemodialysis for acute renal failure: a prospective, stratified, randomized, cross-over study. *Nephrol Dial Transpl*. 1996;11:32-37.
32. Henrich WL, Woodard TD, Blachley JD, Gomez-Sanchez C, Pettinger W, Cronin RE. Role of osmolality in blood-pressure stability after dialysis and ultrafiltration. *Kidney Int*. 1980;18(4):480-488.
33. Jardin F, Prost JF, Ozier Y, et al. Hemodialysis in septic patients—improvement in tolerance of fluid removal with concentrated albumin as the priming fluid. *Crit Care Med*. 1982;10(10):650-652.
34. McCausland FR, Brunelli SM, Waikar SS. Dialysis dose and intradialytic hypotension: results from the HEMO study. *Am J Nephrol*. 2013;38(5):388-396.
35. McCausland FR, Waikar SS. Association of predialysis calculated plasma osmolarity with intradialytic blood pressure decline. *Am J Kidney Dis*. 2015;66(3):499-506.
36. Daugirdas JT. Pathophysiology of dialysis hypotension: an update. *Am J Kidney Dis*. 2001;38:S11-S17.

How to cite this article: Kopecny L, Palm CA, Segev G, Cowgill LD. Ultrafiltration during intermittent hemodialysis in dogs with acute kidney injury. *J Vet Intern Med*. 2023;37(3):1021-1029. doi:10.1111/jvim.16649