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Renal Replacement Therapy in Healthy Adult Horses

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Renal Replacement Therapy in Healthy Adult Horses

Abstract

Background

Renal replacement therapy (RRT) has been implemented extensively in people to facilitate recovery from acute renal failure (ARF). RRT has not been explored in horses, but might provide a further treatment option in horses with ARF.

Objective

To investigate efficacy and safety of RRT in horses.

Animals

Five healthy adult horses.

Methods

A prospective study was performed on horses restrained in stocks and intravenously connected to a commercial RRT machine to allow continuous venovenous hemodiafiltration to be performed for 6 hours. The RRT machine was set at the following flow rates: blood flow rate 250 mL/min; dialysate rate 3,000 mL/h; prefilter replacement pump 3,000 mL/h; and postfilter replacement pump rate 2,000 mL/h. Balanced electrolyte solution was used as dialysate and replacement fluid. Heart rate, respiratory rate, body temperature, direct arterial blood pressure, urine output, and various clinicopathologic parameters were measured over the study period.

Results

Renal replacement therapy was successfully performed in horses, resulting in a mean creatinine clearance of 0.127 mL/kg/min (68.9 mL/min) and urea reduction ratio of 24%. No adverse effects were detected although a significant decrease in rectal temperature was observed ($P \leq .007$). A significant increase in serum phosphorus ($P \leq .001$) and decrease in BUN ($P < .001$) were also noted. A significant prolongation of prothrombin ($P < .01$) and partial thromboplastin time ($P < .0001$) were observed along with a decrease in platelet count ($P \leq .04$).

Conclusions and Clinical Importance

Renal replacement therapy can safely and effectively be used in adult horses.

Keywords

Creatinine clearance, Dialysis, Effluent, Heparin, Renal failure

Disciplines

Large or Food Animal and Equine Medicine | Other Veterinary Medicine | Veterinary Physiology

Comments

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Conclusions and Clinical Importance: Renal replacement therapy can safely and effectively be used in adult horses.

Key words: Creatinine clearance; Dialysis; Effluent; Heparin; Renal failure.

Acute renal failure (ARF) is characterized by a marked decrease in glomerular filtration rate and manifests clinically as abrupt and sustained increases in BUN and creatinine concentrations along with derangements in fluid, electrolyte, and acid–base homeostasis.¹ Conventional treatment principles of ARF include reversal of inciting or underlying cause, judicious administration of IV fluids, and correction of electrolyte and acid–base abnormalities.^{2,3} In people and companion animals, renal replacement therapy (RRT) may be instituted if ARF remains refractory to conventional treatment to the extent that 50–70% of human ICU patients with ARF will currently receive RRT.^{4–8} The use of RRT in horses is not well described, but successful outcomes have been reported using intermittent hemodialysis (IHD) in an adult horse with myoglobin-induced ARF and a foal with oxytetracycline-induced ARF.^{9,10} In addition, case reports have described the use of peritoneal dialysis to facilitate recovery of horses with ARF.^{11–13}

Renal replacement therapy is a blood purification modality that has become the treatment of choice for ARF in some medical facilities.^{7,8} Renal indications for instituting RRT in people include reduced

Abbreviations:

ACT	activated clot time
ARF	acute renal failure
Ca	calcium
Cl	chloride
CrCl	creatinine clearance
CRI	constant rate infusion
CRRT	continuous renal replacement therapy
HCO ₃	bicarbonate
IHD	intermittent hemodialysis
K	potassium
Kt/V	urea clearance over time
Na	sodium
Phos	phosphorus
PT	prothrombin time
PTT	partial thromboplastin time
RRT	renal replacement therapy
URR	urea reduction ratio

glomerular filtration rates leading to solute imbalance or oliguria resulting in extracellular fluid volume overload that does not respond to other forms of treatment.^{14,15} Nonrenal indications for RRT include facilitating clearance of various drugs, toxins, toxic metabolites, or inflammatory cytokines.^{6,15,16} RRT can be broadly categorized into continuous renal replacement therapy (CRRT) and (IHD). CRRT is similar to IHD in that the patient's blood is divided among and passed through thousands of straw-like semipermeable membranes contained within a dialyzer. In addition to diffusion principles that promote blood purification in IHD, CRRT has the ability to use convection (solvent drag) and adsorption (adhesion) to promote blood purification.^{5,7,8} Other advantages of CRRT over IHD include the ability to employ a slow, continuous, and

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gradual purification process, which provides better control of blood pressure as well as electrolyte and acid–base balance.^{4,5,16} The continuous nature of CRRT allows the modality to more closely mimic the function of the healthy kidney and the convective process of CRRT allows more effective removal of larger molecules with limited diffusibility.^{4,5,16} A technical advantage of CRRT is the ability to use prepackaged sterile fluids as compared with hemodialysis which requires significant amounts of pure dialysate that must be produced on-site with specialized water treatment facilities.

Despite advancements in equine critical care, investigation of RRT has not been described. The lack of consideration of RRT in horses may be a result of the perceived high cost of equipment or labor-intensive nature of instituting treatment. With the advent of more cost-effective equipment and demand for advanced treatment, RRT may be a realistic treatment option for the equine patient with renal failure. The objectives of this study were to develop a protocol by which RRT can be implemented, utilizing a commercial CRRT machine, and to evaluate the safety and efficacy of RRT in adult horses. Of note, although a CRRT machine was utilized for this study, therapy, as it pertains to this study, will be referred to as RRT as the treatment period was only 6 hours, and not technically continuous (ie, 24+ continuous hours).

Materials and Methods

Horses

Five healthy adult mares (age range 3–11 years) from the Iowa State University teaching herd were used after the study protocol was approved by the University Animal Care and Use Committee. The mean body weight was 544 kg (range 486–609 kg). Horses were housed individually in box stalls and allowed to acclimatize to the environment 24 hours before experimentation. Health status was based on the results of physical examination and evaluation of a complete blood count and biochemistry profile performed 24 hours before experimentation. Horses were fed free choice grass hay and had unlimited access to water.

Instrumentation

On the morning of experimentation, each horse was sedated with xylazine^a (0.3 mg/kg, IV), the hair was clipped, skin aseptically prepared, and local anesthetic administered SC over 4 sites including the right jugular vein, left jugular vein, cephalic vein, and transverse facial artery for intravenous or intra-arterial catheter placement. A 14-gauge 5.25-inch over-the-needle polyurethane catheter^b was inserted into the right jugular vein to allow for sampling of blood during the experiment. To provide a continuous rate infusion (CRI) of sedation, a 16-gauge 3-inch over-the-needle polyurethane catheter^c was inserted into the right cephalic vein to allow for administration of a detomidine CRI. A 20-gauge, 1.5-inch over-the-needle polyurethane catheter^d was inserted into the transverse facial artery to allow for arterial blood pressure monitoring. A 14 French over-the-wire double lumen dialysis catheter^e was placed in the left jugular vein. All catheters were flushed with heparinized saline and secured in place by suturing to the skin. Lastly, a 20 French indwelling

urinary catheter^f was placed aseptically into the urinary bladder and connected to a closed urine collection system.

Monitoring Vital Parameters

One hour after instrumentation was completed, the transverse facial artery catheter was interfaced with an arterial blood pressure monitor^g and baseline arterial blood pressure (mean, systolic, diastolic) was recorded (Time 0). In addition, baseline heart rate, respiratory rate, and rectal temperature values were collected before initiation of the detomidine CRI. An ECG^g was attached to the horse utilizing a base-apex lead to monitor heart rhythm. Vital parameters (heart rate, respiratory rate, rectal temperature, arterial blood pressure) were measured at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 12, and 24 hours.

Continuous IV Sedation

Detomidine^h (50 mg) was diluted with 0.9% sodium chloride to a concentration of 1 mg/mL. Immediately after collection of baseline data (Time 0), a loading dose of 8.4 µg/kg of detomidine was administered as an IV bolus. Subsequently, detomidine was administered, utilizing an electronic syringe pump, at a dose of 0.5 µg/kg/min for 15 minutes, which was decreased to 0.3 µg/kg/min for 15 minutes and decreased again to 0.15 µg/kg/min thereafter.¹⁷

Anticoagulation

A baseline prothrombin time (PT), partial thromboplastin time (PTT), and platelet count were measured after instrumentation was complete (Time 0). Immediately before the commencement of RRT (ie, immediately after detomidine bolus), a bolus dose of 100 IU/kg of sodium heparinⁱ was administered IV through the dialysis catheter to provide systemic anticoagulation; subsequently, a CRI of heparin (50 IU/kg/h) was initiated, as previously described.¹⁸ Anticoagulation was monitored by measurement of PT, PTT, and platelet count every hour during RRT and then 6 and 12 hours after discontinuation of RRT and heparin CRI.

Experimental Protocol

Each horse was placed in stocks and administered the loading dose of detomidine, immediately followed by the CRI of detomidine, as described. The loading dose of heparin was administered and the RRT procedure was initiated. A commercial CRRT machine^j that incorporates an extracorporeal circuit with an integrated 1.5 m² filter^k was utilized. The CRRT machine mode was set to deliver continuous venovenous hemodiafiltration for 6 hours with the blood flow rate set to remove 250 mL of blood/min. The dialysate rate was set at 3,000 mL/h with the prefilter replacement pump set at 3,000 mL/h and the postfilter replacement pump rate set at 2,000 mL/h. The CRRT machine was set to produce no net change (gain or loss) in patient fluid balance (ie, dialysate plus pre- and postfilter replacement fluids were automatically added and removed within the dialysis circuit and in total, equaled the volume of effluent; Fig 1). The effluent was comprised of a combination of the dialysate and pre- and postfilter replacement fluids. Balanced electrolyte solution^l was used as the dialysate and replacement fluid.

Free choice availability to hay and water was provided during the 6-hour experimental period, vital parameters were measured every 30 minutes, and the ECG was constantly monitored for the presence of cardiac arrhythmias. In addition, 12 mL of blood was

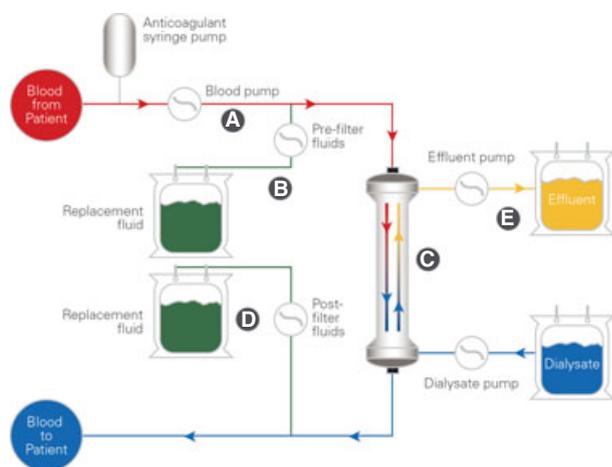


Fig 1. Schematic diagram of dialysis circuit used for RRT in 5 horses. (A) Blood is actively extracted from the patient via a peristaltic pump at selected rate (ie, 250 mL/min) and (B) prefilter fluids are incorporated with the blood (ie, 3,000 mL/h). (C) The direction of flow of the dialysate (ie, 3,000 mL/h) travels in the opposite direction of the blood. (D) Postfilter fluids (3,000 mL/h) are also incorporated. (E) The effluent pump controls the amount of effluent collected; the effluent is a combination of dialysate, pre- and postfilter fluids, and controls the net fluid gain or fluid loss in the patient.

collected at baseline (Time 0) from the right jugular vein catheter and placed into EDTA (platelet count), sodium citrate (PT, PTT), and clot tubes (BUN, creatinine, sodium [Na], potassium [K], chloride [Cl], bicarbonate [HCO_3], calcium [Ca], phosphorus [Phos]) to measure various biochemical parameters. Subsequently, 12 mL of blood was collected every hour (1, 2, 3, 4, 5, and 6 hours) to measure the aforementioned blood parameters during RRT. Effluent was collected at 1, 2, 3, 4, 5, and 6 hours and placed in sterile tubes for measurement of aforementioned biochemical parameters. Urine output was measured hourly over the study period. To evaluate efficacy of RRT, the creatinine clearance (CrCl), urea reduction ratio (URR), and urea clearance over time (Kt/V) were calculated using the following formulas:

Creatinine clearance (mL/min) of the effluent fluid¹⁹:

$$\text{CrCl} = \left(\frac{\text{Ultrafiltrate [Cr]} \times \text{Dialysate output [mL]}}{\text{Plasma [Cr]} \times \text{Time [minute]}} \right)$$

Creatinine clearance based on body weight (CrCl; mL/kg/min) of the effluent fluid²⁰:

$$\text{CrCl} = \left(\frac{\text{Ultrafiltrate [Cr]} \times \text{Dialysate output [mL]}}{\text{Plasma [Cr]} \times \text{Time [minute]} \times \text{Body weight (kg)}} \right)$$

Urea reduction ratio (%) of the blood²¹:

$$\text{URR} = \frac{\text{preBUN} - \text{postBUN}}{\text{preBUN}} \times 100$$

Urea clearance over time, normalized to patient volume of distribution (Kt/V):

$$\text{Urea clearance over time} = Kt/V^5$$

K = urea clearance (mL/min), t = time (estimated for 24 hours or 1,440 minutes), V = patient's volume of distribution (estimated by $0.6 \times \text{BWT}$).

Statistical Analysis

Sample mean \pm SD values were calculated for each response variable. Data were analyzed using a repeated measures analysis of variance (ANOVA) model, with time as a fixed effect and horse as the subject of repeated measures. PTT was rank transformed before analyses because of upper-censoring at 245 seconds by the analyzer. Difference in mean response among times was assessed using an overall F -test followed by Tukey's t -tests for posthoc pairwise comparison. P -values $\leq .05$ were considered significant.

Results

Monitored Vital Parameters

Heart rate was significantly lower at 2.5, 4, and 5 hours ($P < .05$), whereas respiratory rate was significantly lower at time 2.5 hours ($P < .05$) when compared with baseline (Table 1). Rectal temperature was significantly lower at 3, 3.5, 4, 5, and 6 hours ($P \leq .007$) when compared with baseline. No significant differences were detected in systolic, diastolic, or mean blood pressure at any time, when compared with baseline values. Second-degree atrioventricular block occurred (2–4 incidences/min) in 2 horses (Horse 2, 2–6 hours; Horse 4, 2–4 hours), whereas occasional ventricular premature contractions occurred (2–6 incidences/min) in 2 other horses (Horse 1, 4 hours; Horse 3, 6 hours) upon evaluation of the heart rhythm via ECG. Normal sinus rhythm was present 24 hours after initiation of study.

Continuous IV Sedation

All horses tolerated the detomidine CRI with no major discomfort or anxiety subjectively detected during the RRT procedure. Horses appeared to recover from sedation within 30 minutes of discontinuing the CRI.

Anticoagulation

The PT was significantly prolonged ($P < .01$) at 2–6 hours, whereas the PTT was significantly prolonged ($P < .0001$) at 1–12 hours when compared with baseline measurements (Table 2); no statistical differences in PT or PTT were detected 24 hours after initiation of RRT, when compared with baseline. The platelet count was significantly lower ($P \leq .04$) at 2–6 hours when compared with baseline; no statistical difference was detected at 12 and 24 hours when compared with baseline. Hematoma formation at either the left jugular vein (2 horses) or transverse facial artery (1 horse) occurred upon removal of the catheter, despite prolonged external pressure being applied to the site of catheter insertion. No long-term detrimental effects of anticoagulation treatment were noted.

Serum and Effluent Biochemistry Parameters

During the 6-hour CRRT procedure, a significant increase ($P \leq .001$) in serum phosphorus concentration was detected at 2–6 hours, when compared with

Table 1. Mean \pm standard deviation values of various physical examination parameters and urine output measured from 5 horses over a 6 hour period of renal replacement therapy.

Time (hours)	HR (BPM)	RR (BRM)	Temp ($^{\circ}$ F)	SAP (mmHg)	DAP (mmHg)	MAP (mmHg)	Urine Output (mL)
0	41 \pm 5	20 \pm 8	99.4 \pm 1	145 \pm 14	94 \pm 8	112 \pm 9	0
0.5	34 \pm 5	13 \pm 3	99.2 \pm 1	154 \pm 31	101 \pm 18	123 \pm 24	200 \pm 170
1	32 \pm 8	11 \pm 3	99.1 \pm 0.8	150 \pm 41	105 \pm 25	124 \pm 31	144 \pm 43
1.5	32 \pm 6	13 \pm 2	99.1 \pm 0.8	147 \pm 23	95 \pm 15	113 \pm 22	357 \pm 387
2	34 \pm 6	11 \pm 3	98.8 \pm 1.1	134 \pm 24	94 \pm 9	111 \pm 15	1,192 \pm 856
2.5	30 \pm 8 ^a	9 \pm 3 ^a	98.5 \pm 1.2	133 \pm 17	95 \pm 12	113 \pm 14	2,330 \pm 1,667
3	32 \pm 7	11 \pm 3	98.1 \pm 0.9 ^a	131 \pm 17	92 \pm 8	104 \pm 13	1,360 \pm 764
3.5	31 \pm 9	11 \pm 2	98.0 \pm 1.0 ^a	134 \pm 14	95 \pm 10	104 \pm 15	1,325 \pm 922
4	30 \pm 7 ^a	13 \pm 3	97.7 \pm 1.2 ^a	139 \pm 37	85 \pm 15	102 \pm 15	2,026 \pm 1,807
5	31 \pm 7 ^a	11 \pm 2	98.0 \pm 1.2 ^a	124 \pm 24	82 \pm 16	96 \pm 19	2,310 \pm 1,567
6	37 \pm 12	13 \pm 4	97.3 \pm 0.8 ^a	123 \pm 26	75 \pm 16	94 \pm 19	1,730 \pm 1,823
12	42 \pm 2	15 \pm 3	100.6 \pm 1.8	NP	NP	NP	NP
24	37 \pm 3	21 \pm 9	99.5 \pm 0.3	NP	NP	NP	NP

HR, heart rate; RR, respiratory rate; Temp, rectal temperature; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; NP, not performed.

^aWithin a column, significantly different from baseline (Time 0) measurement.

baseline (Table 2). A significant decrease ($P < .001$) in BUN concentration was also detected at 1–6 hours, when compared with baseline. No significant differences in serum sodium, potassium, chloride, bicarbonate, calcium, or creatinine concentrations were detected at any time point, when compared with baseline values. No significant differences in the concentration of sodium, potassium, chloride, bicarbonate, calcium, phosphorus, or creatinine concentration were detected in the effluent at any time with the exception of a significant decrease in effluent urea nitrogen ($P = .03$) detected at Time 6 hours when compared with 1 hour (Table 3).

RRT Parameters

In general, horses tolerated the high rate of blood extraction (250 mL/min) from the dialysis catheter during the experimental period without complication. Occasional (1–2 episodes/h) brief periods (1–3 minutes) of high negative pressure were detected within the dialysis circuit when the jugular vein would collapse on the dialysis catheter. After a momentary pause of the dialysis procedure, RRT was reinitiated without difficulty. The mean hourly effluent produced and mean hourly dialysate, replacement, and pre- and postfilter replacement fluid volumes utilized during the RRT session in the 5 horses are presented in Table 4. The mean hourly CrCl is also reported in Table 4 with an overall mean CrCl (Times 1–6 hours) of 0.127 mL/kg/min (68.9 mL/min). Likewise, the mean hourly Kt/V is reported in Table 4 with an overall mean Kt/V (Times 1–6 hours) of 0.308. The mean URR was 24% over the 6 hours CRRT period.

Discussion

Acute renal failure is a serious and life-threatening disorder in horses with numerous causes.^{2,3} Renal replacement therapies have been used in people and

companion animals to help improve the outcome of ARF^{4,5}, whereas nonrenal indications for RRT include removal of inflammatory mediators (ie, cytokines) and treatment of toxicities or fluid overload.⁶ In companion animals, CRRT has been used successfully to treat ARF, leptospirosis, tumor lysis syndrome, heatstroke, pre- and postsurgical ureteral obstruction, and various toxicities.⁵ To date, RRT has not been widely used in horses. In the study here, RRT was successfully administered to 5 healthy mares and provided moderate efficacy as a RRT in conjunction with minor alterations in various vital parameters. In light of this information, RRT has the potential to become a viable adjunct treatment for ARF in horses.

Significant changes in monitored vital parameters were observed in the study presented here, although none were considered life threatening. Heat loss commonly occurs in people during RRT consequently promoting hypothermia.^{22,23} Similarly, in the study here, a progressive and significant decrease in rectal temperature was observed during the 6 hour procedure. Hypothermia results from extracorporeal blood flow that is exposed to a cooler ambient environment and RRT fluids, thus returning the patient's blood at a lower temperature. Temperature loss is increased when faster dialysate rates or slower extracorporeal blood flow rates are implemented.²² Intravenous fluid warmers are utilized in some dialysis facilities, but a randomized controlled trial did not demonstrate maintenance of normothermia with the use of IV fluid warmers in people.²³ Another potential variable that may have contributed to hypothermia observed in this study was the CRI of detomidine.²⁴ While the decrease in rectal temperature in this study was mild, monitoring body temperature during RRT is prudent and allows detection of hypothermia and implementation of methods to facilitate warming of the patient (eg, blankets, warmed fluids, higher ambient temperatures). Rectal temperature returned to within normal intervals within 6 hours of discontinuation of RRT in this

Table 2. Mean \pm standard deviation values of various clinicopathologic parameters measured from blood in 5 horses over a 6 hour period of renal replacement therapy.

Time (hour)	PT (seconds)	PTT (seconds)	Platelet ($\times 10^3/\mu\text{L}$)	Na ⁺ (mEq/L)	K ⁺ (mEq/L)	Cl ⁻ (mEq/L)	HCO ₃ (mEq/L)	Ca ⁺⁺ (mg/dL)	Phos (mg/dL)	BUN (mg/dL)	Cr (mg/dL)
0	17.6 \pm 1.3	59.5 \pm 3.3	194 \pm 22	136 \pm 0.8	4.2 \pm 0.2	102 \pm 0.9	31.2 \pm 0.4	12.5 \pm 0.4	2.6 \pm 0.2	14.4 \pm 1.1	1.3 \pm 0.1
1	19.3 \pm 1.5	>245 ^a	159 \pm 21	136 \pm 3.2	3.5 \pm 0.4	100 \pm 2.9	30.6 \pm 1.5	11.0 \pm 0.8	2.8 \pm 0.4	12.2 \pm 1.3 ^a	1.3 \pm 0.2
2	19.9 \pm 1.3 ^a	>245 ^a	158 \pm 12 ^a	136 \pm 3.3	3.5 \pm 0.2	99 \pm 1.9	31.8 \pm 3	11.0 \pm 1.0	3.3 \pm 0.3 ^a	12.2 \pm 1.3 ^a	1.3 \pm 0.1
3	20.6 \pm 1.5 ^a	>245 ^a	158 \pm 14 ^a	134 \pm 6.8	3.7 \pm 0.3	97 \pm 4.3	31.2 \pm 2.3	11.1 \pm 0.9	3.4 \pm 0.2 ^a	11.6 \pm 1.1 ^a	1.3 \pm 0.1
4	21.7 \pm 1.5 ^a	>245 ^a	155 \pm 12 ^a	136 \pm 3.7	3.7 \pm 0.4	99 \pm 2.9	31.4 \pm 2.1	11.5 \pm 0.9	3.7 \pm 0.3 ^a	11.4 \pm 1.1 ^a	1.3 \pm 0.1
5	23.3 \pm 2.1 ^a	>245 ^a	156 \pm 22 ^a	136 \pm 4.4	3.9 \pm 0.3	99 \pm 3.2	31 \pm 2.3	11.4 \pm 0.9	3.7 \pm 0.2 ^a	11.2 \pm 1.1 ^a	1.4 \pm 0.2
6	24.2 \pm 2.8 ^a	>245 ^a	152 \pm 15 ^a	134 \pm 6.6	3.5 \pm 0.7	98 \pm 4.6	30 \pm 3.4	11.1 \pm 1.3	3.7 \pm 0.3 ^a	11.0 \pm 1.4 ^a	1.4 \pm 0.1
12	18.2 \pm 1.4	164 \pm 48 ^a	161 \pm 49	NP	NP	NP	NP	NP	NP	NP	NP
24	18.5 \pm 1.4	65.6 \pm 8.5	165 \pm 33	NP	NP	NP	NP	NP	NP	NP	NP

PT, prothrombin time; PTT, partial thromboplastin time; Na⁺, sodium; K⁺, potassium; Cl⁻, chloride; HCO₃, bicarbonate; Ca⁺⁺, calcium; Phos, phosphorus; BUN, blood urea nitrogen; Cr, creatinine; NP, not performed.

PTT >245 indicates that the parameter was greater than the maximum value measured by analyzer.

^aWithin a column, significantly different from baseline (Time 0) measurement.

study. Other significant changes included modest decreases in heart and respiratory rates at variable times. These changes were not perceived as clinically important and were likely related to the CRI of detomidine, which is known to cause cardiovascular and respiratory depression.^{20,25-27} In addition, transient arrhythmias were noted during RRT. A low incidence of arrhythmias (<5%) has been reported in people treated with CRRT, but these patients tend to have significant underlying medical disorders (ie, sepsis, acidemia, electrolyte derangements).²⁸ The authors suggest that the arrhythmias noted in this study were related to detomidine administration, as this drug has been associated with second-degree atrioventricular block, sinoatrial block, premature supraventricular depolarization, and premature ventricular contractions^{26,27}; in addition, normal heart rhythm was recorded shortly after discontinuation of detomidine CRI. Alternatively, the arrhythmias observed may have been incidental observations as second-degree atrioventricular block, and ventricular premature contractions have been documented in clinically healthy horses over a continuous 24-hour ECG monitoring period.²⁹

During any form of hemodialysis, blood traveling through the dialysis circuit undergoes shear stress from rapid removal through the IV catheter and is also exposed to various exogenous substances, including IV catheters, tubing, and dialysis chambers and membranes, all activating, to varying degrees, the coagulation cascade and platelets. Thus, 1 important component in RRT is provision of anticoagulation to prevent, or at least slow, clotting of dialysis membrane filters. Anticoagulation is accomplished via administration of heparin or citrate.³⁰ In the study reported here, 100 IU/kg of heparin was administered as a bolus followed by a CRI of 50 IU/kg/h, as previously described.¹⁸ A significant prolongation of the PT and PTT was observed between 1 and 6 hours when compared with baseline; these parameters returned to baseline values within 18 hours after discontinuation of heparin CRI. The exact prolongation of PTT in this study could not be determined as samples exceeded the upper limit of detection (>245 seconds); however, previous reports of heparin administration at the same dose resulted in a mean \pm SD PTT prolongation of 335 \pm 93 to 684 \pm 334 seconds during a 6 hour period.¹⁸ In addition, a significant decrease in platelet count was observed between 2 and 6 hours. Heparin administration in horses, at doses of 100, 240, and 320 IU/kg SC every 12 hours, has been reported to result in reduction in platelet counts of similar magnitude as that observed in this study.^{31,32} The exact mechanism of heparin-associated thrombocytopenia in horses remains unknown, but a similar phenomenon has been documented in people. Heparin-induced thrombocytopenia (Type 1) in people is a nonimmunogenic process associated with an early, limited, and self-recovering platelet decrease.³³ Heparin-induced thrombocytopenia (Type 2) is associated with a major drop in platelets caused by the formation of platelet-activating antibodies against complexes of platelet

Table 3. Mean \pm standard deviation values of various biochemical parameters measured in the effluent from 5 horses over a 6 hour period of renal replacement therapy.

Time (hours)	Na ⁺ (mEq/L)	K ⁺ (mEq/L)	Cl ⁻ (mEq/L)	HCO ₃ (mEq/L)	Ca ⁺⁺ (mEq/L)	Phos (mg/dL)	EUN (mg/dL)	Cr (mg/dL)
1	133 \pm 1.3	6 \pm 0.2	102 \pm 0.8	24.6 \pm 0.5	5.7 \pm 0.4	1.9 \pm 0.3	9.2 \pm 0.8	0.9 \pm 0.1
2	134 \pm 1.8	3.7 \pm 0.2	102 \pm 0.5	26 \pm 1.6	5.6 \pm 0.6	2.1 \pm 0.3	8.4 \pm 0.5	0.9 \pm 0.1
3	133 \pm 1.6	3.8 \pm 0.2	100 \pm 1.3	25 \pm 1.6	5.5 \pm 0.6	2.3 \pm 0.3	7.8 \pm 1.3	0.9 \pm 0.1
4	134 \pm 1.3	3.97 \pm 0.3	100 \pm 2.3	22.8 \pm 5	5.3 \pm 1.1	2.2 \pm 0.5	6.8 \pm 1.9	0.8 \pm 0.2
5	134 \pm 1.6	4.0 \pm 0.3	101 \pm 1.9	23.2 \pm 4.6	5.3 \pm 0.8	2.3 \pm 0.5	7.2 \pm 1.5	0.8 \pm 0.2
6	134 \pm 1.8	4.1 \pm 0.2	100 \pm 2.3	21.6 \pm 8.4	4.8 \pm 1.3	2.1 \pm 0.8	6.0 \pm 2.5 ^a	0.7 \pm 0.3

Na⁺, sodium; K⁺, potassium; Cl⁻, chloride; HCO₃, bicarbonate; Ca⁺⁺, calcium; Phos, phosphorus; EUN, effluent urea nitrogen; Cr, creatinine.

^aWithin a column, significantly different from baseline (Time 1) measurement.

Table 4. Mean \pm standard deviation values of the volume of effluent produced and volume of dialysate, pre- and postfilter replacement fluid used (mL/h) over 6 hours of renal replacement therapy (see Fig 1) in 5 horses along with the mean \pm standard deviation calculated creatinine clearance (CrCl), urea reduction ratio (URR), and urea clearance over time (Kt/V).

Time (hours)	Effluent (mL/h)	Effluent (mL/kg/h)	Dialysate (mL)	Pre-filter (mL)	Postfilter (mL)	CrCl ^a (mL/min)	CrCl ^a (mL/kg/min)	URR ^a (%)	Kt/V ^a
1	6,352 \pm 1,567	11.2 \pm 2.1	2,389 \pm 60	22,377 \pm 608	1,595 \pm 391	73.6 \pm 16.9	0.1349 \pm 0.03	N/A	0.336 \pm 0.06
2	6,835 \pm 252	12.2 \pm 1.1	2,559 \pm 94	2,566 \pm 94	1,705 \pm 57	76.8 \pm 9.6	0.1421 \pm 0.02	N/A	0.338 \pm 0.06
3	6,819 \pm 368	12.2 \pm 1.1	2,585 \pm 140	2,559 \pm 141	1,707 \pm 81	75.1 \pm 12	0.1415 \pm 0.03	N/A	0.329 \pm 0.06
4	6,598 \pm 270	11.8 \pm 1.2	2,475 \pm 94	2,479 \pm 105	1,647 \pm 60	63.0 \pm 21.0	0.1153 \pm 0.04	N/A	0.291 \pm 0.11
5	6,654 \pm 744	11.8 \pm 1.1	2,492 \pm 285	2,504 \pm 251	1,637 \pm 243	68.0 \pm 16.2	0.1239 \pm 0.02	N/A	0.303 \pm 0.05
6	6,317 \pm 496	11.3 \pm 1.6	2,402 \pm 199	2,390 \pm 191	1,588 \pm 123	56.9 \pm 20.8	0.1041 \pm 0.04	23.6 \pm 7	0.254 \pm 0.12

N/A, not applicable.

^aSee text for formulas.

factor 4 and heparin.³³ Likely a combination of heparin-associated thrombocytopenia, shear forces, and exposure of platelets to exogenous substances contributed to the decreased platelet count.

The dose of heparin in this study appeared to be appropriate for prevention of excessive clot formation within the dialyzer. However, hematoma formation was observed at the catheter site after removal of the catheters in the transverse facial artery and left jugular vein in some horses. The combination of prolonged PT and PTT and either high blood pressure at the arterial site or large bore catheter size at the left jugular site likely made these sites vulnerable to bleeding and hematoma formation. During CRRT in people, heparin dosage is typically adjusted periodically (ie, every 6 hours) to a targeted PTT prolongation of 1.3–2 times the reference value for PTT.^{34,35} The authors speculate that lower doses of heparin may be adequate to provide anticoagulation during RRT in horses; however, future studies that evaluate the heparin dose more rigidly are needed.

A significant decrease in BUN and increase in serum phosphorus was detected in this study. Urea, a small-molecular-weight metabolite (60 Da) produced from the metabolism of nitrogen, is used as a surrogate index for unidentified or unmeasured small-molecular-weight solutes that may contribute to uremia.²¹ As one of the primary objectives of RRT is to remove uremic toxins,

it is not unexpected to observe a decrease in BUN, particularly in light of the fact that the dialysate and replacement fluids are devoid of urea. What is peculiar is the moderate increase in serum phosphorus noted between 2 and 6 hours. Hyperphosphatemia is commonly observed in acute kidney injury in people and consequently phosphorus is not a standard component of dialysate or replacement fluids in CRRT.³⁶ It is therefore common to observe hypophosphatemia rather than hyperphosphatemia during CRRT.³⁶ The serum phosphorus remained within reference limits in the horses in this study, but monitoring of serum electrolytes and minerals is indicated in horses subjected to RRT. The exact reason for the increase in serum phosphorus concentrations in the horses evaluated here remains obscure.

Standard methods to evaluate treatment adequacy and efficacy of RRT include creatinine clearance, urea reduction ratio, and urea clearance over time. Creatinine clearance represents the volume of blood cleared of creatinine per minute exertion of urine, or in the case of RRT, effluent.¹⁶ The mean CrCl over the 6 hour RRT period was 68.9 mL/min or 0.127 mL/kg/min. In a reported equine case investigating peritoneal dialysis, the CrCl in a horse with ARF treated with intermittent or continuous peritoneal dialysis was 12.5 mL/min (0.0322 mL/kg/min) and 40.9 mL/min (0.1054 mL/kg/min), respectively, which is approxi-

mately 20% lower than the CrCl reported in the healthy horses of this study.¹² In another report, the estimated CrCl in 2 horses treated with intermittent peritoneal dialysis was 60 L/wk and 80 L/wk.¹³ Based on the study here, a mean CrCl of 69 mL/min, 6 hour treatment period, and 1 week of treatment (one 6-hour treatment/d) would yield an estimated CrCl of 174 L/wk using RRT. Of note, none of the described artificial methods of mimicking kidney function approaches the efficiency of the kidneys in healthy horses (mean CrCl 2.1 mL/kg/min; range 1.7–2.7 mL/kg/min) clearly demonstrating that there is no current substitute for the function of the healthy equine kidney in an animal of this size.³⁷ Although the CrCl documented in this study does not approach rates equal to the healthy horse or smaller patients, the authors of this study suggest that RRT may help facilitate recovery from ARF, particularly in light of the fact that the CrCl of CRRT moderately exceeds that of intermittent or continuous peritoneal dialysis, both of which have been used successfully to treat ARF in horses.^{12,13}

Urea reduction ratio (URR) represents the percentage decline in urea concentration during a dialysis session and is a function of clearance of urea from the blood by the dialyzer, duration of dialysis treatment, and volume of distribution of urea in the patient.³⁸ The URR is a quantitative measurement of urea clearance and is used as a proxy for adequacy of solute clearance.³⁸ The URR is inversely correlated with body weight such that URR in small dogs and cats treated with intermittent hemodialysis ranges from 45 to 95%.^{21,39–41} In 2 studies in people (mean body weight 71 and 79 kg) with ARF treated with hemodialysis, the mean \pm SD URR was 54 ± 15 and $63 \pm 8\%$.^{39,40} The URR has also been used as a measure of dialysis adequacy in people with end-stage kidney disease with 1 study suggesting that intensity of dialysis should result in a URR of $\geq 60\%$ to improve survival.³⁹ Little information is available with regard to the URR and CRRT; however, in the horses studied here, the mean URR was notably lower (24%) than other species treated with intermittent hemodialysis and was likely a reflection of the slower solute clearance of CRRT as well as the much larger body weight and low BUN concentration (ie, minimal concentration gradient of urea nitrogen between blood and dialysate) of the horses used in this study. Another variable to consider that may have impacted the URR is the diuresis created by the CRI of detomidine; urea clearance may have been increased by the increased urine output.

Urea clearance over time (Kt/V) describes the fractional clearance of urea during a hemodialysis treatment while factoring in patient size. In this formula, K represents urea clearance (mL/min), whereas Kt represents total solute removal per time period (K [mL/min] \times time [min] patient receives treatment per day). Kt is then normalized by dividing Kt by the patient's volume of distribution (V in mL). Urea is equally distributed throughout all body fluid compartments, thus the volume of distribution is estimated by total body water in mL (estimated to be 60% of body weight [kg] in the horse \times 1,000).⁴² Similar to CrCl and URR, the overall mean Kt/V in this study (0.308) was

lower than that which was reported in people or small animals.^{5,43–45} In general, a Kt/V of 1–1.3 is targeted in people with acute kidney injury and has been reported to provide acceptable treatment efficacy in people.^{43–45} Owing to the large size of the horse relative to people and companion animals, it is not unexpected that the Kt/V was notably lower than target values in other species.

It is clear that strict standardization of anticoagulant administration, quantification of adequacy of solute removal, and dose/intensity of CRRT are not well established in people.⁴⁶ However, several recent large prospective trials in critically ill patients with acute kidney injury have investigated the optimal intensity of renal replacement therapy and survival.^{45–49} In these studies, there was no difference in 60- to 90-day survival in patients receiving lower intensity continuous venovenous hemodiafiltration (effluent flow rate of 20–25 mL/kg/h) as compared with treatment at higher intensity (effluent flow rate of 35–40 mL/kg/h)^{45–49}; therefore, the current suggested target dose for CRRT is 20 mL/kg/h.⁵⁰ In the study here, the mean effluent (based on body weight) was approximately half of the target effluent dose in people, ranging from 11 to 12 mL/kg/h. Based on maximum flow rate limitations with commercial CRRT machines, higher doses are not likely possible in horses.

Interpretation of the methods to evaluate treatment adequacy in horses should be made in light of 2 important variables: (1) horses in this study were healthy with serum concentrations of urea and creatinine within reference intervals, and (2) the mean body weight of the horses in this study was 544 kg. It is anticipated that horses with ARF and marked azotemia would demonstrate a higher concentration gradient for diffusion of uremic toxins to occur from the blood to dialysate, thus resulting in higher CrCl, URR, and urea clearance over time during RRT sessions. The user must also be aware that the commercial equipment available for veterinary use was designed for people (ie, body weight <100 kg). Therefore, the efficacy of RRT in people and small animals is greater than in horses because of their smaller body weight. For example, based on an average body weight of a 70 kg person with 5,600 mL blood volume, approximately 22 minutes of RRT (blood flow rate 140 mL/min) is necessary to process a complete blood volume exchange.⁵¹ In comparison, a 450 kg horse with 36,000 mL blood volume would take approximately 144 minutes of RRT (blood flow rate 250 mL/min) to process the complete blood volume.

As noted previously, indications for instituting RRT in people include reduced glomerular filtration rates that result in solute imbalance (eg, azotemia with uremic clinical signs, hyperkalemia [>6 mEq/L], metabolic acidosis [$\text{pH} < 7.2$] caused by renal failure) or oliguria resulting in extracellular fluid volume overload (eg, pulmonary edema) that does not respond to other forms of treatment.^{14,15} Varying degrees of azotemia, uremic encephalopathy, and other metabolic derangements have been reported in horses with ARF.^{9–13,52–56} Urine production in equine ARF varies ranging from oliguria, frequently

noted in the early stages of hemodynamically mediated ARF, to nonoliguria or polyuria; however, anuria is rare.^{2,12,13,53,56} The number of published reports and retrospective studies of equine ARF are sparse, but presumably many cases respond to conventional treatment.^{2,9–13,52,53} However, numerous reports of equine ARF with persistent or worsening azotemia, oliguria, or both have been documented, some of which have prompted clinicians to utilize drugs to promote renal perfusion or urine production (furosemide, mannitol, dopamine) and RRT (peritoneal dialysis, IHD) to facilitate recovery.^{2,9–13,53,56} In this study involving healthy horses, the net fluid change was set to 0; if fluid retention was present in a clinical case of equine ARF, the CRRT machine could be set to provide a net fluid loss to reduce fluid retention in the patient. Furthermore, fluids utilized in RRT can be tailored to specific electrolyte compositions to effectively correct electrolyte derangements such as moderate-to-severe hyperkalemia associated with ARF.³⁶ The authors suggest that given the limited options of advanced treatment for ARF in horses, RRT is a viable treatment option.

Several limitations of this study should be noted. First, CRRT in people is typically administered for prolonged periods of time (ie, days). In the study here, horses were administered RRT for only 6 hours. While a longer treatment period could have been attempted in this study, maintaining a horse under light sedation and restraint for longer than 6 hours may impose undue stress to the horse. In a clinical case of ARF in a horse, the authors suggest a treatment period of 6–8 hours per day, followed by a period of rest, and then recommencement of RRT. Another limitation was the fact that the horses were healthy. In uremic patients, bleeding diathesis, as a result of altered platelet function and excessive production of prostacyclin and nitric oxide, may be present.⁵⁷ Therefore, anticoagulant dosage may need to be modified in clinical situations based on the status of patient hemostasis. Despite these limitations, RRT was successfully administered to healthy horses using a commercially available CRRT machine, dialysate/replacement fluids, and anticoagulant with minimal changes in monitored vital parameters in healthy horses. RRT is unlikely to be as efficacious in clearing uremic toxins in horses, as compared with smaller patients, yet the authors contend that CRRT is worth of consideration as an adjunct treatment in horses with ARF.

Footnotes

- ^a AnaSed, Lloyd Laboratories, Shenandoah, IA
^b 14 gauge × 5.25 inch intravenous catheter, Mila International, Erlanger, KY
^c 16 gauge × 3 inch intravenous catheter, Mila International
^d 20 gauge × 1.5 inch Quickflash Radial Artery Catheter, Arrow International, Reading, PA
^e 14 French × 24 cm split catheter, MedComp, (ASPC24-3), Harleysville, PA
^f Rusch Foley Catheter, Teleflex Medical, Kamunting, Malaysia
^g Passport 2, Datascope Corp, Mahwah, NJ
^h Dormosedan, Pfizer Animal Health, Exton, PA
ⁱ Sodium Heparin, APA Pharmaceuticals, Exton, PA

^j PrismaFlex, Gambro, Lund, Sweden

^k M150 Filter, Gambro, Meyzieu Cedex, France

^l Plasmalyte, Abbot Laboratories, Chicago, IL

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