Evaluation of Urea and Creatinine change during Continuous Renal Replacement Therapy: Effect of blood flow rate

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Abstract

Objective: To determine if faster blood flow rate (BFR) influences solute maintenance in continuous renal replacement therapy (CRRT)

Design: Prospective randomised controlled trial

Setting: Twenty-four bed single centre tertiary level ICU

Participants: Critically ill adults requiring CRRT

Interventions: Patients were randomised to receive one of two BFR: 150 mL/min or 250 mL/min.

Main outcome measures: Delta urea and creatinine (% change from baseline) and delivered treatment for each 12-hour period was used to assess solute maintenance.

Results: One hundred patients were randomised with 96 completing the study (150 mL/min: 49; 250 mL/min: 47). There was a total of 854 12-hour periods (150 mL/min: 421; 250 mL/min: 433). Mean hours of treatment per 12 hrs was 6.3 hrs (SD 3.7) in the 150mL/min group and 6.7 hrs (SD 3.9) in the 250mL/min group, p= 0.6. There was no difference between the two BFR groups for mean delta urea (150 mL/min: -0.06% [SD, 0.015] vs. 250 mL/min: - 0.07% [SD, 0.01], p= 0.42) or mean delta creatinine (150 mL/min: -0.05% [SD, 0.01] vs. 250 mL/min: -0.08% [SD, 0.01], p= 0.18). Independent variables associated with a reduced % change in urea and creatinine were low haemoglobin levels, -0.01% [SD,0.005], p= 0.002; 0.01% [SD,0.005], p= 0.006) and less hours treated; -0.023% [SD,0.001], p= 0.000; -0.02% [SD,0.002], p= 0.001. No effect for body weight was found.

Conclusions: Faster blood flow rate did not affect solute control in patients receiving CRRT, however differences in urea and creatinine were influenced by serum haemoglobin and hours of treatment.

Key words: Continuous Renal Replacement Therapy, solute clearance, circuit life, continuous haemofiltration, acute kidney injury, critical care

Introduction

Acute kidney injury (AKI) is a complication of critical illness that affects up to 50% of intensive care patients.[1-3] The use of Renal Replacement Therapy (RRT) has evolved as the treatment for severe AKI and is required in up to 5-6% of all critically ill patients in intensive care units (ICUs).[4] CRRT is the most common dialytic therapy used to treat AKI worldwide.[5] CRRT techniques are instituted by clinicians with the aim of achieving homeostasis of water, electrolytes, acid base and removal of waste products in this group of patients.[6] Solute control and maintenance has long been a key priority in the provision of the therapy and has been an area of research and focus since the first Acute Dialysis Quality Initiative (ADQI) consensus meeting.[7,8] Subsequently two large multi-centred randomised controlled trials definitively demonstrated that there was no survival benefit in increasing the dose of CRRT from the common dose of 25 ml/kg/hr.[9,10]

While greater CRRT dose does not lead to improved patient outcomes, solute removal (particularly small solutes such as urea and creatinine) remains an important aim of the therapy. Clinicians continue to target a prescription dose and best settings to achieve solute removal for each 24-hour period to remove excessive toxins and maintain solute balance for each individual patient.[8] In addition to a prescribed effluent rate, other clinical variables may contribute to solute clearance in CRRT, including 'down time', membrane composition, membrane fouling and frequent circuit clotting.[11] Recently, the ADQI have recommended research objectives aimed at identifying optimal techniques and practical prescriptions for solute removal.[8] Blood flow rate

(BFR) and modality of CRRT are two common bedside prescriptions that may have a direct impact on solute removal but have not been assessed in any randomised controlled study. An increase in BFR in convective modes such as Continuous Venovenous Haemofiltration (CVVH) may directly assist solute removal by increasing transmembrane pressure, expose additional plasma water to the haemofilter per effluent dose and assist solvent drag across the membrane. Indirectly, faster BFR may decrease blood viscosity in the membrane, increase filtration fraction and decrease membrane fouling with eventual clotting. In diffusive modes such as Continuous Venovenous Haemodialysis/Diafiltration (CVVHD, CVVHDF), faster BFR may assist solute removal by maximising concentration gradients between blood (plasma) flow and dialysate flow rates, decreasing dwell time and sustain diffusive movement of solutes across the membrane.[12]

We aimed to test our hypothesis that faster BFR increases small solute removal (e.g. urea and creatinine) in critically ill patients receiving CRRT. To address this question, we report additional findings from our recently published randomised controlled trial comparing two blood flow rates and the effect on circuit life in patients treated with CRRT.[13]

Methods

Trial design and setting

This study was a prospective, parallel group RCT conducted in a 24 bed, adult, tertiary referral intensive care in Melbourne, Victoria, Australia. The study was registered at the Australian New Zealand Clinical Trials Registry (ACTRN:12615001353583) and approved by Austin Health Human

Research Ethics Committee (HREC project No. H2012/04772). Written informed consent was obtained prior to, or soon after enrolment, by the patient treated or their next of kin.

Eligibility criteria

Critically ill patients in ICU were eligible for the study if they fulfilled the following criteria: 1) age ≥ 18 yrs, 2) AKI (RIFLE classification = F)[14] requiring CRRT. Patients were considered ineligible for the study if they fulfilled any exclusion criterion: 1) required citrate anticoagulation (citrate protocol requires set blood flow rate of 150 mL/min), 2) expected stay in the ICU less than 24 hours.

Interventions

The study compared two BFR settings and the effect on small solute control in CRRT. BFR was either 250 mL/min or 150 mL/min using CVVH and CVVHDF modes. Vascular access was either Niagara 13.5 Fr-catheter (24cm) (Bard, Murray Hill, NJ, USA) or Gamcath Dolphin Protect 13.0 Fr-catheter (25 cm) (Gambro, Hechingen, Germany) dual lumen catheters. Machines used were Prismaflex with AN69ST (ST100) 1.0 m^2 membrane (Gambro Nephral TM, Lund, Sweden) or Infomed HF 440 with DF 140 Polyethersulfone 1.4 m^2 membrane (Infomed, Geneva, Switzerland) for all treatments respectively. We used bicarbonate buffered replacement and dialysis fluid (Baxter, Castlebar, Co. Mayo, Ireland). In CVVH, replacement fluid was delivered into the extracorporeal circuit (EC) before and after the filter (pre and postdilution), with a ratio of 50% predilution and 50% postdilution. Dose in CVVH was standardised at 2000 mL/hour. In CVVHDF,

replacement fluid was delivered 100% postdilution. Dose in CVVHDF was standardised at 1000 mL/hour replacement and 1000 mL/hour dialysate. CRRT was prescribed by the treating intensivist and provided by ICU nurses.

Data collection

We collected baseline data regarding age, gender, weight, BMI, source of admission, severity of illness (Acute Physiology and Chronic Health Evaluation score II, III; Simplified Acute Physiology Score II), diagnostic group, presence of sepsis, mechanical ventilation, inotropes and vasopressors, and basic laboratory variables pertaining to renal function.

Outcome measurements

For all patients, twice-daily (0500 and 1700 hrs) measurement of haemoglobin and biochemistry (serum creatinine and urea) was performed. The primary outcome was small solute maintenance estimated by the change or delta urea and creatinine over these two predefined 12-hour periods each day (% change in serum levels over time). Circuit life was documented for each CRRT circuit as cumulative hours so that delivered treatment hours could be calculated for each 12-hour period (T1 [0500-1700 hrs] and T2 [1700-0500 hrs]).

Randomisation

Patients were screened and entered into the study by ICU clinical staff. Patients were assigned randomly with stratification for modality. Once the treating physician prescribed CRRT and the mode of therapy, patients were randomised using a web based central randomisation service

(Griffith University Clinical Trial Coordinating Centre). A variable block randomisation with parallel allocation was generated by software with inbuilt concealment to allocate to each study group (150mL/min vs. 250 mL/min). Patients stayed in the treatment group allocated at randomization and modality (CVVH or CVVHDF) for treatment throughout their ICU stay. The sample size was without power calculation, was of convenience and associated with the primary investigation.[13]

Data analysis

Linear regression analysis was performed to identify independent variables that may be associated with change in small solute serum levels. Independent variables included modality of CRRT, gender, BMI, weight, Hb and number of hours treated in each 12-hr period. Repeated measures ANOVA was used on the independent variables demonstrating significance. The advantage of this model is that it considers within subject measures over multiple time points. In this study, patients contributed multiple 12-hr periods measuring solute % change over these periods. Data lacking normality of distribution are presented as median with interquartile range (25 and 75%) using Wilcoxon Rank Sum test or mean with SD when normally distributed using student T-test, chi square test and Fishers exact test. A $p < 0.5$ was considered significant. SPSS (IBM, Chicago IL, USA, version 21.0) software was used for all data analysis.

Results

Participants and recruitment

All patients receiving CRRT in the study ICU (n=135) were screened for eligibility between June

2013 and August, 2014. From this, one hundred patients were considered eligible and randomised to the study. Two patients from each group were randomised but did not receive CRRT. The CONSORT diagram for patient enrolment is shown in **Figure 1.** Overall, 96 patients (49 in the 150 mL/min group and 47 in the 250 mL/min group) contributed a total of 854 12-hour treatment interval periods: 421 in the 150 mL/min group and 433 in the 250 mL/min group. Of the patients studied, 50 received CVVH compared to 46 treated with CVVHDF.

At randomisation, patients were similar with respect to age, sex, severity of illness scores (APACHE II, III, SAPS II), admission source and diagnosis (**Table 1**). There was a slight weight difference with patients in the 150 mL/min group heavier (p= 0.027); however, BMI was similar for both groups. Pre-randomisation renal function was also similar for both groups.

Primary outcomes – Solute maintenance

A total of 7745.5 treatment hours were recorded from both groups: 3840.7 in the 150 mL/min group and 3904.8 in the 250 mL/min group (**Table 2**). The mean treatment hours for each 12-hour period was similar (150 mL/min, 6.3 hrs (SD 3.7) (52.5%) vs. (250 mL/min, 6.7 hrs (SD 3.9) (55.8%), p= 0.6 as well as total number of 12-hour periods for each BFR group (Table 2). The median number of 12-hour periods per patient was also similar for both groups (150mL/min, 6 (IQR 4, 12) vs. 250 mL/min, 7 (IQR 4.5, 12), p = 0.4.

Blood plasma concentrations of urea and creatinine were similar for time interval (T1 and T2), blood flow rate and modality (**Table 2**). Linear regression analysis demonstrated no difference in

the delta urea and creatinine for BFR groups, modality of CRRT, gender, BMI and weight. Repeated measures ANOVA revealed no difference between the two BFR groups for delta urea 150 mL/min (-0.06% [0.015]) vs. 250 mL/min (- 0.07% [0.01]), p=0.42 (**Figure 2.**) or delta creatinine 150 mL/min (-0.05% [0.01]) vs. 250 mL/min (-0.08% [0.01]), p=0.18 (**Figure 3.**) There was a significant correlation between the 12-hourly % change in the serum concentration of these two small solutes with decreased haemoglobin levels, -0.01% [0.005], p= 0.002; 0.01% [0.005], p= 0.006) and less hours of CRRT during the 12-hour period (e.g. more down time); -0.023% [0.001], p= 0.000; -0.02 [0.002], p= 0.001.

Discussion

Key Findings

In a cohort of 96 patients requiring CRRT, three key findings have been identified. First, analysis of the data from this study failed to support the hypothesis that faster blood flow would improve small solute clearance. Second, there was an association with number of hours treated with CRRT and change in serum solute levels. Third, lower serum haemoglobin levels are an independent factor associated with difference in urea and creatinine levels.

Relationship to previous studies

The efficiency of solute removal in CRRT has been a key focus since beginning of use for treating critically ill patients with AKI.[15,16] Foundation studies for small solute removal in CRRT were often unable to report BFR as this was determined by arterial blood pressure in Continuous Arterio-

Venous circuits (CAVH), or as a low fixed rate (100 mL/min) determined by primitive blood pumps in the first venovenous circuits. These early reports identified that effluent rates (dialysate or ultrafiltration rates) were the most important determinant of small solute removal as the volume of effluent would approximate the clearance.[15,16] Today, despite significant advances in CRRT technology, 'dosing' or solute clearance in CRRT is still expressed as Total Effluent Volume (TEV) per weight and unit of time (mL/kg/hr)[11] indicating that other factors may be less important in the clearance of solutes across the semi-permeable membrane.

One aspect of CRRT technology that has changed over time is clinician prescribing faster BFR. A recent survey of Australian and New Zealand ICUs indicated a BFR of 150-200 mL/min was the dominant setting, however, faster rates of 200-250 mL/min was now commonplace in ICU's surveyed.[17] Observational studies and recent worldwide practice surveys of CRRT also demonstrate great variability in practice from 80 mL/min[18] to 350 mL/min.[19,20] The prescription of BFR in Intermittent Haemodialysis (IHD) has long been seen as integral to therapy prescription for 'dosing' (solute removal) in direct relation to dialysate flow rates and is well established and standardised for the treatment of Chronic Kidney Disease (CKD) with dialysis.[21] Blood flow rates of ≥300 mL/min are prescribed typically with matching or higher dialysate flow rates (300-500mL/min) to achieve azotemic control in this group of patients.[22,23] One key important difference between IHD and CRRT remains the ability to achieve higher BFR during IHD with the use of long term large bore vascular access catheters and arteriovenous shunts which both allow high BFR prescriptions aimed at targeted dosing regimens accordingly.

Historically, the prescription of BFR in CRRT has been based on the experience gained from IHD therapies and 200mL/min has been common without any evidence for this.[24,25] However, limiting factors for blood flow in CRRT have been the use of short term small bore catheters in haemodynamically unstable patients[26] and the machine technology used to pump venous blood through the extracorporeal circuit. Unlike IHD, the setting of BFR in CRRT has been focussed towards EC patency and prevention of premature clotting (e.g. < 6 hrs) of the circuit.[13,19,27,] The prescription of faster BFR in recent times can be attributed to improvements in vascular access catheters and machine capability rather than concern for solute clearance.

One retrospective review of 15 patients has examined any association with blood flow rates and clearances of urea and creatinine in CVVHDF.[28] Four BFR groupings were audited with a mean rate of 125 mL/min and ranged between 35-175 mL/min. A comparative finding was that BFR of 135-145 mL/min demonstrated a difference in urea and creatinine compared to lower BFR ranges in this mode of CRRT. Consistent with our findings they report differences in delta urea and creatinine were best predicted by number of hours treated.

The acronym CRRT suggests that therapy is continuous and without interruption, however 'down-time' and failure occurs frequently.[29] Reasons for interruptions to treatment are clotting, when the patient requires procedures outside the ICU, or when native assessment of kidney function is trialled.[30] In this study, we identified an effective treatment time approximating 50% (6.3hrs and 6.7hrs/12 hrs). The delivery therapy time is similar with previously reported prescription versus delivery data.[24-33] Similar to this study, it has also been demonstrated that

there is a direct correlation between reduction in hours of treatment, and loss of small solute control in critically ill patients.[11,29,31] While there has been comparative prescribed vs. actual delivered dose and therapy reports, it remains unclear the optimal number of CRRT hours per day to maintain small solute control in this group of patients. However, there is recent acknowledgement that clinicians who prescribe CRRT should be aware of the effect of delivery time with comparison to prescribed treatment and should form an integral quality indicator measure in process reassessment, monitoring, reporting and benchmarking for CRRT.[34]

Based on the results identified in this study we suggest the number of hours of active treatment should be routinely reviewed as a component of practice. This information should be reviewed twice daily and then be considered in the context of solute levels and planned activities that might lead to 'down time' with CRRT prescriptions altered accordingly.

In this study, we report that low serum haemoglobin (Hb) levels are an independent variable that affects small solute removal. Patients with lower serum Hb count demonstrated a smaller reduction in serum urea and creatinine levels over a 12-hour period. To our knowledge this is the first study to report this finding.

Strengths and Limitations

This RCT of 100 patients presents for the first time an investigation into the effect of blood flow rate on solute maintenance in two commonly used modes of CRRT. This analysis is based on 7745 hours (>300 days) of treatment time. This number of patients and treatment time is

representative of a tertiary level intensive care unit and provides important findings for current CRRT practice. This study has some limitations. Solute clearance was reported as the % change in serum level over time. A direct measurement of serum solute levels and effluent solute levels would provide a more precise indication of control and represent a closer assessment for clearance. However, we did not measure effluent biochemistry.

The study was conducted in a single tertiary level ICU, where training and expertise amongst nurses for their ability to troubleshoot alarm conditions may influence delivered time/12-hours compared to other centres where circuits terminate prematurely due to low skill level or delays in reinstitution of therapy may be due to poor training. One further limitation may be the defined BFR used in this study. We chose 150 mL/min and 250 mL/min as a result of current intensive care practices. Blood flow rates less than 150 mL/min or greater than 250 mL/min may have yielded a different finding.

Conclusions

A blood flow rate of 250 mL/min does not improve solute clearance compared with a blood flow rate of 150 mL/min in CVVH or CVVHDF. Independent factors that affect solute removal include hours of effective treatment and haemoglobin levels.

Declaration of conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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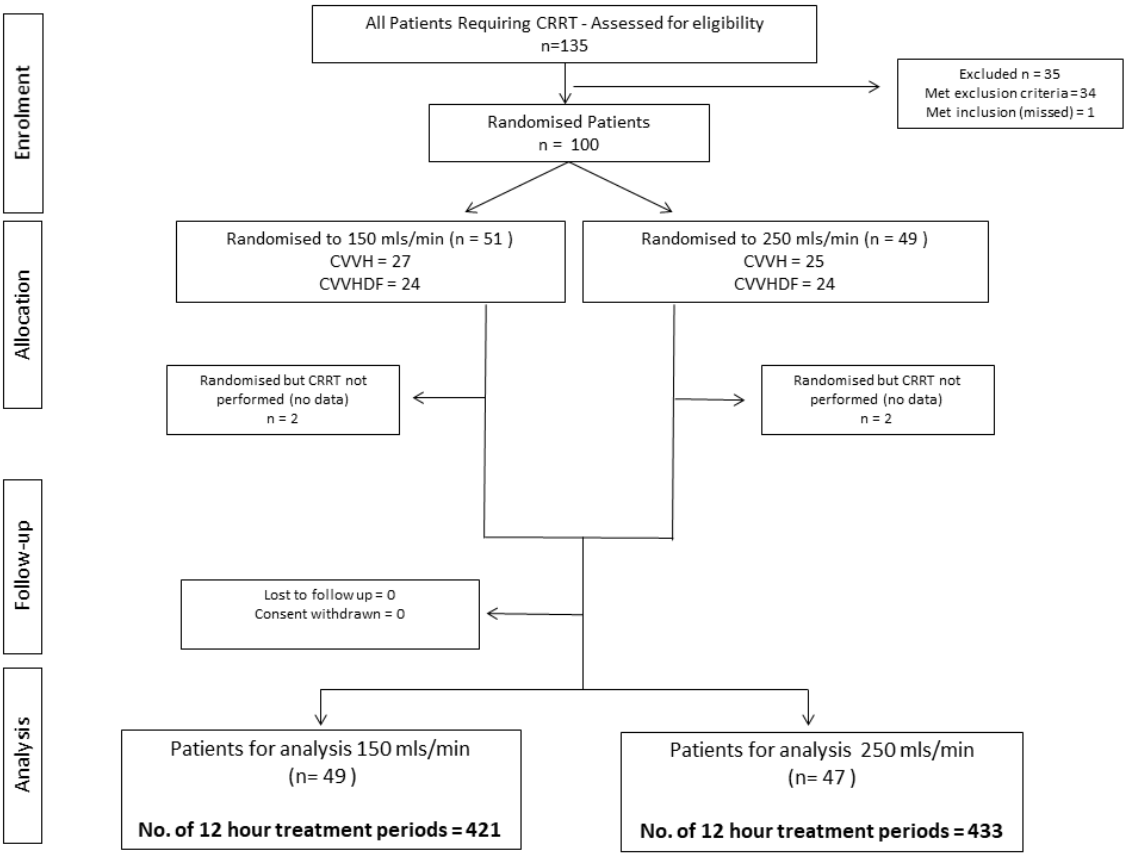

Figure 1. Flow diagram of participants showing assessment of eligibility, enrolment, treatment allocation and follow-up in the trial. CRRT = Continuous Renal Replacement Therapy, CVVH = Continuous VenoVenous Hemofiltration, CVVHDF = Continuous VenoVenous Hemodiafiltration

TABLE 1. Baseline demographic and clinical characteristics

ADMISSION VARIABLES	150 ML/MIN N = 49	250 ML/MIN N = 47	P-VALUE
AGE	61.08 ± 15.96	60.77 ± 18.31	0.93
GENDER (M/F)	34/49 (69%)	24/47 (51%)	0.10
BMI	29.01 ± 5.48	27.59 ± 6.85	0.26
WEIGHT	85.19 ± 20.39	75.85 ± 20.30	**0.03**
APACHE II	22.16 ± 6.47	23.13 ± 6.55	0.47
APACHE III	85.65 ± 23.17	87.21 ± 26.28	0.76
SAPS II	56.22 ± 14.19	55.55 ± 15.21	0.82
SOURCE OF ADMISSION - NO. /TOTAL NO. (%)			
ED	13 (27.7%)	12 (25.5%)	
WARD	17 (34.7%)	17 (36.2%)	
POST OP (ELECTIVE)	7 (14.3%)	6 (12.8%)	
POST OP (EMERGENCY)	5 (10.2%)	4 (8.5%)	
TRANSFER OTHER ICU	5 (10.2%)	5 (10.6%)	
TRANSFER OTHER HOSPITAL	2 (4.1%)	3 (6.4%)	

ADMISSION DIAGNOSIS - NO. /TOTAL NO. (%)			
CARDIOVASCULAR	6 (12.2%)	5 (10.6%)	
CARDIAC SURGERY	11 (22.4%)	8 (17.0%)	
RESPIRATORY	0	1 (2.1%)	
GASTROINTESTINAL	6 (12.2%)	6 (12.8%)	
LIVER FAILURE	5 (10.2%)	6 (12.8%)	
LIVER TRANSPLANT	10 (20.4%)	13 (27.7%)	
ACUTE RENAL/GENITOURINARY	5 (10.2%)	5 (10.6%)	
HEMATALOGICAL	4 (8.2%)	1 (2.1%)	
INFECTION/ABSCESS	2 (4.1%)	2 (4.3%)	
MECHANICAL VENTILATION – NO. (%)	41 (83.7%)	36 (76.6%)	0.44
VASOPRESSOR/INOTROPE – NO. (%)	41 (83.7%)	41 (87.2%)	0.77
SEVERE SEPSIS – NO. (%)	24/49 (49%)	26/47 (55.3%)	0.55
LAB DATA PRIOR TO RANDOMISATION			
SERUM CREATININE	317.20 ± 171.61	297 ± 181.54	0.16
SERUM UREA	23.62 ± 14.94	21.19 ± 10.03	0.33

Independent T-test and chi-square test

TABLE 2. CRRT treatment times and solute levels

	150 mL/min		250 mL/min	
	CVVH	**CVVHDF**	**CVVH**	**CVVHDF**
No. of 12 hr. time periods	169	252	261	172
Total Treatment time (hours)	1527.7	2313	2331.3	1573.5
Hours of treatment/12 hrs mean (SD)	6.3 (3.7)		6.7 (3.9)	
Urea level mmol/L				
T1 0500 – 1700 mean (SD)	15.7 (7.6)	16.7 (8.7)	13.2 (5.9)	13.1 (6.2)
T2 1700 – 0500 mean (SD)	15.2 (7.5)	16.4 (7.7)	12.7 (5.2)	13.4 (6.1)
Creatinine level µmol/L				
T1 0500 – 1700 mean (SD)	217.0 (127.3)	226.7 (152.7)	167.8 (82.8)	209.1 (126.2)
T2 1700 – 0500 mean (SD)	218.3 (144.9)	216.6 (118.8)	165.0 (87.1)	202.3 (102.9)

Figure 2. Urea change by grouping (repeated measures ANOVA)

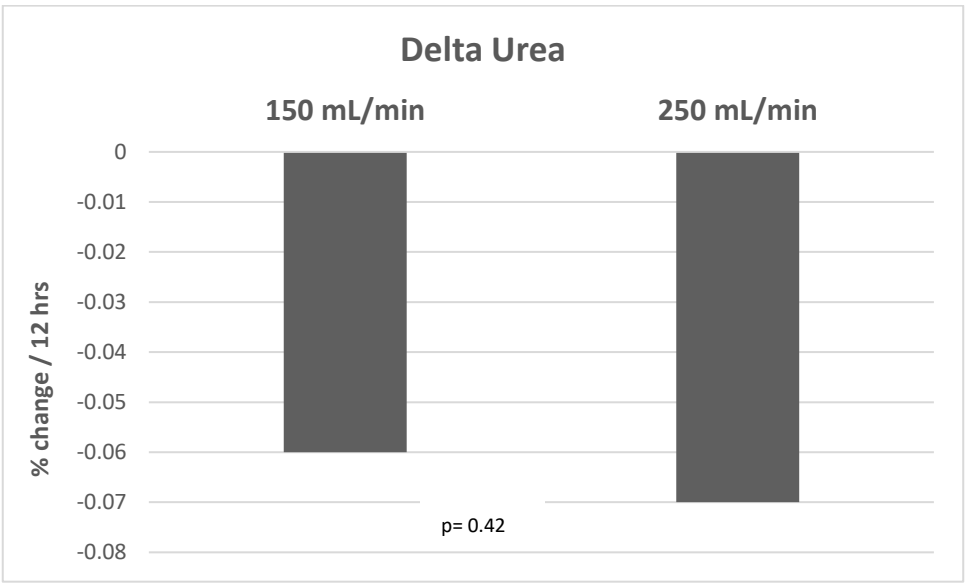

Figure 3. Creatinine change by grouping (repeated measures ANOVA)