Relationship between Blood Flow in Central Venous Catheters and Hemodialysis Adequacy

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Central venous catheter dysfunction is a frequent problem and often is defined as a blood flow <300 ml/min. This prospective, cross-sectional study included 259 patients and examined the relationship between catheter blood flow and dialysis adequacy as measured by urea reduction ratio (URR), single pool urea kinetics, and online effective ionic dialysance clearance. Dialysis adequacy at blood flow rates of <300, <275, and <250 ml/min; sensitivity; specificity; and positive and negative predictive values were calculated. Mean blood flow was 352 ml/min (SD ± 48.8). Mean blood flow <300 ml/min occurred in 10.5% of the patients, and only 26% had a URR of <65%. Maximum blood flows <300 ml/min occurred in 6.9% of patients, and only 22.2% had URR <65%. The positive predictive value of mean blood flow of <300 and <275 ml/min to predict a URR <65% was 22 and 40%, respectively. Using receiver operator characteristic curves, the area under the curve was not significantly different for blood flows of 300, 275, or 250 ml/min. This study indicates that mean blood flows <300 ml/min are not commonly associated with dialysis inadequacy. Setting a single blood flow cut point of <300 ml/min to define the need for intervention will result in a significant number of unnecessary interventions. There is a need to reexamine the definition of catheter dysfunction and expand the definition beyond blood flow rates.

Clin J Am Soc Nephrol 1: 965–971, 2006. doi: 10.2215/CJN.01090306

Cuffed, tunneled, dual-lumen central venous catheters (CVC) have become an acceptable form of hemodialysis (HD) vascular access when other permanent vascular accesses are unavailable, despite the associated high complication rates and mortality risk (1–4). In Canada, up to 70% of patients initiate HD with a CVC, and 33% continue to use catheters 90 days after dialysis initiation (5). This is far in excess of the National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-DOQI) recommendation that CVC be used in <10% of prevalent HD patients (6).

A common complication of the CVC is its inability to deliver adequate dialysis as a result of dysfunction. The definition of CVC dysfunction varies across the literature and includes variable rates of blood flow ranging from <100 to 350 ml/min (7–16). The NKF-DOQI vascular access guideline defines CVC dysfunction as failure to attain and maintain extracorporeal blood flow that is sufficient to perform HD without significantly lengthening the HD treatment and considered insufficient extracorporeal blood flow to be <300 ml/min (6). This recommendation was opinion based and has been interpreted as the need to maintain blood flows >300 ml/min to ensure adequate dialysis. As a result of these guidelines, CVC often are run in the reverse configuration, thrombolytic agents such as thromboplastin inhibitor (t-PA) are used, or catheters are rewired when blood flow is reduced to <300 ml/min. With the increase in CVC prevalence and the corresponding increase in thrombolytic use and subsequent cost consequences, there is a clear need to clarify the relationship between CVC blood flow and dialysis adequacy. The primary objective of this study was to determine the relationship between mean blood flow in CVC and HD adequacy as measured by three parameters: urea reduction ratio (URR), single pool urea kinetics (spKt/V), and online effective ionic dialysance (EID) as measured by Diascan (Hospal Gambro, St. Leonard, Canada).

Materials and Methods

Study Population

We undertook a prospective, cross-sectional study with participants who were recruited from two regional, university-based tertiary HD care programs at London Health Sciences Centre and the University Health Network–Toronto General Hospital. Research ethics board approval and individual patient consent were not required because this was undertaken as a quality improvement study and did not require additional investigations or alteration in delivery of care. Approval for access to patients was sought from the medical directors of each dialysis unit to collect the data as part of a cost management and quality assurance program, and the confidentiality of patients was maintained throughout the study.

Patients were included when they were on maintenance HD and using a cuffed-tunneled permanent CVC, located in the internal jugular vein, and were hemodynamically stable (de-

Received March 30, 2006. Accepted May 18, 2006.

Published online ahead of print. Publication date available at www.cjasn.org.

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 ISSN: 1555-9041/105-0965

fined as stable BP on dialysis without the need for saline bolus for the previous 2 wk). Patients received thrice-weekly, in-center dialysis using a single-use, high-flux polysulfone dialyzer. Patients at both centers underwent dialysis using the Integra (Gambro) dialysis machine. Patients at London Health Sciences Centre underwent dialysis using Permcath (Quinton Instrument Co., Seattle, WA) 12f caliber and 36 to 45 cm length, with a 2.5-cm separation between the arterial (proximal) lumen and venous (distal) tip. University Health Network patients used Uldall-Cook Catheter (Cook Canada Inc., Stouville, Canada), HIGHFLOW Dialysis Catheter (CardioMed Supplies Inc., Gormley, ON, Canada), Opti-flow/HemoGlide dual-lumen permanent dialysis catheter (Bard Access Systems, Mississauga, Canada), and Vaxcel Plus Chronic Dialysis Catheter (Boston Scientific, Boston, MA).

Assessment of Dialysis Adequacy

The Kt/V is a method of assessing the amount of dialysis that is delivered in terms of urea removal. This parameter was calculated using the Daugirdas formula $Kt/V = -\ln (R - 0.03) + [(4 - 3.5R) \times (UF/W)]$, where UF is the ultrafiltration volume in liters, W is the postdialysis weight in kg, and R is the ratio of the postdialysis-to-predialysis urea (17). Patients with residual renal function were included in this study, but the renal clearance was not included in the Kt/V. The URR is a second method to estimate dialysis adequacy and was calculated by the equation (pre-urea − post-urea)/pre-urea. Blood samples for the determination of plasma urea concentrations were drawn at the start and the end of the same dialysis as per the recommended guidelines using the slow flow method (18). Blood urea samples were analyzed using an enzymatic conductivity rate method (Synchron LX System; Beckman Instruments, Inc., Mississauga, Canada). The third measure of dialysis adequacy used the Diascan to measure the EID. EID uses conductivity measurements of both blood and dialysate to determine the clearance of sodium ions across the dialysis membrane. Several researchers have shown a relationship between EID and urea clearance and that it is possible to use ionic dialysance as an indicator of treatment efficacy (19–23). The principle previously has been described extensively (24). The EID expresses clearance (K) as ml/min. K was used in the Diascan Kt/V calculation, where V was calculated as 60% of target body weight (kg) for men and 55% of target weight for women, and t was time on dialysis (in minutes). Dialysis treatment time varied according to the patient prescription. Dialysate flow rates were held constant at 500 ml/min during each treatment. Ultrafiltration rates depended on each patient's requirements but were kept constant during sampling periods.

All blood measurements and Transonic monitoring was done during the midweek dialysis session concurrent with monthly blood work. Access recirculation was measured using the Transonic HDO1 monitor (Transonic Systems Inc., Ithaca, NY) (25). Three research nurses, trained in HD and in the use of the Transonic equipment, undertook data collection and Transonic measurements. The mean blood flow for that session (ml/min) was calculated by dividing the total liters processed by the number of minutes on dialysis. Demographics, cause of ESRD, comorbid conditions, and location of dialysis were collected at baseline. Adequate clearance was defined as a single pool (sp) Kt/V ≥1.2, URR ≥65%, and Diascan Kt/V ≥1.0.

Statistical Analyses

Mean and SD were calculated for continuous variables. Sensitivities, specificities, positive predictive values (PPV), and negative predictive values (NPV) of mean blood flow categories (<250, <275, and <300 ml/min) as an indicator of URR >65% were calculated. Receiver operator characteristic (ROC) curves were used to determine the relationship between blood flow rates and URR ≥65%.

Bivariate analyses were performed to evaluate the relationship between URR ≥65% and the following variables: Mean blood flow, catheter locking solution, percentage of recirculation, and line configuration. The bivariate analyses used a succession of independent sample *t* test for equality of means and repeated measures ANOVA (with categorical determinants), and correlation analyses (with continuous determinants). Variables whose coefficients were significant at $P < 0.05$ were included in a multivariate analysis to determine the relationship to URR. All statistical analyses were conducted using SPSS for Windows, Release 10.1.0, Standard Version (SPSS Inc., Chicago, IL).

Results

A total of 259 patients completed the study. A subgroup of 89 patients had all three measures of dialysis adequacy (%URR, Kt/V, and Diascan Kt/V), whereas the remainder had measures of URR only. The baseline demographics and clinical characteristics of the 259 patients as well as the subgroup of 89 patients are presented in Table 1. The mean patient age was 66.0 ± 15.2 yr, and 51.0% were female. The percentage with hypertension, diabetes, and coronary artery disease were 79.5, 46.4, and 42.3%, respectively. The catheter and dialysis characteristics are described in Table 2 for both the total and the subgroup. The mean catheter age was 57.4 ± 61.6 wk with a range from 2 to 379 wk. The average duration of dialysis was 216.8 min, and the mean blood volume processed was 76.14 L. The calculated mean blood flow was 352.1 ± 48.8 ml/min. Recirculation was present in 108 (41.7%) of CVC; 28.7% occurred with CVC in the straight configuration, and 71.3% occurred in the reversed configuration. Recirculation of >10 and >20% occurred in 27.3 and 7.6% of the CVC, respectively. The catheter locking solution was heparin 1:500, heparin 1; 10,00, and 4% citrate in 32.3, 51.0, and 14.4% of lines, respectively. The remainders were locked with t-PA or were participants in the Pre-CLOT study (26).

The mean %URR for the total group was 73.8% (range 44 to 97%). The mean URR as well as the proportion of patients with a %URR <65 for each category of blood flow rate is described in Table 3. The mean URR for each blood flow category was not different ($P = 0.07$). Ten percent of patients had a URR <65%. Mean blood flow of <300 ml/min occurred in 27 (10.5%) patients, and 26% of these had URR <65%. Mean blood flow of >400 ml/min occurred in 11.3% of patients, and 13.8% of those had a mean URR <65%.

Table 1. Baseline demographic and clinical characteristics[a]

	Total (n = 259)	Subgroup (n = 89)
Demographic characteristics		
age (yr)	66.2 (15.2)	68.6 (14.3)
gender (% female)	51.0	43.8
Cause of ESRD (%)		
diabetes	35.4	40.4
hypertension	19.3	15.7
glomerulonephritis	13.9	7.9
polycystic kidney disease	3.2	3.4
other	26.2	31.5
unknown	2.0	1.1
Comorbid conditions (% yes)		
hypertension	79.5	80.7
diabetes	46.4	55.1
coronary artery disease[b]	42.3	42.7
congestive heart failure	16.7	22.1
peripheral vascular disease[c]	15.9	22.4

[a]Data are mean (SD) or %.
[b]Includes coronary artery bypass surgery, angina, and myocardial infarction.
[c]Includes history of peripheral vascular disease, limb amputation, absent foot pulses, and symptoms of claudication.

In the subgroup of 89 patients, the mean %URR was 74.6% (± 6.1), spKt/V was 1.65 (± 0.3), and Diascan Kt/V was 1.16 (± 0.23). The %URR, spKt/V, and Diascan Kt/V, categorized by blood flow rate, are presented in Table 4. The percentage of patients with URR <65%, spKt/V <1.2, Diascan Kt/V <1.0, and Diascan Kt/V <1.2 was 6.7, 5.9, 20, and 54.1%, respectively. Mean blood flow of <300 ml/min occurred in four patients, and only one patient had inadequate dialysis as measured by a URR <65%, spKt/V <1.2, and Diascan Kt/V <1.0.

Intervention to improve blood flow usually is based on a trend in blood flow or a single blood flow measurement *versus* a mean blood flow for the entire session. To explore this, we examined the maximal blood flow achieved during each dialysis session. The mean %URR and the proportion of patients with URR <65% for each category of maximal blood flow are listed in Table 5. The difference in mean %URR by maximum blood flow classification approached statistical significance (P = 0.055). Maximal blood flows <300 ml/min occurred in 6.9% of patients, and 18% had URR <65%.

We explored the diagnostic accuracy of mean blood flow to determine an adequate clearance as defined by URR ≥65%. We examined mean blood flow rates of <250, < 275, and <300 ml/min. The sensitivity, specificity, PPV, and area under the curve (AUC) in a ROC curve for mean blood flow rate are reported in Table 6. The PPV value, that is the proportion of patients who had a blood flow rate less than targeted when the URR indicated inadequate dialysis (URR <65%), increased from 22 to 40% when the target blood flow decreased from 300 to 250 ml/min. Lowering the target blood flow from 300 to 250 ml/min resulted in a small, NS decrease in NPV from 91.5 to 90%.

The AUC indicates the overall predictive accuracy of a test. A test with perfect predictive accuracy has a combined AUC of 1.0, whereas a test with no predictive accuracy has an AUC of 0.5. The AUC for blood flows of 250, 275, and 300 ml/min were 0.53, 0.55, and 0.57 (P = 0.89).

Patient age, gender, mean blood flow, percentage of recirculation, catheter age, catheter locking solution, and predialysis weight were examined in a bivariate analysis to examine the association with %URR. Line configuration and maximal blood flows were not included because of the close correlation with percentage of recirculation and mean blood flows, respectively. The following variables were significantly associated with increased %URR: Lower predialysis weight (kg; P = 0.001), higher mean blood flow (ml/min; P = 0.012), lower percentage of recirculation (P = 0.001), female gender (P = 0.04), and increased patient age (P = 0.04). Catheter capping solution was not associated with dialysis adequacy. Using variables that were significant at $P < 0.05$ in the bivariate analysis and including dialysis time, several variables continued to be associated with increased URR, including higher mean blood flow (P = 0.001), female gender (P = 0.001), longer dialysis time (P = 0.001), and increased age (P = 0.004). As expected, a higher dialysis weight (P = 0.001) and increased recirculation were associated with lower %URR. Altogether, these six independent variables explained a significant variation in %URR using the following regression equation with inclusion of standardized β coefficients in order of decreasing influence on %URR: URR = 50.3 − 0.476 (predialysis weight) + 0.288 (mean blood flow) + 0.223 (if female) + 0.222 (time) − 0.202 (recirculation) + 0.147 (age).

The clinical interpretation of this is as follows: Each increase of 1 kg in predialysis weight results in a decrease of 0.476% in URR. Each increase of 1 ml/min in mean blood flow results in an increase of 0.288% in URR. Female patients' URR averages 0.223% higher than male patients' URR. Each increase of 1 min in session length results in an increase of 0.222% in URR. Each increase of 1 yr in patient age results in an increase of 0.147% in URR.

Discussion

Current vascular access guidelines recommend an intervention in a CVC when one fails to attain and maintain extracorporeal blood flow that is sufficient to perform HD without significantly lengthening the HD treatment. The guidelines then state a blood flow of <300 ml/min could be considered insufficient (6). The results of this study would challenge the validity of this recommendation. In this study, we found that 10.5% of dialysis sessions had a mean blood flow of <300 ml/min, and 75% of these achieved adequate dialysis as defined by a URR ≥65%. When we examined other measures of dialysis adequacy, only one of four patients had inadequate dialysis with mean blood flows <300 ml/min. Even when we looked at the proportion of patients with a maximal blood flow of <300 ml/min throughout the dialysis session, only 22% of

Table 2. Catheter and dialysis session variables[a]

	Total (n = 259)	Subgroup (n = 89)
Catheter age (wk)	57.4 (61.6)	56.2 (56.4)
Locking solution (%)		
heparin 1:10,000	51.0	
heparin 1:5000	32.3	93.3
4% citrate	14.4	2.2
t-PA	1.2	1.1
Pre-CLOT study protocol	1.2	3.4
Dialysis machine (%)		
Integra	97.5	95.5
Cobe	0.8	—
Fresenius	1.7	4.5
Dialysis shift (%)		
morning	39.0	41.6
afternoon	42.9	42.7
evening	18.1	15.7
Dialysis		
predialysis weight (kg)	71.7 (22.2)	76.9 (24.6)
weight loss during dialysis (kg)	1.92 (1.12)	2.08 (1.19)
blood volume processed (L)	76.14 (13.82)	75.45 (14.45)
time on dialysis (min)	216.8 (30.4)	206.2 (29.2)
mean blood flow (ml/min)	352.1 (48.8)	366.5 (40.1)
URR (%)	73.8 (7.4)	74.6 (6.1)
% with lines reversed	34.0	27.0
% with recirculation	41.7	37.2
spKt/V	—	1.65 (0.30)
Diascan Kt/V	—	1.16 (0.23)

[a]Data are mean (SD) or %. spKt/V, single pool Kt/V; t-PA, thromboplastin inhibitor; URR, urea reduction ratio.

Table 3. URR by mean blood flow (n = 259)

Blood Flow (ml/min)	% of Patients	URR (% ± SD)	% with URR <65%[a]
<250	1.9	71.8 ± 11.4	40.0
250 to 300	8.6	70.5 ± 10.7	22.7
301 to 350	39.7	73.5 ± 7.3	7.8
351 to 400	38.5	75.2 ± 6.1	6.1
>400	11.3	73.1 ± 7.7	13.8
Total	100.0	73.8 ± 7.5	10.0

[a]Percentage within blood flow grouping.

patients had inadequate dialysis. A mean blood flow cut point between 250 and 300 ml/min had low predictive accuracy in determining a dialysis session with a URR <65%. Last, we have shown that several variables play a role in determining dialysis adequacy. Interventions to maintain adequacy, based on blood flow alone, will result in an inappropriate increase in intervention and cost.

CVC are used in an increasing proportion of patients who are on HD (2,5). The reported incidence of catheter dysfunction ranges from 5 to 80%, depending on the definition, population, and catheter characteristics (7–16). The interpretation of studies that use blood flow as a measure of catheter dysfunction are challenging without knowledge of blood pump setting, use of average *versus* episodic measures of blood flow, percentage of recirculation, and other dialysis variables. There is an increasing use of long daily, nocturnal dialysis and slow low-efficiency dialysis, all of which use lower blood flows (27,28). Defining dysfunctional catheters by blood flows of <300 ml/min in this population would lead to unnecessary intervention in the majority of patients.

Few, if any, studies have defined catheter dysfunction as the inability to deliver an adequate dialysis prescription, which is the overall goal of dialysis. The availability, acceptance, and further validation of online measurements of EID may aid in describing the dialysis dose at each session and allow for identification of inadequate dialysis in a more timely and precise manner. In this study, we empirically used a Diascan Kt/V >1.0 as the measure of adequate dialysis after we identified that >50% of the patients had a Diascan Kt/V <1.2. This Diascan Kt/V target has not been validated with clinical outcomes. We chose a lower Diascan Kt/V target because EID has been shown consistently to underestimate delivered dialysis dose, even after correcting for recirculation and urea distribu-

Table 4. URR, spKt/V, and Diascan Kt/V by mean blood flow (n = 89)

Blood Flow (ml/min)	% of Patients	URR (% ± SD)	% with URR <65%[a]	spKt/V (±SD)	% with spKt/V <1.2	Diascan Kt/V (±SD)	% with Diascan Kt/V <1.0[a]
<250	1.1	65.7	0	1.28	0	0.57 ± —	100.0
250 to 300	3.4	69.5 ± 10.8	33.3	1.37 ± 0.49	33.3	1.09 ± 0.27	33.3
301 to 350	26.4	74.7 ± 4.1	0	1.64 ± 0.23	0	1.18 ± 0.20	19.0
351 to 400	52.9	75.0 ± 6.3	6.5	1.67 ± 0.030	4.8	1.16 ± 0.24	23.9
>400	16.1	76.0 ± 6.4	7.1	1.71 ± 0.33	7.1	1.23 ± 0.19	0.0
Total	100.0	74.8 ± 6.0	6.7	1.66 ± 0.30	5.9	1.17 ± 0.23	20.0

[a]Percentage within blood flow grouping.

Table 5. URR by maximum blood flow (n = 259)

Blood Flow (ml/min)	% of Patients	URR (% ± SD)	% with URR <65%
<250	0	—	—
250 to 300	6.9	69.9 ± 9.9	22.2
301 to 350	34.4	73.2 ± 8.1	13.5
351 to 400	46.3	74.7 ± 6.6	6.7
>400	12.4	74.5 ± 6.5	6.3
Total	100.0	73.8 ± 7.5	10.0

Table 6. Sensitivity and specificity of mean blood flow as an indicator of URR ≥65%[a]

Mean Blood Flow (ml/min) Cut Point	Sensitivity	Specificity	Area under the ROC Curve
250	0.080	0.987	0.534
275	0.160	0.961	0.561
300	0.240	0.914	0.577

[a]ROC, receiver operator characteristic.

tion volume (19–29). Further studies using EID clearance and its relationship to blood flow and adequacy using a CVC need to be performed.

We calculated the sensitivity, specificity, PPV, and NPV of mean blood flow as a diagnostic tool to predict dialysis adequacy in CVC. A mean blood flow of <300 ml/min had a PPV of 22%, whereas a mean blood flow <250 ml/min had a PPV of 40%. This indicates that at a mean blood flow of <300 ml/min, only 22% of patients had a URR <65%, whereas 40% had a URR <65% at a blood flow of <250 ml/min. The tradeoff between sensitivity and specificity was examined using the ROC curves. The AUC was not significantly different for the blood flow cut points of 250, 275, and 300 ml/min.

There are significant clinical and cost implications of defining catheter malfunction on the basis of blood flow alone. The misconception that blood flows <300 ml/min lead to inadequate dialysis often results in nursing personnel's reversing the line to maintain flows >300 ml/min. Carson *et al.* (30) recently described the relationship among blood flow, line configuration, percentage of recirculation, and clearance. Despite documented recirculation, it is possible to achieve acceptable clearance if the blood flow is sufficiently high; however, there are tradeoffs, and some patients will have unacceptable clearances in the reversed configuration (30). Patients may be subjected to unnecessary line changes and increased intervention with t-PA. The costs that are attributed to the use of t-PA and line exchange are not known. A recent cost analysis of vascular access calculated CVC at $9180 Can (median $3812; interquartile range $2250 to $7762) per patient-year (16). In this study, catheter dysfunction was defined as blood flow of <200 ml/min, and the cost of t-PA was $199 per patient-year at risk. Increasing the intervention target to a blood flow of 300 ml/min would significantly increase costs. In our institutions, the cost of 2 mg of t-PA to each port is approximately $120.00 Can. If all patients in this study who had a blood flow <250 ml/min were treated (n = 5), then the cost of t-PA for that session would have been $325.00 Can. If we intervened in all lines with a mean blood flow <300 ml/min, as per K/DOQI recommendations, then we would have treated 28 lines at a cost of $1820.00 Can. The cost of t-PA would have increased five to six times from changing the target blood flow for intervention from 250 to 300 ml/min. Importantly, this use would be justified if mean blood flow <300 ml/min correlated with an important clinical consequence, such as inadequate dialysis; however, our data suggest that 22 (80%) of 27 lines would have been treated unnecessarily at an excess cost of $1365.00 for a single dialysis session.

Dialysis adequacy was associated with patient variables age, predialysis weight, and female gender, as well as dialysis variables time, mean blood flow, and percentage of recirculation. Although this is well-established knowledge in nephrology (31,32), it serves as a reminder that multiple variables influence the delivery of adequate dialysis dose, in addition to blood flow.

The question, then, is which blood flow rate should be used to assist in determining the need for intervention to maintain adequacy? Clearly this cannot be established for a general HD population. For a 40-yr-old, 100-kg man, a mean blood flow of 300 ml/min or more may be needed to maintain adequacy, whereas an 80-yr-old, 55-kg woman may have adequate clearance with a mean blood flow of 275 ml/min. The recent Canadian Hemodialysis Clinical Practice Guidelines on vascular access have defined CVC dysfunction as the inability to maintain pump speed >200 ml/min for one run or difficulty aspirating from either lumen of the catheter (33). This may be a more conservative estimate of the blood flow cut point. None of the patients in our study had blood flows <200 ml/min, so we were not able to examine the relationship between dialysis adequacy and this blood flow cut point. On the basis of the trend of our data, blood flows <200 ml/min would result in inadequate dialysis in the majority of patients.

Our study has a number of limitations. We used a calculated mean blood flow that was based on the liters processed and time on dialysis, which some consider inferior to recorded average blood flow from the blood pump or the gold standard of blood flow as measured using ultrasound dilution techniques (34–36). Interventions in CVC usually are based on an intermittently low blood flow or inability to withdraw blood at the initiation of dialysis *versus* mean blood flow as used in this study. To address this, we examined dialysis sessions with maximum blood flows <300 ml/min and found that 82% of these sessions provided adequate clearance, thus confirming our original results. Given the cross-sectional nature of our study, we were unable to examine trends in blood flows and dialysis adequacy.

The strengths of our study include the use of a large number of dialysis patients from two separate sites, which increases the generalizability of the results. We were able to correlate various levels of blood flow with three separate and complementary measures of dialysis adequacy.

Conclusion

In this study, mean blood flow rates <300 ml/min were not commonly associated with dialysis inadequacy. Setting a single blood flow cut point of <300 ml/min to define the need for intervention will result in a significant number of unnecessary interventions and associated increased costs. There is a need to reexamine the definition of catheter dysfunction and expand the definition beyond blood flow rates.

Acknowledgments

B.R.H. is supported by a Population Health Award from the Alberta Heritage Foundation for Medical Research and a New Investigator Award from the Canadian Institute of Health Research. C.E.L. is supported by a New Investigator Award from the Canadian Institute of Health Research.

We are indebted to Kerri Gallo and Paul Heidenheim for data collection and statistical support.

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