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Clinical Image

Characterization of Cardiovascular Health for Chronic Dialysis Patients Using Continuous Non-Invasive Cardiac Output Monitoring

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Abstract

The principle of fluid removal during intermittent hemodialysis (IHD) is to induce a relative hypovolemic state by ultrafiltration followed by vascular refill from the interstitial and cellular compartments (plasma refill rate). However, if the ultrafiltration rate (UFR) greatly exceeds the plasma refill rate then hypovolemic cardiovascular collapse may ensue. The objective of this study was to determine if progressive changes in heart rate (HR), cardiac output (CO) and thoracic fluid content (TFC) using the non-invasive bioreactance cardiac output monitor (NICOM, Cheetah Medical, Tel Aviv) can tract UFR and identify the onset of cardiovascular insufficiency during routine IHD. We hypothesized that steady state TFC and the change in CO would parallel UFR and total volume removal during IHD. We measured these parameters over the course of IHD in 20 chronic dialysis patients on two separate consecutive treatment days corresponding to weekend (2-day interval) and weekday interval (1-day interval)(40 runs). Data were also separated by total fluid removal (< or ≥2500 ml/treatment). No patients experienced cardiovascular collapse during IHD. Seven runs were lost for technical reasons. There was no relation between change in HR or CO and UFR or day of dialysis. However, change in TFC inversely correlated with UFR ($r=0.6$, $p<0.001$) with the greatest TFC decrease seen for UFR ≥2500 ml/treatment ($p<0.01$). The increase in cardiac output in response to a passive leg raising maneuver (ΔCO) significantly increased over the course of IHD. We conclude that NICOM-derived TFC and ΔCO could guide UFR during IHD whereas static hemodynamic measures are insensitive to dialysis-induced fluid removal in patients who do not experience cardiovascular collapse during IHD. A larger prospective clinical trial would be needed to address the issue of identifying cardiovascular instability.

INTRODUCTION

There were 485,000 end stage renal disease patients in the U.S. as of 2005 with 785,000 projected by 2020. Mortality while on chronic hemodialysis is very high reaching 65% at 5 years after starting hemodialysis [1]. The prevalence of cardiovascular disease and left ventricular hypertrophy in these patients is 40% and 75%, respectively [2]. Cardiovascular disease is the most common cause of death in dialysis patients accounting for over half of patient deaths. Most of this excess mortality is due to heart disease and consequently heart failure with its associated fluid retention. Thus, both fluid overload and heart failure commonly co-exist in patients on chronic hemodialysis [3]. Moreover, intradialytic hypotension (IDH) resulting from the excessive removal of fluid in patients at risk, primarily those with underlying cardiac disease (left ventricular hypertrophy or dysfunction, coronary artery disease), is an underappreciated problem which may contribute to the increased mortality of end-stage renal disease (ESRD) patients through cardiac ischemia/acute coronary syndrome, cardiac arrhythmias, vascular autoregulatory dysfunction, and endothelial abnormalities with increased thrombogenecity. Patients with frequent IDH have

been found to have a significantly higher mortality rate compared to patients without IDH [4].

Efficacy of fluid removal during dialysis is dependent upon the accurate assessment of a patient's fluid and cardiovascular status and ability to tolerate functional hypovolemia during fluid removal. The problem with current methods to assess fluid status or estimated dry weight in these patients is that they have traditionally relied on the presence or absence of relatively non-specific symptoms or the subjective interpretation of gross measurements (pre- and post-dialysis weight, blood pressure, heart rate). More invasive testing, such as with a pulmonary artery catheter and arterial catheterization are performed on patients with advanced stages of cardiovascular insufficiency. Although these invasive measures give accurate estimates of cardiac output, vasomotor tone and cardiac performance they cannot be easily applied to chronic ambulatory patients.

The clinical assessment of achieving an ideal dry weight should be reliable, simple, inexpensive and suitable for repeated determinations. Objective methods that attempt to provide reasonable accurate estimates of the dry weight and fluid removal needs include relative blood volume monitoring, natriuretic peptide measurements, extravascular lung water indices, and bioimpedance methods [5-7]. Bioimpedance technology is based on passing a electrical current through the body, estimating the body fluid volume by the amount of resistance this current encounters in the body tissues. Davies and Davenport recently showed that bioimpedance is accurate and reproducible for the assessment of body fluids [8].

If non-invasive techniques could report similar hemodynamic parameters, then it may be useful in detecting cardiovascular insufficiency before overt cardiovascular collapse occurs. Thus we tested the ability of a non-invasive cardiac output monitor (NICOM) to assess cardiovascular status in patients undergoing chronic hemodialysis. The primary objective of this study was to determine if cardiac output (CO) and other indirect measures of preload such as change in CO in response to passive leg raising (PLR) and thoracic fluid content (TFC) changed before easier measures of cardiovascular status, such as heart rate (HR) or blood pressure (BP) did. In order to amplify the potential sensitivity of this comparison we stratified patients by ultrafiltration rate (UFR) into low and high volume removal by comparing the response in the same patient following either one-day (weekday) or two-day (weekend) intervals from their previous dialysis session. Since we did not know in advance the relative difference in these measures during the dialysis session, we performed this pilot study to define better such changes with the goal of defining sample size to conduct an appropriately statistically powered larger clinical study. The secondary objectives of this study were to assess the ability of the NICOM device to continuously track circulatory status so as to identify impending hypovolemic hypotension as a marker of cardiovascular insufficiency.

MATERIAL AND METHODS

The research protocol was approved by the University of Pittsburgh Institutional Review Board for Human Experimentation and informed consent was obtained before data collection in all subjects. We studied 23 chronic dialysis patients receiving in-patient regular hemodialysis at the University of Pittsburgh Medical Center-Presbyterian Dialysis Unit as part of their routine patient care. All patients were hemodynamically stable and were routinely dialyzed 3 times a week for 3-4 h. Each patient was studied a maximum of three times in succession over sequential hemodialysis runs attempting to include the short (weekday) and long interval (weekend). The majority of patients were studied twice. The inclusion criteria included: Males and females age 18 years and older on chronic dialysis for at least three months, admitted to the University of Pittsburgh Medical Center, Presbyterian University/Montefiore campus for elective procedures, i.e. endoscopy, stress test, orthopedic surgery, etc. We excluded patients that did not get informed consent and had pre-existing cardiovascular insufficiency requiring ongoing intravenous therapeutic intervention. No changes were made in the dialysis procedure during recording and the patients were dialyzed according to their prescriptions determined by the nephrologist in charge of the inpatient care. All patients were dialyzed using Fresenius 2008K machine with a polyflux dialyzer. The blood flow ranged from 300-350 ml/min, the dialysate flow rate was 600 ml/min and the dialysate temperature was set at 36°C. The dialysate fluid bath varied according to their prescription. The dialysis duration and constant ultrafiltration rate were established based on the amount of fluid prescribed to be removed on that particular day.

Data collection

Monitoring was continuous from 5 minutes before starting dialysis to 10 minutes after completion of dialysis while the patient rested in a semi supine position in the dialysis bed. We also performed four PLR maneuvers, the first just before dialysis, then at 30 min and 1 hour into the dialysis therapy and finally at the end of a regular dialysis treatment (usually 3.5 to 4 hours). Patient-specific demographic data, including age, height, weight diagnoses and medications was collected from the medical record during the course of dialysis therapy. Routine hemodynamic monitoring of continuous heart rate and intermittent sphygmomanometer-derived blood pressure was done in its usual fashion and these data were collected periodically. Patients were monitored with the NICOM® system (Cheetah Medical, Inc. Tel Aviv, Israel) through four disposable surface pre-gelled double electrodes placed on the patient's skin providing the connection for measurements of current flowing along the thorax. Two electrodes placed on upper chest and two placed on the upper abdomen act as the source of a constant magnitude, high-frequency (HF) measurement current that provides homogeneous coverage of the thorax with an HF electrical field. Typical frequency range of the measurement current is 75 kHz. This current produces a high frequency voltage across the thorax, which is proportional to changes in thoracic bioreactance. The sensing electrodes also detect ECG signals. NICOM® analyzes the tissue response to the known electrical input and the frequency of the emitted current is compared with the originally delivered current. This difference represents the thoracic bioreactance, which is proportional to the amount of blood flow in the thoracic cavity. The NICOM system accuracy has been previously described [9]. It reports several cardiac functional parameters, including cardiac output (CO), cardiac index (CI), stroke volume index (SVI), ventricular ejection time

(VET), cardiac contractility (dX/dt), total peripheral resistance (TPR) and thoracic fluid content (TFC).

Passive leg raising (PLR) test

All subjects were placed in a semi-recumbent supine position with 30° head of the bed elevation. Then the bed was rotated to place the head supine thus raising the legs 30° for two minutes before returning the subject to a baseline 30° head of bed elevation for an additional 10 minutes to define return to baseline. Data was analyzed during the initial baseline to define stability of the signal and to serve as the reference values to the passive leg raising and lowering maneuver. The time course of the HR, SV, and TFC response to the PLR maneuver during a dialysis session is shown in Figure 1.

RESULTS

Of the 23 subjects we recruited, three could not have their data analyzed because of either they did not complete at least two evaluations or because the signal quality was bad in quality (determined by three independent observers). Thus, we analyzed the remaining 20 subjects (12 males) whose age ranged between 25 to 81 years of age (mean age 49 years). They represented the racial distribution of the dialysis population in our medical center (13 Caucasian, 6 African American, 1 Hispanic).

Overall the average hemodialysis prescribed time was 204 min (Table 1). The average ultrafiltration rate was 2400 ml in the 1-day interval (weekday) period and 3212 ml in the 2-day (weekend) interval hemodialysis session. Thus, we divided the dialysis treatment sessions in terms of ultrafiltration rate achieved per session and we compared the change in hemodynamic parameters between treatments with UF ≥2500 ml·hr^{-1} vs. those with UF <2500 ml·hr^{-1}, a value that approximately reflected the mean UF in the 1-day interval.

There was no difference in the change from baseline for CO, CI, HR, SV and SVI during dialysis runs between the ≥2500 ml·hr^{-1} (higher) vs. those with UF <2500 ml·hr^{-1} (lower) UF groups (Table 2). In general TFC progressively decreased in all subjects in proportion to fluid removal (figure 1 and table 4). The TFC change from baseline was significantly higher in the ≥2500 ml·hr^{-1} UF rate group (-10.9±1.6 vs. -4.2±1.3, p<0.007) (Table 3).

PLR caused CO to increase in all subjects between the initial study and progressively throughout the dialysis run. The increase in CO in response to a PLR remained stable in the group with

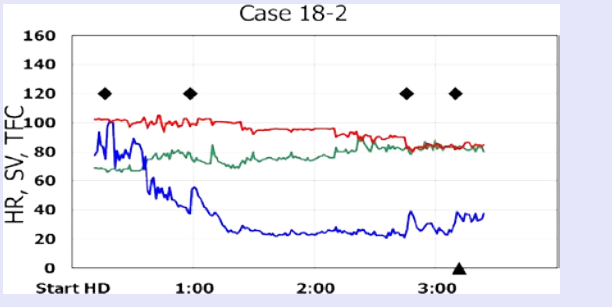

Figure 1 Time course of HR (green), SV (blue) and TFC (red) throughout a hemodialysis session.

Table 1: Comparison of HD differences between one and two day dialysis-free intervals.

	HD duration (min)	Total UF UF rate (ml)	Wt pre HD	
			(ml·hr-1)	(kg)
1-day interval	206	2400	695	70.93
2-day interval	216	3212	841	73.18

Abbreviations: HD: Hemodialysis; UF: Ultrafiltration; Wt Prehd: Weight Before Hemodialysis

Table 2: Change in Hemodynamic Variables during Dialysis by Ultrafiltration Rate*.

	UF< 2500	UF≥ 2500	p
CO (l·min^{-1})	-0.59±789	-.34±7.31	NS
CI (l·min^{-1}·M^{-2})	-.59±7.86	-.37±7.30	NS
HR (beats·min^{-1})	3.19±2.21	10.14±2.87	NS
MAP (mmHg)	-2.11±4.08	0.43±2.49	NS
SV (ml)	-3.59±6.99	-8.86±6.68	NS
SVI (ml·M^{-2})	-3.69±6.93	-8.86±6.65	NS
TFC (arbitrary units)	-4.24±1.39	-10.93±1.69	0.007

*Ultrafiltration rate in ml hr^{-1},
Abbreviations: CO: Cardiac Output; CI: Cardiac Index; HR: Heart Rate; SV: Stroke Volume; SVI: Stroke Volume Index; TFC: Thoracic Fluid Content

Table 3: Comparisons of Hemodynamic Variable Changes with Hemodialysis by Ultrafiltration Rate*.

UF < 2500 (n=14 sessions)			
	Pre HD	**Post HD**	**p**
CO	4.92±0.67	4.82±0.76	NS
CI	2.64±0.30	2.56±0.35	NS
HR	78±3	81±4	NS
SV	63.4±8.4	59.0±8.3	NS
TFC	91±8	88±7	0.008
UF≥ 2500 (n=19 sessions)			
	Pre HD	Post HD	p
CO	4.69±0.60	4.40±0.43	NS
CI	2.56±0.26	2.42±0.21	NS
HR	79±3	86±4	0.001
SV	60.9±8.7	51.6±5.1	NS
TFC	110±11	100±11	0.005
Combined (n=33 sessions)			
	Pre HD	Post HD	p
CO	4.79±0.44	4.58±0.40	0.55
CI	2.59±0.19	2.49±0.19	0.54
HR	79±2	84±2	0.005
SV	62.0±6.0	54.8±4.6	0.11
TFC	102±7	95±7	0.005

Abbreviations: CO: Cardiac Output; CI: Cardiac Index; HR: Heart Rate; SV: Stroke Volume; SVI: Stroke Volume Index; TFC: Thoracic Fluid Content

an UF rate >2500 ml·hr^{-1} (Figure 2) but had a great variability in the group that have lower UF rate suggesting that vascular refill during dialysis maintained a relatively constant effective circulating blood volume in most patients especially in patients with high UF rate.

DISCUSSION

Our study has two primary findings. First, that by separating two different UF rates in the same patient (i.e. fluid removal in a weekday and weekend dialysis interval) clear differences in TFC could be seen (Table 2). An UF ≥2500 ml/treatment corresponded to a larger absolute TFC reduction. It is also apparent that only when the UF is ≥2500 ml/treatment that an increase in HR is seen at the end of dialysis (Table 3). These data suggest that such a sequential study design approach could be used in the future to separate different UF rates on hemodynamic and humeral responses in dialysis-dependent patients. TFC is an indicator of total fluid volume, both intracellular and extracellular. In our study TFC trended fluid changes well similar to what was described by van De Water et al. [8].

Another finding from our study is the significant correlation between the change of TFC by NICOM and the hemofiltration rate (Figure 2). Also the delta of CO during the PLR maneuver increased through the course of the dialysis treatment (Table 4). This corroborates findings described previously by Kossari et al. [10] and provides consistency to the potential clinical utility of using a NICOM device to track down fluid removal while on dialysis. Third, that despite markedly different UF rates and fluid removal volumes, the monitoring of routine hemodynamic variables and even the newly studied CO and CO change to PLR parameters were insensitive to monitor fluid removal. This result is unfortunate because the clinical assessment of estimated dry weight is error-prone and results in both over- and under-estimation by approximately 50% [11]. Non-specific symptoms often lack the sensitivity to detect either volume overload prior to dialysis or volume depletion in mild to moderate stages during fluid removal. However, since none of our subjects had an episode of cardiovascular insufficient for which a PLR maneuver preceded it, we are not sure if closer monitoring and other functional hemodynamic parameters might increase our sensitive to identifying patients at increased risk of cardiovascular collapse during dialysis.

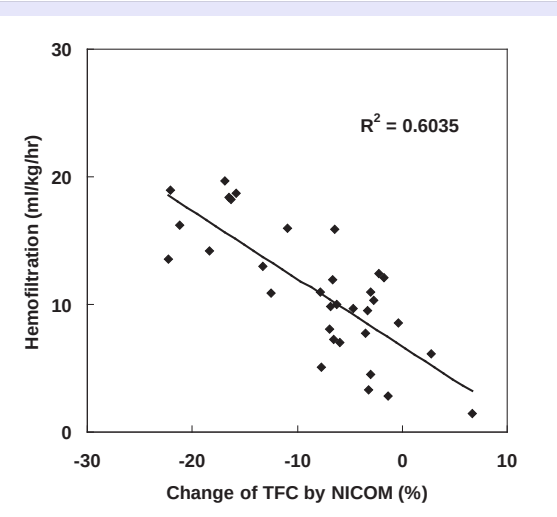

Figure 2 Relationship between hemofiltration rate (ml/kg/hr) and percentage of change of thoracic fluid content (TFC), n=20 patients, the comparison of percentage of change of CO between <2500 and ≥2500 ml groups, revealed p=0.23 at baseline, p=0.021 at 30 min and p=0.013 at end of HD.

Table 4: Percentage Change (Δ) in Cardiac output (CO), Heart Rate (HR) and Thoracic Fluid Content (TFC) Induced by a Passive Leg Raising (PLR) Maneuver over Hemodialysis (HD).

	Pre	60 min into HD	end HD	p-value
ΔCO	6.4±2.1	17.9±4.5	16.5±3.9	0.03
ΔHR	0.1±0.2	0.3±0.2	-0.2±0.3	0.6
ΔTFC	1.5±1.0	0.6±1.3	1.1±0.9	NS

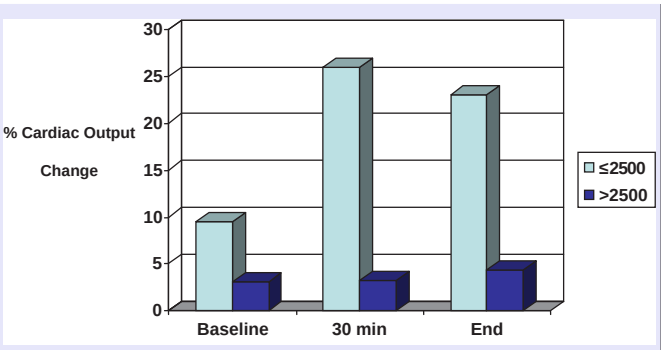

Figure 3 Percentage of change of cardiac output following passive leg raising (PLR) by ultrafiltration rate, □ UF ≤ 2500 ml, ■UF greater than 2500 ml.

Routine periodic hemodialysis treatment accomplishes two goals: blood purification and fluid removal. Effectiveness of hemodialysis is estimated mainly by solute clearance [12]. However, fluid removal (ultrafiltration) is also a major component of the dialysis prescription and it has been difficult to be addressed properly. The principle of fluid removal during dialysis is to induce a relative hypovolemic state by ultrafiltration followed by refilling of the vascular space from the interstitial and cellular compartments at a steady rate (plasma refill rate). If the rate of removal exceeds the plasma refill rate then the degree of hypovolemia increases. If the level of hypovolemia exceeds the body's natural sympathetic response mechanisms of vasoconstriction, then circulatory insufficiency rapidly develops as manifest by tachycardia, hypotension and decreased end-organ function. Normal compensatory mechanisms consist of plasma refilling, increased cardiac contractility/rate, and increased arterial/arteriolar and venous vascular tone/resistance.

Recently, Onofriescu et al. [13] studied 131 hemodialysis patients with the aim to compare the long term effect of bioelectrical impedance (BIA) based versus clinical-based assessment of dry weight on blood pressure, pulse wave velocity and serum N-terminal fragment of B-type natriuretic peptide. The primary outcome was all-cause mortality over 2.5 years (the duration of the intervention). Secondary outcomes were change in relative arterial stiffness, fluid overload, and blood pressure over

2.5 years. Bioimpedance measurements were performed using a Body Composition Monitor device. Pulse wave velocity analysis was performed at baseline, 2.5 years (end of intervention), and 3.5 years (end of study). They assessed relative fluid overload and blood pressure at 3-month intervals. The unadjusted heart rate for all-cause death in the bioimpedance group (vs the clinical-methods group) was 0.100 (95% CI, 0.013-0.805; P=0.03). After 2.5 years, they found a greater decline in arterial stiffness, relative fluid overload, and systolic blood pressure in the bioimpedance group than the clinical-methods group. They suggested that the study showed improvement in both surrogate and hard end points after strict volume control using bioimpedance to guide dry weight adjustment. Thus suggesting that is not inferior and possibly better than clinical criteria for assessing dry weight and guiding UF in HD patients.

In the study by Hur et al. [14], dry weight was based by routine clinical practice and fluid overload was assessed by BIA spectroscopy in both groups. In the intervention group fluid overload information was provided to treating physicians and used to adjust fluid removal during dialysis. In the control group fluid overload information was not provided to treating physicians and fluid removal was adjusted according to usual clinical practice. The primary outcome was regression of left ventricular mass index during a 1-year follow-up. Improvement in blood pressure and left atrial volume were the main secondary outcomes. Fluid overload was assessed twice monthly in the intervention group and every 3 months in the control group before the mid- or end-week hemodialysis session. Echocardiography, 48-hour ambulatory blood pressure measurement, and pulse wave analysis were performed at baseline and 12 months. Baseline fluid overload parameters in the intervention and control groups were 1.45±1.11 (SD) and 1.44±1.12 L, respectively (P = 0.7). Time-averaged fluid overload values significantly decreased in the intervention group but not in the control group (intervention group mean difference: -0.5±0.8 L vs control group mean difference: 0.1±1.2 L). Left ventricular mass index regressed from 131±36 to 116±29 g/m (2) (P < 0.001) in the intervention group, but not in the control group (121±35 to 120±30 g/m(2); P = 0.9). In addition, values for left atrial volume index, blood pressure, and arterial stiffness parameters decreased in the intervention group, but not in the control group. The authors concluded that assessment of fluid overload with BIA spectroscopy provides better management of fluid status, leading to regression of left ventricular mass index, decrease in blood pressure, and improvement in arterial stiffness.

Celik G et al. [15] studied consecutive adult hemodialysis patients with ESRD who had been undergoing dialysis for > 3 months, 3 days a week for 3 – 4 h, who were free of overt cardiovascular disease. Ultrafiltration volume was correlated with age, sodium, hemoglobin, extracellular water (ECW)/total body water (TBW) ratio and ECW/intracellular water (ICW) ratio. The ECW/TBW ratio was correlated with age, body mass index, dry weight, predialysis systolic and diastolic blood pressure, and ECW/total body weight ratio. They showed that ECW/ICW correlated with age, albumin, adequacy of dialysis (Kt/V), URR, TBW and ultrafiltration volume. These results indicate that ECW is closely associated with several hemodynamic parameters and ultrafiltration volume in hemodialysis. These data indicated the close relationship between BIA-derived volume parameters and hemodynamic and biochemical parameters of hemodialysis in patients with ESRD who were undergoing hemodialysis. Taken together, our study and these previous studies suggest that BIA may be suitable for routine clinical use to assist in the accurate determination of dry weight and so prevent under- or over-hydration and their deleterious consequences.

Clinical perspective

All patients receiving dialysis will eventually reach a level of functional hypovolemia at the end of their dialysis treatment. This state allows them a capacitance reserve until they return 48 or 72 hours later for their next dialysis treatment. Regrettably, ESRD patients on dialysis can and often do develop circulatory insufficiency during routine fluid removal at levels above their dry weight. Presumably, this is because either their plasma refill rate is not adequate to match the fluid removal rate or their vascular responsiveness is blunted relative to prior ultrafiltration treatments making the same decreased intravascular volume too low to sustain cardiovascular stability. Presently there is no good method of accessing impending circulatory insufficiency during dialysis. Since worsening effective hypovolemia should exist if either excess volume removal or inadequate vascular responsiveness were developing, we reasoned that changes in vasomotor tone and volume responsiveness should identify these patients at risk of immediate cardiovascular compromise sooner than is presently possible by measuring only static heart rate and blood pressure. Specifically measuring the change in blood pressure to change in blood flow should define vasomotor tone, and the dynamic changes in both supine to PLR maneuver would identify the relative degree of functional hypovolemia, increasing the sensitivity and specificity of hemodynamic monitoring to detect impending cardiovascular collapse. Although we saw a progressive increase in estimated vasomotor tone as dialysis proceeded, there were no differences between high and low UR rates in this increase.

The development of circulatory insufficiency and associated intradialytic hypotension during hemodialysis is common, occurring in an estimated 20-30% of outpatient hemodialysis treatments [16]. The achievement of ultrafiltration (removal of excessive fluid) without inducing hemodynamic compromise and the symptoms (malaise, nausea/vomiting, muscle cramps, chest pain, shortness of breath, abdominal pain) and morbidity (cardiac ischemia, cardiac arrhythmias, cerebral ischemia, mesenteric ischemia, ischemic colitis) associated with intradialytic hypotension is often difficult to accomplish. Preserving residual renal function is an important goal. Researchers have identified several factors that can predict a decline in residual renal function. Of these, peritoneal dialysis is more adept at preserving residual renal function than hemodialysis, and intra-dialytic hypotension and episodes of dehydration are associated with a more rapid decline in residual renal function [17]. Several studies have shown that residual renal function is an important prognostic marker for dialysis patient. This is most likely due to both fluid removal and uremic toxin clearance [18].

Ideally, during a hemodialysis session, the ultrafiltration rate exactly matches the physiological plasma refill rate for the intravascular volume. If a reliable, safe and inexpensive method

could be developed to identify when patients are progressing into the insufficiency state, then the rate of fluid removal could be automatically reduced or temporarily stopped to prevent the adverse effects of dialysis-induced circulatory insufficiency. Ultrafiltration and/or dialysate sodium modeling (variations of ultrafiltration rate and dialysate sodium concentration) have been proposed to identify these thresholds [13]. However, their sensitivity has not been documented. There are multiple advantages of BIA including user friendly, low cost, multiple continuous bed-side examination, and high reproducibility of measurements. The inter-observer and intra-observer errors are usually quoted as <2%, thus making it an ideal device for monitoring the impact of an intervention designed to alter fluid status [6]. The majority of hemodialysis patients gain weight in the interdialytic interval, and BIA studies have shown that the major increase in ECW occurs in the trunk and legs [6,19]. As ECW expansion is predominantly in the legs and trunk with a relatively normal plasma volume, most hemodialysis patients who are volume overloaded based on BIA assessments do not have the classic physical signs of pitting peripheral edema, pulmonary rales, raised jugular venous pulse wave, or additional heart sounds [6]. A non-invasive monitor, like NICOM and its derived parameters may potentially be that device. Clearly, a larger clinical trial with more subjects experiencing intradialyatic cardiovascular insufficiency will be needs to address this question. The present study merely documents that these hemodynamic parameters can be collected continuously and non-invasively and change differently with UF rates but does not allow us to predict the number of patients needed to define the development of intradialyatic hypotension. In our study we found a significant larger decrease of thoracic fluid content in HD sessions was larger amounts of ultrafiltation were conducted.

The major limitations of the study are sample size and lack of untoward cardiovascular events. No significant hemodynamic episodes occurred with the prescribed UF rates, i.e. heart rate and blood pressure responses did not differ between the two groups. Thus, it is possible that lack of differences in change of CO or TPR was due to the fact that there were episodes of significant volume contraction. This however was a pilot study to test feasibility. It is possible that NICOM was insensitive to show difference in physiological response because the patients were not stratified by co-morbidities that might affect the expected responses. In a larger study we might consider to stratify patients based on variables that might influence response. As an example of this, we will consider: age (age <60 vs. age >60), presence or absence of diabetes, ejection fraction prior to study (EF < 40% vs. EF > 55%), average SBP preHD (SBP<120 vs. SBP > 160), but did not have enough subjects to populate these subgroups. Importantly, cardiovascular insufficiency during IHD carries increased morbidity. Its occurrence is both unpredictable and inconstant across patient groups. Thus, a larger patient cohort would be required to observe enough of these events to test the hypothesis that identifiable cardiovascular events precede over cardiovascular collapse.

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