

Original Article

Continuous haematocrit monitoring during intradialytic hypotension: precipitous decline in plasma refill rates

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Abstract

Background. Intradialytic hypotension (IDH) during ultrafiltration remains a major source of haemodialysis related morbidity, despite technological advances including continuous haematocrit monitoring and automated blood volume controlled dialysis machines. We hypothesized that studying the relationship between ultrafiltration rate and plasma refill rate (UFR, PRR) before and during IDH would provide insight into its mechanism and possible prevention.

Methods. We retrospectively identified 17 patients (mean age 50 years) with IDH treated solely by turning off the ultrafiltration, none having received hypertonic saline, mannitol or albumin. All patients had archived data for continuous haematocrits, UFR, ultrafiltration goal, vital signs and symptoms. We used the Crit-Line IIITM optical haematocrit monitor to calculate the PRR for intervals preceeding and during IDH.

Results. Prior to IDH the PRR was 1360 ± 550 ml/h; which was less than the UFR of 1471 ± 602 ml/h and was associated with a 4.4% rise in haematocrit. However, during IDH the PRR was dramatically lower ($P < 0.001$): only 242 ± 151 ml/h. The PRR was not correlated ($P > 0.05$) with the absolute, per cent change or rate of rise in haematocrit, UFR, ultrafiltration goal or heart rate.

Conclusions. On-line haematocrit monitoring allows for the calculation of plasma volume changes, UFR and PRR, and the mismatch in those rates helps explain the physiology of hypotension episodes. The precipitous fall in PRR during sudden IDH supports activation of the cardiodepressor Bezold-Jarisch reflex. As both the UFR and PRR variables can change during a single dialysis session, this supports the use of devices with automated continuous adjustments of the UFR and suggests additional profiling methodologies.

Keywords: haematocrit monitoring; intradialytic hypotension; plasma refill rate

Introduction

Intradialytic hypotension (IDH) remains a relatively common [1,2], morbid complication during haemodialysis [2] despite increasing technological sophistication of dialysis hardware and application of techniques to maintain intravascular volume. Defined as greater than a 30 mmHg drop in systolic blood pressure, IDH complicates up to 30% of all treatments [2,3]. Of greatest clinical concern are abrupt episodes of severe hypotension, which have been attributed to the activation of the Bezold-Jarisch reflex [4] leading to sudden loss of sympathetic tone. Integral to these events is thought to be a uraemic defect in various haemodynamic compensatory mechanisms. In this regard there is a large body of literature addressing the roles of the autonomic nervous system dysfunction [4–6], changes in vasoactive substances [7–9] and their effects on the peripheral vasculature, as well as the role of plasma refilling in the maintenance of intravascular volume [7,10]. With there having been studies of ultrafiltration-induced haemoconcentration associated with IDH [11–14], there has been a growing interest in developing dialysis machines with sensor-controlled feedback loop technology [15–18]. These commercially marketed devices have succeeded in achieving fluid removal along a predefined trajectory by varying the dialysate sodium concentration and automating ultrafiltration so as to follow a well-defined haemoconcentration profile [15]. However, this very enticing machine is not universally available and a substantial proportion of patients nevertheless do not respond with less symptoms or hypotension. We believed that further investigation into the mismatch of the ultrafiltration rate (UFR) with respect to the plasma refill rate (PRR) before and after IDH would provide more insight into its mechanism for these challenging patients and allow

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optimization of this or future technology. It was also important to include patients with wider ranges of desired fluid removal, since grossly fluid overloaded subjects were excluded from most prior studies (typically having a ultrafiltration goal of ~ 3 l). Specifically, the PRR can be derived from continuous haematocrit measurements, and monitored during haemoconcentration (with ultrafiltration) and then haemodilution (with plasma refill when UFR is turned off because of hypotension). We retrospectively identified patients with sudden IDH with the aim of characterizing the clinical parameters, haematocrit values and fluid flux rates before and during hypotension.

Subjects and methods

Study population

As part of routine patient care, 150 end-stage renal disease patients at the University of Florida Chronic Dialysis Unit (Gainesville, FL) underwent automated continuous optical haematocrit monitoring using the Crit-Line IIITM device (In Line Diagnostics, Kaysville, UT). This instrument generated printed plots of the haematocrit vs time during the dialysis treatment with high accuracy [14]. In addition all haemodialysis machine parameters, vital signs and nursing interventions were recorded and archived by the dialysis unit software (FDS08, Fresenius Medical Care, Lexington, MA). Institutional Review Board approval was obtained, and we retrospectively reviewed all of the approximately 450 haematocrit data plots and their associated dialysis records for a 1-year interval. 25 Crit-Line data plots were identified for study based on the inclusion criteria that they exhibited a characteristic peak and decline in haematocrit during IDH (Figure 1), consisting of a fall in systolic blood pressure of at least 30 mmHg. The episodes also had to have been treated solely by turning off the ultrafiltration (i.e. no administration of saline, mannitol or albumin).

We excluded any plot that was not interpretable by two independent examiners or did not have an associated archived treatment record. Patients were also to be excluded if they had clinically unstable ischaemic coronary artery disease, arrhythmias, symptomatic congestive failure, had been labelled as having diabetic or other symptomatic

autonomic neuropathy in the interdialytic interval, active gastrointestinal bleeding or illicit substance abuse. As such, four data plots were found to be uninterpretable and another four were excluded due to incomplete records. No patients met the exclusion criteria based on clinical history. The resultant final pool consisted of 17 patients.

Study protocol

For each of the 17 dialysis treatments the Crit-Line data plots were paired with dry weight and ultrafiltration goal data from nursing notes and the automated reports of time, heart rate, blood pressure and UFR by the haemodialysis machine. Demographic data, including the presence or absence of co-morbid conditions, anti-hypertensive medications, the serum albumin from that calendar month, and the most recent URR were extracted from the medical record.

For the calculation of the various fluid flux parameters we utilized the calibrated measurements of haematocrit from the Crit-Line plots, which were recorded at the beginning of dialysis, at the hypotensive event and after recovery (Figure 1). These timed haematocrit points were matched to corresponding blood pressures, heart rates and the UFR from the machine-generated reports. The duration of the hypotensive event was also noted, as defined by blood pressure recovery and resolution of symptoms.

Plasma volumes (PV) were calculated using the formula [19] $PV = (1 - Hct)(b + cW)$: wherein the haematocrit (Hct) is expressed as a fraction (i.e. range 0–1); b is a constant of 1530 for males, 864 for females; c is a constant of 41 for males, 47.9 for females; and W is the dry weight expressed in kilograms. We determined the rate of change in PV by calculating the volumes at two arbitrary separate time points t_1 and t_2 , and dividing the difference of the plasma volumes by the time interval. This value was then used to calculate the rate of plasma refilling, since during haemoconcentration the net rate of change in $PV = UFR - PRR$. We first calculated the PRR in the time interval between 45 and 60 min, which corresponded to an interval of haemodynamically stable dialysis for every subject. Specifically, the difference in plasma volumes at those two time points, divided by the 15-min time interval, subtracted from the UFR yielded the PRR. During IDH, the difference in plasma volumes between the beginning of the hypotensive event and the larger value at recovery (after haemodilution by the refilling plasma compartment) was divided by the duration of the hypotensive event. This change in plasma volume over the recovery time was manifest by the slope of the declining haematocrit on the Crit-Line plot. As we selected treatments in which the UFR was always set to zero during the IDH event and as there were no other interventions (i.e. no hypertonic saline, mannitol or albumin administration), this haemodilution slope solely represented the rate of plasma refilling (Figure 1).

Statistical methods

Statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC). All statistics were expressed as the mean $\pm$ standard deviation (SD). Comparison of PRR, systolic BP, haematocrit and heart rate during stable dialysis and during IDH was performed with paired two-tailed Student's t -test. A P value of <0.05 was considered to be

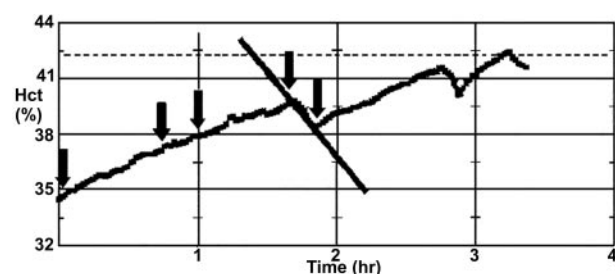


Fig. 1. Crit-Line plot of haematocrit vs time. The timed haematocrit, blood pressure and heart rate measurements are indicated by the arrows. Note the characteristic peak and decline in the tracing with haemoconcentration preceding the episode of IDH. The solid line characterizes the haemodilution during blood pressure recovery while the machine's UFR is set to zero, and corresponds to the PRR.

statistically significant. A two-sided *z*-score was calculated to evaluate if the proportion of females in the study population differed significantly from that of the haemodialysis unit as a whole. Univariate and multivariate regression analyses were used to compare the trends in continuous variables with the trend in PRR during IDH. Pearson correlation coefficients were calculated to determine the strength of correlation between the variables tested.

Results

Patient characteristics

Seventeen haemodialysis treatments from an equal number of distinct patients underwent further analysis. These subjects consisted of 13 females and four males, mean age 50 years (range 28–78), as described in Table 1. Nine patients were Caucasian, eight were African American. Six patients were diabetic, four had peripheral vascular disease, four had a history of stable coronary artery disease and congestive failure. Causes of renal failure included diabetes mellitus ($n=6$), hypertensive nephropathy ($n=5$), congenital renal disease ($n=2$), cyclosporine nephrotoxicity ($n=1$), SLE ($n=1$) and interstitial nephritis ($n=2$). Women were over-represented in our study population ($n=13$, 76%) compared with our haemodialysis population as a whole (50%), to a significant degree ($P<0.05$, *z*-score 2.16). The eight treatment records that had been excluded from the study because of incomplete data or hardware problems had a female preponderance (six of the eight). The chart review indicated that seven patients were on ACE inhibitors, six on beta-blockers and two on calcium channel blockers. Serum albumin concentration was 3.5 ± 0.4 g/dl (range 2.9–4.3 g/dl). Pre-dialysis haematocrits were $32.0\pm 4.6\%$ (range 18.0–38.5%).

Table 1. Baseline patient characteristics

	Mean	SD
Age (years)	50.1	17.2
URR (%)	74.1	9.3
Serum albumin (g/dl)	3.5	0.4
Dry weight (kilograms)	77.0	25.5
Haematocrit (%)	32.0	4.6
Systolic blood pressure (mmHg)	146.8	24.4
Mean arterial pressure (mmHg)	103.3	20.2
Heart rate (b.p.m.)	82.4	12.3
Ultrafiltration goal (ml)	4141	1368

Table 2. Findings during IDH

	Stable dialysis (mean $\pm$ SD)	Intradialytic hypotension (mean $\pm$ SD)	<i>P</i>
PRR (ml/h)	1360 $\pm$ 550	242 $\pm$ 151	<0.001
Systolic blood pressure (mmHg)	146.8 $\pm$ 24.4	100.7 $\pm$ 22.5	<0.001
Mean arterial pressure (mmHg)	103.3 $\pm$ 20.2	72.8 $\pm$ 15.1	<0.001
Heart rate (b.p.m.)	82.4 $\pm$ 12.3	78.3 $\pm$ 15.8	>0.5
Haematocrit (%)	31.9 $\pm$ 4.6	36.2 $\pm$ 5.4	<0.001

Haemodialysis parameters

All patients were maintained on thrice weekly in-centre haemodialysis on Fresenius 2008H machines with F80B dialysers (Fresenius Medical Care, Lexington, MA). Fourteen were prescribed a treatment time of 240 min, three were prescribed 210 min. Patients were prescribed subcutaneous Epogen[®] (Amgen Inc., Thousand Oaks, CA) per protocol to achieve a target haematocrit between 33 and 36%. The patients' dry weights were 77 ± 26 kg (range 33–129) with intradialytic fluid gains of 4.1 ± 1.41 (range 1.2–7.0). The URR was $74\pm 9\%$ (range 68–86).

Haemodynamic and fluid flux measurements

The pre-dialysis systolic blood pressure was 147 ± 24 mmHg (range 109–195) and the mean arterial pressure was 103.3 ± 20.2 mmHg (range 71.5–144.1), with a heart rate of 82 ± 12 b.p.m. (range 64–104). The treatments had an ultrafiltration goal of 4141 ± 1368 ml (range 1200–7000), which represented an average of 5.7% of the patients' dry weight. The episode of IDH occurred 118 ± 29 min (range 75–160) into haemodialysis and lasted 19 ± 7 min (range 8–33). The events were all characterized by a sudden fall in systolic pressure of at least 30 mmHg, which also reflected a significant ($P<0.001$) decline in systolic blood pressure (43 ± 30 mmHg, range 14–96) compared with the pre-dialysis value. The heart rate had an insignificant ($P>0.5$) rise of only 4 ± 2 b.p.m. (range 2–7). Prior to the hypotension the UFR was constant at 1471 ± 602 ml/h, and the resultant haemoconcentration was manifest by an absolute rise in the haematocrit (from the initiation of dialysis to the IDH) of 4.4 percentage points, representing a change of 12.8%. During this haemodynamically stable interval the PRR was calculated to be 1360 ± 550 ml/h (range 340–1840). As indicated in Table 2 the hypotensive episode was associated with a dramatic fall ($P<0.001$) in the PRR to 242 ± 151 ml/h (range 75–627).

There was no statistically significant correlation between PRR during the episode of IDH and the magnitude of blood pressure change, nor with absolute change in haematocrit, per cent change in haematocrit or rate of haematocrit change from initiation of treatment to the hypotensive event. Similarly, there was no significant relation between PRR and ultrafiltration goal, expressed as an absolute value or as a percentage of dry weight. The use of ACE inhibitors was correlated with a slightly, but significantly, lower

PRR (145 ± 48 vs 309 ± 164 ml/h, $P = 0.022$). There was no significant association with other medication usage, serum albumin levels, URR, co-morbid conditions, age or race.

Discussion

The present study highlights the problem faced by practicing nephrologists who encounter IDH, in that it is difficult to identify clinical parameters that can be used to consistently identify hypotension-prone patients. Widely available, haematocrit monitors have been advocated as yet another technology useful in characterizing the degree of ultrafiltration associated with IDH and hence possibly lead to its prevention. There is great appeal to the concept of a monitor-predicted 'crash haematocrit [13]' unique to each patient, beyond which further haemoconcentration is likely to result in IDH. While its utility has not been rigorously established in large populations, it has become a common tool to guide both chronic and acute haemodialysis fluid removal. More recently, however, dialysis machines have become equipped with feedback microprocessors that monitor haemoconcentration with integrated haematocrit sensors. Fluid removal is accomplished with initially high losses that rapidly diminish, and the trajectory is maintained by varying both ultrafiltration and dialysate tonicity. These novel devices have a tremendous appeal, and can reduce IDH and ultrafiltration-induced symptoms; however, these machines are not available in all markets, were studied with net fluid losses of only ~ 31 [16,18], and there were a substantial number of subjects that were considered non-responders [16]. We believe that by using a simple methodology of haematocrit measurements we were able to derive plasma volume values that provided insight into the fluid fluxes associated with IDH and ultimately might be used to further optimize ultrafiltration profiles using a variety of technologies.

By calculating the PRR we demonstrated that prior to hypotension the patients tolerated the mismatch between ultrafiltration (1471 ml/h) and plasma refill (1360 ml/h), which was manifest by the rising haematocrit. This is typical of the large subset of patients who develop symptoms and hypotension late into their dialysis sessions. Many of these individuals have blunting of their normal physiologic responses due to their uraemic autonomic neuropathy. Prior investigations have demonstrated a variety of haemodynamic abnormalities, including problems with sympathetic end-organ responsiveness and the efferent parasympathetic baroreceptor pathway [4–6]. For example, these defects may attenuate the ultrafiltration-induced contraction of the capacitance vessels (the DeJager-Krogh phenomenon) that ought to normally cause a compensatory shift in vascular volume from the periphery to the central circulation.

We suggest that continuously monitoring plasma refill would be a technically simple method of allowing

the manual setting of the dialysis machine's UFR to stay within a safe user-defined range of the PRR when sophisticated microprocessor controlled automation is unavailable. This would be especially relevant if there is a decline in PRR integral to dialysis clearance, as has been suggested: refill would slow with diminishing osmolarity of the vascular compartment as well as with removal of such low molecular weight factors as ANP, which are thought to enhance blood vessel wall permeability [7]. Importantly, grossly fluid overloaded patients might be able to sustain more prolonged high rates of ultrafiltration, as long as there is compensatory plasma refill. Our finding of PRR values up to nearly 21/h for as long as 1 h into treatments (that have ultrafiltration goals as high as 7l) suggests that automated machines would benefit from having additional options for fluid removal trajectories. Thus, programming a targeted near-exponential decline in blood volume may not be optimal for all individuals. In addition, an option for maximizing UFR within PRR limits (avoiding an excessive UFR to PRR mismatch) would permit automation of 'testing down' the patient's dry weight, as the exact trajectory end-point would not be predefined. This would add value to the feedback methodology particularly as there are alternative machines that already exponentially profile UFR, albeit without the benefit of blood volume monitoring. Gradually correcting the dry weight value would also iteratively make the calculated plasma volume more accurate, as the uncertainty of that term is a potential drawback of the formula.

The precipitous fall in PRR, from 1360 to 242 ml/h, supports the multiple previous investigations, which used diverse physiologic tests (i.e. intraneural micro-electrodes, forearm vascular resistance and spectral analysis of heart rate variability) to demonstrate an abrupt loss of sympathetic tone [4]. This cardiodepressor (Bezold-Jarisch) reflex is initiated by cardiac stretch receptors, which are maladaptively triggered by the hyperdynamic left ventricle becoming hypovolaemic (collapsed on echocardiography) [4,10,20] due to ultrafiltration. The rapid decline in PRR that we observed is consistent with increased vascular bed capacitance after the sudden loss of sympathetic nervous system drive. Interestingly we did not observe the bradycardia associated with this reflex in normal subjects, which we believe is suggestive of the uraemic parasympathetic system defect. The dramatic measured decrease in PRR is more remarkable in that it may have occurred despite a conjectured hypovolaemia-induced fluid shift from the splanchnic bed into the vascular compartment. It is not clear whether automated PRR monitoring could ever be designed so as to detect the onset of this rapid reflex in time to launch effective fluid rescue protocols. This may in part explain the non-responsive subjects in trials of the microprocessor technology, and hypotension would have been exacerbated by their tendency to not have the increase in heart rate seen in the responders [16]. In the absence of such sophisticated automation, however, our fluid flux findings do support some commonly used nursing

protocols. For example, during IDH nurses typically turn the ultrafiltration off rather than gradually lowering the UFR. Furthermore, choosing a discontinuous ultrafiltration profile from the options available on many haemodialysis machines might allow prophylactic refilling of the vascular compartment after a period of unintentional excessive fluid removal, thereby avoiding IDH. Interestingly, this finding also justifies the programming of marketed feedback circuitry, in that some published examples show the microprocessor-determined UFR varied from ~ 11 /h down to approximately zero [15,16].

We cannot fully explain why there was a greater proportion of women in our study group of patients with IDH compared with the general population in our dialysis unit. Although perhaps a chance association, it may be due to these particular individuals having greater adiposity and smaller vascular spaces. Thus, their ultrafiltration volumes would be a greater portion of plasma volume than that predicted by using a per cent of total body weight. The biologic significance of lower PRR in IDH patients using ACE inhibitors is similarly unclear, although we cannot exclude a mechanism based on blockade of the renin-angiotensin system in the setting of other uraemic autonomic defects. Further studies would be needed to clarify both these issues, especially as a potential weakness of this investigation is its single study of a small number of subjects in this intentionally well-defined subset of hypotension-prone patients.

In summary, the use of on-line haematocrit monitoring allows for the calculation of plasma volume changes and a comparison of the ultrafiltration and PRR. The UFR to PRR mismatch provides insight into the physiology of hypotension, and might help identify IDH-prone patients. Simple methodologies for monitoring the UFR to PRR mismatch would be useful in lieu of the elegant automated machines, and have particular promise in the absence of knowing the ideal ultrafiltration goal or fluid removal trajectory.

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Conflict of interest statement. None declared.

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