Intradialytic hypotension: a case for going slow and looking carefully

Neha Garg¹ and William H. Fissell¹,²

¹Department of Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH, USA and ²Department of Biomedical Engineering, Cleveland Clinic, Cleveland, OH, USA

Correspondence and offprint requests to: William H. Fissell; E-mail: fisselw@ccf.org

Intradialytic hypotension (IDH) is one of the most common reasons for modification of the dialysis prescription and remains a significant clinical barrier for effective treatment [1, 2]. The differential diagnosis is broad and may differ between hospitalized inpatients and outpatients, or patients with acute versus chronic renal failure. There are cases to be made for all three major categories of hypotension: hypovolemia, distributive shock and pump failure. In this issue of Nephrology Dialysis Transplantation, du Cheyron reports on the use of two commercially available technologies to control IDH in hospitalized patients with acute renal failure by controlling hypovolemia and core temperature, a putative culprit in distributive shock during dialysis. Rather than using hematocrit change for end-point detection and dry weight estimation, a closed-loop negative feedback control system continuously adjusts ultrafiltration rates based on relative blood volume (RBV) changes during the dialysis session. In addition, the impact of iso-thermal dialysis, in which the dialysate temperature was continuously controlled to hold the patient’s body temperature constant, was tested. The authors report on 572 treatments in 74 acute kidney injury patients where each treatment session was randomized to standard therapy with cooled and high-sodium dialysate (n = 188) or blood volume controlled (n = 190) or blood volume and temperature controlled (n = 194) dialysis. No differences were observed in the incidence of IDH or the need for intervention between the control group and the intervention groups.

Du Cheyron’s report is an important contribution to our understanding of how technologies developed for the outpatient setting may not yield clinical benefit in the inpatient setting. Critically ill patients who are mechanically ventilated and receiving vasoactive amines are physiologically quite different from ambulatory outpatients. The factors that impact applicability of this report to general practice are worthy of discussion.

Hypovolemia

Intravascular hypovolemia due to ultrafiltration remains the leading element in the differential diagnosis, and a number of technologies and strategies have evolved to manage fluid removal in dialysis, such as variations in dialysate tonicity, the timing of ultrafiltration versus dialysis, administration of hypertonic saline, ultrapure dialysate and tools to estimate changes in plasma volume [3]. The rationale for considering intravascular volume change in the pathogenesis of IDH is evident: the circulating blood volume is generally between 5 and 6 L, of which 1.5–2 L are cellular elements of blood and the balance plasma water. Typical interdialytic weight gain may be ≥3 L; thus the volume of water removed during the dialysis session is similar to total plasma water. Even small imbalances between the ultrafiltration rate and plasma refilling from the interstitium will acutely reduce the circulating volume and thus cardiac preload. Clearly, subjects in shock requiring pressors will have significantly altered vascular permeability and microvascular blood flow heterogeneity that undermine the central premise of vascular refilling from peripheral compartments.

Studies examining the RBV monitoring have not universally supported the technology. Barth et al. prospectively evaluated 60 patients prone to intradialytic morbid events using the RBV monitoring during 585 treatment sessions [4]. Inter-individual variability in the RBV at which hypotension was observed was high; half of the patients developed IDH when the RBV exceeded 90%, while some tolerated an RBV as low as 70%. The intra-individual variability was small and patients seemed to demonstrate consistent associations between RBV changes and IDH during consecutive sessions. The elderly and those with congestive heart failure or diabetes were more likely to develop hypotension at high RBV values. Reddan et al. reported the results from a randomized multicenter study of 443 subjects randomized to management with or without online blood volume monitoring (BVM) data, and noted increased risk of hospitalization and death in patients in whom the management included BVM data, but the control group appeared to have very low rates of hospitalization and mortality compared with the general US population, and comparisons between the intervention group and the historical controls.
did not reveal significant differences in the primary outcome measures [5].

In du Cheyron’s study, very reasonable maximum RBV thresholds between 80 and 90% were prescribed, but almost no subjects encountered the threshold. This may be attributable to the very long dialysis sessions (6 h) compared with more typically prescribed 3.4 or 4 h [6, 7], keeping ultrafiltration rates low and reducing the likelihood that ultrafiltration would exceed plasma refilling. This is a wise, but maybe not generally feasible, approach to managing dialysis in the critically ill patient. The applicability of blood volume monitoring to sessions involving more aggressive ultrafiltration is not addressed by du Cheyron’s report.

Distributive shock

A second, perhaps less obvious, contributor to IDH has been systematically investigated for over three decades, namely heat accumulation and thermally mediated vasodilation [8]. Gotch et al. modeled heat regulation in dialysis and suggested that significant heat accumulation might provoke vasodilation and hypotension [9]. Maggiore et al. reported the results of a small-randomized trial suggesting that isothermal dialysis using a proprietary feedback system reduced the frequency of IDH in IDH-prone patients [10].

Nakamura et al. have shown venous pooling in the calf muscle of patients prone to IDH when compared with normotensive controls [11]. This was studied in more detail by Esforzado et al. who conducted the autonomic function tests in patients prone to IDH when compared with normotensive dialysis patients and healthy controls [12]. The hand grip test (an index of sympathetic efferent arc) was significantly impaired in IDH-prone patients when compared with the other two groups and was associated with a decreased α-receptor density and reduced β-receptor response. Converse et al. directly measured muscle sympathetic nerve activity and regional vascular resistance during dialysis and demonstrated acute vasodilatation from sudden and paradoxical withdrawal of autonomic activity in IDH-prone patients [13]. This phenomenon, termed the Bezold-Jarisch reflex, has been ascribed to hyperstimulation of low pressure cardiopulmonary receptors by reduced venous return and rapid contractions of near empty ventricles.

Local vasoactive agents like adenosine and dialysate constituents like acetate have also been implicated in IDH. Adenosine is a purine nucleotide produced from the breakdown of ATP and is produced in response to local ischemia. Shinzato et al. measured the levels of adenosine metabolites before and after IDH in hypotension-prone patients [14]. They found elevated levels immediately after hypotensive episode in those who developed acute hypotension. This was reversed after administration of caffeine which acts as an adenosine receptor blocker.

Three-quarters of the subjects in du Cheyron’s report were mechanically ventilated and likely required some sedation, and half were receiving vasopressors. Since sympathetically mediated vasoconstriction is a basic mechanism by which arterial pressure is maintained in the setting of hypotension, these subjects are fundamentally different from the outpatients in whom the BVM technology has been studied. The majority of the plasma volume resides in the venous system (notably skin and splanchnic veins) and changes in autonomic innervation or abnormal pooling of blood in venous beds can significantly reduce venous return with a corresponding decline in the stroke volume. Venous beds that are predominantly under noradrenergic control via α1 receptor activity seem to be resistant to autonomic feedback in dialysis patients despite chronically high basal catecholamine levels. The role of inadequate endogenous vasopressors in provoking IDH in the intensive care unit (ICU) is not clear in the present study; only 10–13% of subjects required initiation or significant increase in vasopressors, although the number of subjects who required more modest, but still effective, increases in pressor requirements was not presented.

Pump failure

Recent literature has identified the role of cardiac impairment as both a cause and effect of dialysis-associated hypotension. Zuber et al. in 1989 were the first to show electrocardiogram (EKG) signs of ischemia in 8/32 patients undergoing chronic maintenance dialysis [15]. McIntyre et al. at the University of Nottingham, Derby, UK have extensively studied the occurrence of subclinical myocardial ischemia as manifested by new regional wall motion abnormalities occurring during dialysis [16–18]. Tok et al. demonstrated impaired coronary flow reserve in dialysis patients with decreased diastolic peak flow velocities in coronary vessels after dipyridamole-induced hyperemia [19]. The decreased functional capacity of microcirculation was not seen in age- and gender-matched controls with a similar left ventricular mass index and attributed to pathologic changes like capillary rarefaction, intramyocardial arteriolar wall thickening and peripheral arterial stiffness seen predominantly in dialysis population. Selby and McIntyre discussed hemodynamic consequences of thermal modeling in dialysis in an excellent review, noting that the hemodynamic stability associated with isothermal or cooled dialysate was also associated with reduced intradialytic myocardial stunning [20].

The subjects reported by du Cheyron had either risk factors for coronary artery disease or coronary artery disease, suggesting that myocardial ischemia may have played an underappreciated role in a few subjects who did experience IDH. Myocardial stunning is a common finding in severe sepsis unrelated to preload [21, 22] and consequently mechanisms of reduced inotropy seen in outpatient maintenance dialysis may be completely different from those in critically ill subjects.

The striking features of the present study may be slightly oblique to the authors’ primary end-point. First, the overall prevalence of IDH in acutely ill hospitalized inpatients was fairly low (15–18% of treatments) compared with previous reports of up to 50% of ambulatory outpatient treatments in susceptible subjects [10]. The ultrafiltration rates were low (500 mL/h) compared with typical intermittent dialysis, but quite high when compared with continuous therapies. This suggests, but does
not prove, that symptomatic IDH in inpatients may be generally addressed by a less-used modality, sustained low-efficiency hemodialysis, which provides a longer interval for ultrafiltration [23]. Second, only 4% of sessions reached the prescribed minimum change in the RBV, and the mean RBV was >85%, suggesting that only rarely was interstitial refilling outpaced by ultrafiltration, even in a non-obese, overhydrated population.

Du Cheyron’s report speaks strongly to the need for critical care nephrologists to maintain a broad differential diagnosis in considering the causes of IDH and to seek alternate explanations, instead of focusing on volume considerations alone. The physiology of critical illness and sepsis leads to different mechanisms of hypotension in the ICU compared with those in the outpatient setting. Tools that are of only equivocal value in one setting may have even less clinical utility in other settings.

Conflict of interest statement. None declared.


References


Received for publication: 13.4.2012; Accepted in revised form: 14.5.2012