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A Brief Review of Intradialytic Hypotension with a Focus on Survival

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Abstract

Intradialytic hypotension (IDH), a common complication of ultrafiltration during hemodialysis therapy, is associated with high mortality and morbidity. IDH, defined as a nadir systolic blood pressure of less than 90 mmHg on more than 30% of treatments, is a relevant definition and is correlated with mortality. Risk factors for IDH include patient demographics, anti-hypertensive medication use, larger interdialytic weight gain, and dialysis prescription features as dialysate sodium, high ultrafiltration rate, and dialysate temperature. A high frequency of IDH events carries a substantial death risk. An ultrafiltration rate >10mL/hr/kg, and even more so >13mL/hr/kg, is highly predictive of cardiovascular and all-cause mortality. Evidence suggests that IDH causes acute reversible segmental myocardial hypoperfusion and contractile dysfunction (myocardial stunning), which can result in long-term loss of myocardial contractility, leading to premature death. IDH also has negative end-organ effects on the brain and gut, contributing to mortality through stroke, and endotoxin translocation with associated inflammation and protein-energy wasting. Given strong association of IDH and dialysis mortality, a paradigm shift to its approach is urgently needed. Randomized controlled trials are required to prospectively test drugs and monitoring devices which may reduce IDH.

Keywords

Intradialytic hypotension; blood pressure; hemodialysis; mortality; ultrafiltration

Background and Definition

Nephrologists have battled the well-known hemodialysis complication of intradialytic hypotension (IDH) in all settings and forms of hemodialysis. It is seen in acute inpatient and outpatient maintenance treatments and also in continuous and intermittent treatments. The

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National Kidney Foundation Disease Outcomes and Quality Initiative (KDOQI) has defined IDH as a drop in systolic blood pressure (SBP) of greater than or equal to 20 mm Hg or mean arterial pressure of greater or equal to 10 mm Hg, presence of end-organ ischemia, and requirement for intervention to increase blood pressure or improve symptoms.[1] Kooman et al. similarly defined IDH in their 2007 European Best Practices Guidelines (EBPG) for IDH.[2] In both these clinician-oriented guideline definitions, there was a requirement for a clinical event requiring an intervention.

More recently, observational studies on large population cohorts have been considering various BP-only definitions of IDH where the nadir and absolute change in intradialytic blood pressure have been used.[3–5] Flythe et al. has recently studied these discrepancies in defining IDH and the utility of nadir-SBP based definitions of IDH.[3] In their study, nadir-based IDH definitions, cut-off SBPs of 90 and 100 mmHg, did show the most consistent association with mortality in the HEMO and large dialysis organization (LDO) cohorts that were studied. The use of nadir-SBP based IDH definitions are gaining popularity in the literature as they allow for large population cohort studies which may or may not have access to nursing intervention information. As these studies shed more light on the associations of nadir-SBP and mortality, they may provide clinicians with greater guidance on nadir-SBP cut-offs for IDH.

The frequency of IDH in in-center hemodialysis traditionally has been cited to be about 20% in reviews[6,7] though individual studies have a varying frequency of 5–30%.[8–11] Recent studies by Sands et al. are similar to these reports. In their study of 1137 patients with 44,807 total treatments, the frequency of IDH was 17.2% in total where patient IDH frequency variability was high. There were 75% of patients with at least one episode of IDH and 58.8% patients had a IDH frequency of 1–35% and 16.2% of patients had >35% IDH frequency.[12] With the use of varying IDH definitions, the frequency of IDH can vary dramatically from 10–70%. Flythe et al.'s study of various IDH definitions in the HEMO cohort and a LDO cohort showed "nadir-only" definitions had an IDH frequency of about 10% where "SBP drop only" definitions of IDH had a greater frequency of 50–69%. In 2014, Silversides et al. did find in 472 ICU patients requiring renal replacement therapy, 87.3% of patients had at least one or more IDH events.[13]

Pathophysiology of Intradialytic Hypotension

In its simplest form, IDH occurs when dialysis ultrafiltration exceeds the rate of plasma refill from normal physiologic compensatory mechanisms. Typically when there is decreased effective plasma volume with ultrafiltration, blood pressure is maintained by increasing plasma refill, vascular resistance, and cardiac output. IDH occurs when this corrective mechanism is insufficiently activated relative to ultrafiltration rate (UFR).

Plasma refill or venous capacity is largely controlled by decreased regional filling and venoconstriction that is actively and reflexively mediated. Normally, decreased regional filling can increase venous return by the DeJager-Krogh phenomenon.[6,14] Here, blood supply is shifted centrally by a passive recoil of regional venous beds which decreases their capacity; the splanchnic and cutaneous vascular beds assist the most in increasing venous

return. The shifted blood volume is then able to increase cardiac preload. In addition to increasing vascular resistance to the splanchnic and cutaneous vascular beds, in hypovolemia, there is also increased vascular resistance to the renal and skeletal vascular beds to assist with further venous return and thus increasing cardiac output.[6]

Cardiac output is also affected by the heart rate and contractility, but perhaps less so than dictated by conventional wisdom. Heart rate itself seems to have a modest effect in improving cardiac output in both animal and humans.[15–17] Contractility as well seems to have a minor role in cardiac output. In animal studies that removed the ability of the animal to respond to hypovolemia with increase cardiac inotropy via anesthesia or denervation of the beta-adrenergic response, the animals had little change in hemodynamic response to simulated hypovolemia.[16–18] In human patients, Ie et al. observed no difference in myocardial contractility in those with or without frequent episodes of IDH.[19] As such, the main driving force for cardiac output is preload or venous return where increasing heart rate and contractility may be of only limited benefit.[6]

Dysregulation of these physiologic compensatory mechanisms will then result in hypotension and IDH in dialysis patients. Patients with impaired cardiac function such as those with systolic and/or diastolic dysfunction are likely to have decreased cardiac output which further contributed to their risk for IDH. In studies of UFR in patients with and without systolic dysfunction, there were higher rates of BP drops in patients with systolic dysfunction.[20,21] Left ventricular hypertrophy and diastolic dysfunction were also found to be worse in patients more prone to IDH.[21,22]

Autonomic dysfunction and impaired baroreceptor sensitivity can limit the compensatory cardiac responses in IDH as well. In patients with reduce cardiac output and stroke volume, hemodialysis patients maintain the MAP by increasing total peripheral resistance; this may be due to background sympathetic over-activity[23], a well recognized phenomenon in kidney disease patients.[24] Additionally, in patients with impaired baroreceptor response, as in those with increased sympathetic overactivity[25], there is a tendency to have increase peripheral resistance versus patients without autonomic dysfunction.[23,26–28] Given that IDH prone patients have an increased total peripheral resistance during dialysis already, these patients may not be able to mount an increase in their peripheral resistance to compensate for further decreases in blood volume and maintain their MAP. This reduced baroreceptor variability found in CKD and ESRD patients is also associated with increased hemodynamic instability and sudden cardiac death.[29]

Risk Factors of IDH

In healthy individuals, these hemodynamic mechanisms can compensated for up to a 20% decline in circulating blood volume before hypotension occurs[30,31] but in dialysis patients much smaller declines of blood volume can be tolerated before the occurrence of hypotension.[32] Patient-related, non-modifiable demographic risk factors include older age, female sex, Hispanic ethnicity and longer dialysis vintage.[5,12] Patient co-morbidities associated with risk for IDH include diabetes mellitus, coronary artery disease, systolic dysfunction, left ventricular hypertrophy and elevated cardiac troponin[5,12,20,21,33,34]. Patient

factors that are more amenable to treatment and change include hyperphosphatemia, anti-hypertensive medication use, ingestion of a meal before hemodialysis, increased body mass index, lower albumin levels, and interdialytic weight gain.[5,12,35–37]

Related to the dialysis prescription, UFR and total volume removal is an associated risk factor IDH[5,12] and UFR is independently associated with cardiovascular mortality.[38–40] Other dialysis-related factors include dialysate sodium and calcium levels, dialysate temperature and acetate buffers. In some, but not all studies, patients treated with low dialysate sodium (≤135 mmol/l) have more IDH[41–43] while higher dialysate calcium is associated with a lower incidence of this complication[44]. In regards to dialysate buffers, previously acetate use was frequent in the past and was demonstrated to cause frequent IDH.[45,46] In a non-randomized cross-over study, converting the buffer in the dialysate from acetate to bicarbonate reduced the incidence of IDH in patients by 50% [47] (Table 1).

Prevention and Management of Intradialytic Hypotension (Table 2)

Acute Management

IDH may be caused by potentially life-threatening conditions, and these must be rapidly evaluated and treated as needed. Conditions include acute hemolysis, air embolus, dialyzer reaction, coronary ischemia, pulmonary embolism, pericardial tamponade, bleeding, and sepsis[48,49]. Acute management steps for all causes should occur simultaneously. Ultrafiltration should be stopped, oxygen administered, and the patient should be placed supine and in Trendelenburg position. Intravenous fluids should be administered to restore blood pressure. Isotonic 0.9% normal saline is used commonly, however the optimal resuscitation fluid is not known. One randomized controlled trial[50], and a systematic review[51] both concluded that 5% albumin is no more effective than 0.9% saline in the treatment of IDH. Severe and/or refractory hypotension should prompt immediate patient transfer to hospital for further evaluation and management.

Prevention

Preventive strategies should be employed in patients with recurrent episodes of IDH, and can be categorized into changes to HD treatment, patient behavior or medications.

HD Treatment

- Patient weight – Common clinical practice entails reassessment of the “dry weight”, with progressive increase in prescribed weight with recurrent episodes of IDH. In the vast majority of outpatient HD units, scheduled treatment sessions leave individual dialysis session lengths relatively inflexible, and so the “dry weight” approach often necessitates unacceptably high ultrafiltration rates when IDWG is high. Both high IDWG[52] and rapid UFR greater than 10mL/hr/kg [38] are independently associated with mortality in HD patients. A novel approach would entail prescription of a “maximum weight”, ensuring ultrafiltration rates do not exceed 10mL/hr/kg, although this may require frequent additional treatments per week in patients with high IDWG.

- Dialysate composition – in non-hypercalcemic patients, ensure dialysate calcium is ≥2.25mmol/L, as lower levels have been associated with IDH[53]. While high dialysate sodium (>140mEq/L) or sodium modelling is commonly employed to manage IDH, these practices are associated with increased thirst and increased IDWG, and should be avoided[54,55].
- Dialysate temperature – Cooling dialysate can reduce the risk of IDH. A recent meta-analysis of 26 trials reported that IDH was reduced by 68% (95% CI 44–82%) when using cooled dialysate compared to standard temperature dialysate[56]. Cooling can be achieved using an empiric fixed reduction in temperature, or through a biofeedback device. The mechanism by which cooled dialysate reduced IDH is not clearly understood, but likely involves increased systemic vascular resistance by activation of the sympathetic nervous system[49].
- Dialysis frequency and duration – modifying a patient's routine hemodialysis schedule to longer hours and/or more frequent treatments per week may reduce the risk of IDH, as more frequent sessions will decreased IDWG, and longer sessions will decrease ultrafiltration rates[57]. In refractory cases, switching dialysis modality to peritoneal dialysis may be of benefit[58].
- Monitoring devices – Intradialytic monitoring of volume status and/or automated regulation of ultrafiltration rates can be achieved through several methods including hematocrit monitoring[59,60], multifrequency bioimpedance[61–63] and biofeedback ultrafiltration[64]. However, use of these devices has not been established to reduce risk of IDH.

Medications—Holding the dose of anti-hypertensive medication immediately prior to dialysis, and preferential prescription of once daily anti-hypertensives may be of benefits for patients prone to IDH. Midodrine, a selective alpha-1 antagonist can be used off-label for the prevention of IDH and given 30 minutes prior to dialysis initiation[65]. However, some patients experience significant side effects of pruritus, supine hypertension, and pilomotor reactions which may limit its use.

Patient Education—HD patients should be educated on the benefits of a low salt diet, since limiting dietary salt intake to ≤ 5g/day lowers IDWG and decreases episodes of IDH[49,66]. Patients prone to IDH should also be educated on the deleterious effects of food ingestion during dialysis on blood pressure[67,68].

The Implications of Conventional "Volume Control" on Mortality

While a recent decline has been observed, mortality rates in ESRD patients still remains unacceptably high [69]. Understanding has grown in recent years on the impact of factors related to the clinical practice of achieving "volume control" on mortality in the ESRD population. IDH is so commonly observed in clinical practice, that clinicians may be unaware of its strong association with mortality. A prospective Japanese study of 1244 patients[4] demonstrated that the lowest intradialytic systolic blood pressures had the highest risk of 2 year mortality. A study from a 10,000 patient cohort reported a nadir systolic blood

pressure of <90mmHg on >30% of treatments was associated with a 1.56 times risk of mortality compared to patients not meeting this definition of IDH[3]. More frequent IDH episodes is also associated with incrementally greater mortality[70]. Given the lack of high-quality, large interventional trials, our understanding is gained largely from observational studies. Two key factors drawn from the literature are closely interconnected clinically; interdialytic weight gain (IDWG) and UFR.

The first study to demonstrate an association between IDWG and mortality was a large US study of 34,107 hemodialysis patients over 2 years[52]. When interdialytic fluid gains were analyzed in 0.5 kg increments, a significant and graded rise in mortality was observed with increased fluid gain. Wong et. al analyzed associations of IDWG and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS)[71]. In this international study of 21,919 hemodialysis patients, IDWG of ≥ 5.7%, compared to 2.5% to <4% was associated with significantly higher mortality. In addition, several other studies have assessed mortality after the 3-day window in every conventional thrice weekly hemodialysis schedule, when IDWG is generally highest. Karnik et al analyzed over 5 million hemodialysis treatments in over 77,000 United States hemodialysis patients and found that cardiac arrests were most likely to occur on a Monday, after the “long interdialytic interval”[72]. Another study of 32, 065 hemodialysis patients in the United States compared death rates on the day after the long interdialytic interval compared to other days[73]. All-cause mortality, cardiac-related mortality and cardiac arrest were all significantly more common on the day after the long interdialytic interval than on other days. While these studies lay the foundation for our understanding of conventional “volume control” practices on mortality, they did not specifically assess the impact of UFRs during hemodialysis treatments.

Clinical practice currently widely dictates use of a prescribed “dry weight” during hemodialysis. Thus, to understand the correlations of IDWG and IDH on mortality, we must assume rapid UFRs in ESRD patients with high IDWG, in an attempt to achieve the prescribed dry weight during a relatively fixed treatment time. In an international study from DOPPS of 22,000 patients from seven countries, UFR > 10ml/hr/kg was associated with a higher risk of mortality (RR=1.09; p=0.02), as well as a higher risk of IDH (RR = 1.33; p=0.045)[74]. Similarly, in a re-analysis of a HEMO study cohort of 1846 patients, Flythe et al examined the risk of mortality comparing UF rates in 3 groups: 10ml/kg/hr, 10–13ml/kg/hr and greater than 13ml/kg/hr[38]. Patients in the highest UF rate group had adjusted all-cause mortality and cardiovascular-related mortality of 1.6 and 1.7 respectively, compared to the lowest UF rate group. More recently, Assimon et al conducted a similar analysis, but with a large study cohort of 118,394 hemodialysis patients and normalized UFR to anthropometric measures such as body weight, body mass index and body surface area[75]. A UFR > 13ml/hr/kg was associated with a 1.3 times higher risk of mortality than UFR ≤ 13mL/hr/kg. While methodologically rigorous, these studies are observational and thus residual confounding cannot be excluded. However, these results strengthen the literature and our understanding of the implications of IDH on mortality.

The End Organ Damage from IDH: Heart, Brain and Gut

There are several postulated mechanisms by which IDH can increase risk of mortality, including myocardial stunning, ischemic brain damage, and gut endotoxin translocation. Myocardial stunning is the recurrent acute reversible segmental myocardial hypoperfusion and contractile dysfunction caused by the circulatory stress of hemodialysis. McIntyre et al have published an important series of papers which use positron emission tomography to demonstrate the deleterious effects of hemodialysis on myocardial stunning, and how this pathophysiologic process is crucially dependent on rate of ultrafiltration and IDH (including asymptomatic IHD) [76–79]. Recurrent myocardial stunning can result in long-term loss of myocardial contractility, which is associated with increased mortality[78].

Brain imaging studies of dialysis patients have reported MRI findings of brain ischemia, including cerebral infarcts[80–82], atrophy[83] and leukoaraosis[84]. Leukoaraosis is caused by ischemic injury, is a risk factor for dementia and strokes, and occurs in the vascular watershed areas of the brain[79,84]. Although studies are currently lacking, IDH should intuitively increase the risk of these ischemic injuries to the brain with subsequent long term consequences of cognitive decline, dementia and stroke. Studies are currently underway combining brain imaging with neurologic outcomes in the face of IDH[79].

Translocation of endotoxin across the gut wall occurs in the setting of bowel edema and hypoperfusion[85]. Endotoxemia has been studied in CHF patients[86] and is a strong proinflammatory stimulus associated with the malnutrition and wasting[87]. Patients initiated on hemodialysis have three times the endotoxin levels of stable stage 5 CKD, likely related to poor mesenteric blood flow while on hemodialysis[88,89]. These high endotoxin levels contribute to the inflammation-related adverse effects on malnutrition and cardiovascular outcomes seen in dialysis patients.

Conclusions and Recommendations

IDH is a common complication of hemodialysis therapy, with strong associations to mortality and end organ damage. Randomized controlled trials of various agents to reduce IDH such as droxidopa[90] and sertraline[91] have been conducted and show promise, but all require further testing before widespread use. Similarly, devices used during hemodialysis treatment such as hematocrit monitoring[59], bioimpedance analysis[63] and biofeedback ultrafiltration[64] have been studied but also require further testing. While such exciting new drugs and devices remain on the horizon for IDH, simpler strategies can be employed in the interim. Renal fellows should be educated early in their training on the importance of proactively managing patients to avoid IDH, and steered away from centering dialysis prescriptions around a “dry weight”. Nephrologists should be cognizant that rapid UFR is strongly associated with mortality, although high quality randomized controlled trials are needed to test the hypothesis that lowering UFR reduces mortality. It may be prudent to offer additional ultrafiltration sessions for patients with large IDWGs, given that more frequent dialysis/nocturnal dialysis patients have less episodes myocardial stunning[92]. The current prescriptive method of volume control is often crude and requires a paradigm shift, with a proactive approach, individualized patient risk assessment and management plan.

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Table 1

Risk factors for Intradialytic Hypotension

Risk Factor	Reference	Effect on Intradialytic Hypotension	Comments
Patient-related Factors			
Demographics			
Increasing age	Tisler 2003	+	
	Sands 2014	+	
Male sex	Tisler 2003	−	
	Sands 2014	−	
Hispanic ethnicity	Sands 2014	+	
Longer hemodialysis vintage	Sands 2014	+	
Co-Morbid Disease			
Diabetes mellitus	Sands 2014	+	Systolic Dysfunction LVH Elevated cardiac Tn
	Takeda 2006	+	
Coronary artery disease	Tisler 2003	+	
Cardiac Dysfunction	Van der Sande 1998	+	
	Chao 2015	+	
	Hung 2014	+	
Other Patient Factors			
Hyperphosphatemia	Tisler 2003	+	CCB, nitrate use
Anti-hypertensive medications	Tisler 2003	+	
	Takeda 2006	−	
Higher BMI	Sands 2014	+	
Lower albumin	Nakamoto 2006	+	
Diuretic Use	Tisler 2003	−	
Hemodialysis-related Factors			
Increased IDWG	Stefansson 2014	+	
	Takeda 2006	+	
Lower pre-dialysis BP	Sands 2014	+	
	Takeda 2006	−	
Increased UFR	Sands 2014	+	>10mL/hr/kg increases risk
	Van der Sande 1998	+	
	Flythe 2011	+	>13mL/hr/kg highest risk
	Movilli 2007	+	
	Saran 2006	+	
Lower dialysate sodium	Levine 1978	−	Dialysate Na ≤135 mmol/L

Risk Factor	Reference	Effect on Intradialytic Hypotension	Comments
	Raja 1983	−	
	Steward 1972	−	
Lower dialysate calcium	Kyriazis 2000	+	
Acetate buffer	Noris 1998	+	
Longer interdialytic interval	Sands 2014	+	

LVH: Left ventricular hypertrophy; Tn: troponin; BMI: body mass index; IDWG: interdialytic weight gain; BP: blood pressure; UFR: ultrafiltration rate; CCB: calcium channel blocker

Table 2

Prevention and Management of Intradialytic Hypotension

ACUTE MANAGEMENT[a]	
Evaluation for life-threatening causes	Hemolysis, Air embolus, Dialyzer reaction, Coronary ischemia, Pulmonary embolus Pericardial tamponade, Bleeding Sepsis
Stop Ultrafiltration	
Place patient in Trendelenburg	
Administer Oxygen	
Replace intravascular volume	
Early termination of dialysis and transfer to hospital, if IDH is severe and/or refractory	
PREVENTION	
I. Patient Education	
Low salt diet	≤5g/day to reduce IDWG
Avoid eating during dialysis	To prevent drop in peripheral vascular resistance
II. HD treatment	
Weight	Avoid “dry weight” goal if it necessitates UFR >10mL/hr/kg
Dialysate Calcium	Keep ≥ 2.25 mmol/L
Dialysate Temperature	Empiric reduction by 0.5 or 1.0°F, or isothermic biofeedback reduction
Dialysis Frequency or modality	More frequent and/or longer hemodialysis. If IDH refractory, consider peritoneal dialysis
Monitoring devices	Blood volume monitoring, bioimpedance, biofeedback ultrafiltration
Dialysate Sodium	Sodium modelling and/or high sodium (>140mEq/L) not recommended, as associated with increased IDWG
III. Medication	
Stop anti-hypertensives prior to hemodialysis	Preferential use of once or twice daily medication dosing
Midodrine	Use limited by side effects (pruritus, pilomotor reactions)

[a]Steps in acute management should occur simultaneously

IDH: intradialytic hypotension; IDWG: Interdialytic weight gain; HD: hemodialysis;