

Mechanisms, Clinical Implications, and Treatment of Intradialytic Hypotension

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Abstract

Individuals with ESKD requiring maintenance hemodialysis face a unique hemodynamic challenge, typically on a thrice-weekly basis. In an effort to achieve some degree of euvoolemia, ultrafiltration goals often involve removal of the equivalent of an entire plasma volume. Maintenance of adequate end-organ perfusion in this setting is dependent on the institution of a variety of complex compensatory mechanisms. Unfortunately, secondary to a myriad of patient- and dialysis-related factors, this compensation often falls short and results in intradialytic hypotension. Physicians and patients have developed a greater appreciation for the breadth of adverse outcomes associated with intradialytic hypotension, including higher cardiovascular and all-cause mortality. In this review, we summarize the evidence for adverse outcomes associated with intradialytic hypotension, explore the underlying pathophysiology, and use this as a basis to introduce potential strategies for its prevention and treatment.

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Physiologic Regulation of BP

In normal individuals, BP is maintained by a complex array of effector and feedback mechanisms. This complex physiology is classically simplified into the equation: BP = cardiac output × total peripheral resistance. Cardiac output is determined by stroke volume and heart rate, whereas stroke volume is dependent on preload, afterload, and contractility. In response to hypotension, the sympathetic nervous system stimulates increased heart rate and contractility in order to increase cardiac output and raise BP. The sympathetic nervous system and renin-angiotensin-aldosterone system, as well as various vasoactive hormones including arginine vasopressin, respond by increasing total peripheral resistance (*via* vasoconstriction) to maintain adequate BP. In normal individuals this results in a relatively stable BP over time, with minimal fluctuations. In patients with ESKD requiring hemodialysis, the situation is quite different.

BP Patterns in Patients on Hemodialysis

Interdialytic

As a result of the intermittent nature of the typical thrice-weekly hemodialysis schedule, BP in patients on hemodialysis exhibits marked variability, tending to be highest in the immediate predialysis period, decreasing during the intradialytic period, and gradually increasing again during the next interdialytic period. Observational evidence suggests the presence of a U-shaped association of predialysis systolic BP with all-cause and cardiovascular mortality, whereas 44-hour interdialytic ambulatory or home BP monitoring has reported greater risk, with average interdialytic systolic BP >140 mm Hg (1). The BP in Dialysis (Clinicaltrials.gov identifier: NCT01421771) pilot trial randomized 126

participants to predialysis systolic BP of 110–140 mm Hg (intensive arm) or 155–165 mm Hg (standard arm). Although not powered for outcomes, rates of intradialytic hypotension (IDH), vascular access thrombosis, and hospitalization were more common in the intensive arm (2). Larger and more definitive randomized controlled trial data are needed to guide the most appropriate target BP for patients on hemodialysis.

Intradialytic

During hemodialysis the majority of patients experience an overall decline in BP, on average in the range of 28–40 mm Hg (3,4). When modeled, this decline is not linear, with a relatively steeper decline noted in the first quarter of hemodialysis, followed by a less steep decline (5). Although the pathogenesis of the early decline remains poorly understood, it seems less likely to be explained by excessive volume removal during this early period. As will be discussed later, an alternative hypothesis relates to relatively rapid decline in plasma osmolality and impaired implementation of compensatory mechanisms.

The transition between a “normal” decline in intradialytic BP and what might be considered excessive (defined as IDH) is not clear, and likely varies from patient to patient. For the purposes of this review, we will assume that IDH is acute and profound enough to result in impaired end-organ perfusion. Further, it will be assumed that other acute medical emergencies are not present (*e.g.*, sepsis, acute myocardial infarction, tamponade, pulmonary embolism, dialyzer reactions, *etc.*).

IDH

Definitions and Measurement

The National Kidney Foundation defines IDH as a decrease in systolic BP by ≥20 mm Hg or a decrease in

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mean arterial pressure of 10 mm Hg associated with symptoms (6). Some have defined IDH on the basis of the need to implement a corrective measure, *e.g.*, administration of saline, reduction in ultrafiltration volume, or reduction in blood flow, whereas others have examined definitions on the basis of a threshold decline in systolic BP, change from predialysis BP, or absolute nadir in the absence of symptoms (7). A major limitation in the comparison of such studies relates to the lack of standardized BP measurements, possibly resulting in overestimation of BP (8). Further sources of variability exist in relation to the use of inappropriate cuff size, readings taken in beds versus chairs, and the use of lower extremity readings. Furthermore, there is no clear evidence to guide the optimal frequency of intradialytic measurements. Despite these inconsistencies, there is a body of literature that supports an association of various definitions of IDH with adverse clinical outcomes.

IDH and Cardiac Outcomes

In a proof-of-concept study of four patients without severe coronary stenosis, hemodialysis itself was associated with reduced myocardial perfusion (9), whereas greater intradialytic decline in systolic BP has been associated with the development of regional wall motion abnormalities, and eventually a decline in left ventricular ejection fraction (10). Interestingly, in a study of seven nondiabetic participants undergoing hemodialysis with minimal ultrafiltration, a reduction in myocardial blood flow was detected within the first 30 minutes of the session. This occurred in the absence of significant changes in BP or volume removal, suggesting that other (poorly understood) factors must be involved (11). Furthermore, IDH has been independently associated with higher risk for cardiovascular mortality, myocardial infarction, and hospitalization for heart failure/volume overload (12).

The prevalence of ventricular arrhythmia in patients receiving maintenance hemodialysis is estimated to range between 21% and 34%, using 24–48 hour Holter monitoring (13,14). However, in a recent study using implanted loop recorders ($n=66$), rates of atrial and bradycardic arrhythmia were more common, and appeared to increase during and after hemodialysis (15,16), highlighting the need to examine IDH as a potential risk factor for such events.

IDH and Vascular Access Outcomes

In a *post hoc* analysis of 1426 participants of the Hemodialysis study (IDH defined as any BP drop requiring intervention), Chang *et al.* (16,17) reported that those with the highest quartile of IDH (compared with the lowest; systolic BP decline of 44 mm Hg versus 26 mm Hg) had a two-fold greater adjusted risk of developing thrombosis of an arteriovenous fistula during follow-up.

IDH and Cerebral Outcomes

Hypoperfusion of the cerebral circulation is also a major concern, with prior studies reporting that decline in intradialytic BP is significantly associated with a reduction in middle cerebral artery blood flow velocity (18). In addition, a recent physiologic study ($n=58$; mostly white men) reported a significant correlation between decline in mean arterial pressure and intradialytic cerebral ischemia

(defined as decline in cerebral oxygen saturation $\geq 15\%$ from baseline for at least 2 minutes) (19). Mizumasa *et al.* (20) used magnetic resonance imaging to assess for progressive frontal lobe atrophy in a 3-year prospective study of 32 nondiabetic patients, without previous symptomatic neurologic lesions. They reported significant inverse correlation between the Frontal Atrophy Index (a measure of the ratio of frontal brain area to the intracranial frontal space) and the number of IDH episodes ($r=0.45$; $P<0.05$; IDH defined as symptomatic systolic BP decline >50 mm Hg within 30 mins of hemodialysis initiation). Cognizant of the potential downstream effects of cerebral hypotension, McIntyre and colleagues (21) performed a randomized study of cooled versus standard temperature hemodialysis (a strategy to mitigate against IDH) in 73 patients. Although changes in tissue water content are not specific for cerebral ischemia, over 1-year of follow-up they found that the use of cooled dialysate resulted in fewer episodes of IDH and significantly fewer abnormal cerebral white matter changes.

IDH and Residual Kidney Function

The rate of residual kidney function decline appears to be greatest in the first 3 months after hemodialysis initiation, suggesting that interventions to preserve residual function should be targeted toward incident patients (22). In a prospective study of 279 such patients, IDH was independently associated with approximately 1 ml/min per 1.73 m² lower mean urea and creatinine clearance at 3 months (23).

IDH and Mortality

Observational data has shown that IDH is associated with both greater cardiovascular and all-cause mortality. For example, Shoji *et al.* (3) reported a greater risk of death with intradialytic systolic BP decline of ≥ 40 mm Hg in 1244 Japanese patients over a 2-year follow-up period. In a larger study from the United States, Flythe *et al.* (7) reported a 30%–56% greater adjusted risk of death for those that had a systolic BP decline to <90 mm Hg during hemodialysis versus not in at least 30% of exposure period treatments. When stratified by prehemodialysis systolic BP, intradialytic nadir systolic BP <100 mm Hg was most strongly associated with mortality in patients with prehemodialysis systolic BP ≥ 160 mm Hg, whereas intradialytic nadir systolic BP <90 mm Hg was most strongly associated with mortality in patients with prehemodialysis systolic BP <160 mm Hg. There was also evidence to suggest a dose-response relationship between frequency of IDH episodes and mortality. Interestingly, there were no significant associations of absolute BP declines (*e.g.*, 20 or 30 mm Hg decline from the predialysis BP) with mortality outcomes, perhaps suggesting the presence of a critical threshold below which end organ hypoperfusion occurs.

IDH: Pathophysiology and Preventive Measures

Despite the lack of mortality-powered prospective studies, the totality of observational evidence suggests that minimizing the magnitude and frequency of IDH is a worthwhile clinical pursuit. It is noteworthy that ultrafiltration goals in patients undergoing thrice-weekly hemodialysis in the United States are often in the range of 2.7–3.0 L (7) (roughly one total plasma volume). Therefore it is assumed that a major etiological factor for IDH relates to

the development (at least transiently) of intravascular hypovolemia. The primary compensatory mechanisms activated in response to this acute insult include cardiac responses to maintain cardiac output, venous capacitance and return (augmenting preload), arteriolar vasoconstriction (increasing total peripheral resistance), and plasma refilling from the interstitial and intracellular compartments (minimizing intravascular hypovolemia) (24,25). The following section will provide a brief review of these mechanisms and discuss potential strategies that may be useful to counteract or prevent IDH (Figure 1, Table 1).

Maintenance of Cardiac Output

Heart Rate. A typical physiologic response to hypovolemia is an increase in heart rate, although some have questioned the absolute importance of this for the maintenance of BP in nondialysis experimental conditions (26). Conversely, the prevalence of tachyarrhythmia in patients on hemodialysis appears to be higher in the peridialytic period (15,16). Particularly in the setting of underlying diastolic dysfunction, loss of the atrial component of ventricular filling in atrial fibrillation may further exacerbate reduced ventricular preload.

With respect to hypotensive-prone patients on hemodialysis, one must keep in mind the myriad of “cardioprotective” medications that have negative chronotropic effects. On the one hand, medications that result in negative inotropy and chronotropy may lead to more IDH; on the other hand, slowing of heart rate and improved ventricular compliance may augment diastolic filling and minimize IDH. As outlined in a recent review of this topic, despite a paucity of prospective evidence on the optimal combinations and timing of antihypertensive medications in patients on hemodialysis, individualized adjustment in an attempt to minimize IDH may be considered for select patients (27).

Contractility. Heart failure is an important risk factor for IDH and is present in approximately one third of patients on hemodialysis (28). Diastolic dysfunction is also common, with as many as 74% having left ventricular hypertrophy at initiation of hemodialysis (29). Diastolic dysfunction results in a narrow range of tolerated filling pressures, such that small reductions in cardiac preload and left ventricular volume can result in significant decline in cardiac output and BP. Systolic dysfunction, although less prevalent than diastolic dysfunction, was reported in 15% of incident patients on dialysis (29). It therefore seems intuitive that augmenting cardiac contractility would also lead to improvements in BP. However, as with heart rate, this may be less important in the setting of reduced preload.

Strategies that have been used with these pathophysiologic mechanisms in mind include the use of higher dialysate calcium, which has been shown to augment myocardial contractility (30). Even in patients with significant cardiac compromise, higher dialysate calcium has been shown to minimize the decline in intradialytic BP (31). However, one must be cognizant of potential downsides of calcium loading and vascular calcification. Intricately related to the ionized calcium concentration, use of higher dialysate bicarbonate concentrations have also been associated with IDH (32). The effects of dialysate potassium concentration are less clear. Although interventions that reduce the rapidity of potassium changes during hemodialysis

have been shown to reduce the risk of premature ventricular complexes (33), others have questioned the broader clinical effect of serum and dialysate potassium gradients (34). Finally, magnesium appears to play an important role in maintaining myocardial electrical stability and regulating vascular smooth muscle tone. Although the relationship between magnesium and IDH remains poorly studied, lower dialysate magnesium concentration has also been associated with decreased cardiac contractility and IDH (35).

Preload: Role of Venous Capacitance and Return

In the setting of hypovolemia, the need to augment cardiac output *via* increased cardiac preload appears to be of primary clinical importance. The majority of circulating blood volume is located in the venous system, which has a large and modifiable capacity, and therefore can be mobilized to enhance preload. In the setting of hypovolemia, vasoactive hormones and increased sympathetic nervous system activity results in arteriolar vasoconstriction and reduction of blood flow to venous beds. This, in turn, results in lower pressure in the venous capacitance system and subsequent passive elastic contraction of the vessel walls, augmenting venous return. This “DeJager–Kroger phenomenon” appears to be particularly relevant in the splanchnic and cutaneous circulations (36). Not forgetting simple and noninvasive approaches, placing the hypotensive patient in the Trendelenburg position represents an immediate strategy to augment venous return in the outpatient unit.

Of additional clinical relevance in this regard is the observation of increased splanchnic blood flow associated with the historical use of acetate-based dialysate. In animal and human studies there appears to be a role for local production (potentially from ischemia-induced consumption of ATP) and action of adenosine (inhibiting norepinephrine release) (37,38), giving plausibility to some reports of beneficial effects of caffeine (an antagonist of adenosine) (39). Similarly, ingestion of food results in greater splanchnic blood flow, and may result in postprandial hypotension in those with autonomic dysfunction. Thus, it may be prudent to restrict intradialytic food intake in patients who are prone to hypotension. Alternatively, the use of splanchnic vasoconstrictors have been suggested by some small studies, including a systematic review that reported less decline in BP and fewer patient symptoms with the use of midodrine (40). In relation to the cutaneous circulation, it has been recognized that cooling the dialysate can promote cutaneous vasoconstriction, increasing peripheral vascular resistance and promoting venous return (41). The ongoing Major Cardiovascular and Other Patient-Important Outcomes With Personalized Dialysate Temperature study (clinicaltrials.gov identifier: NCT02628366), a randomized trial of standard versus cooled dialysate temperature, will examine the effect on all-cause mortality and cardiovascular outcomes.

Arteriolar Vasoconstriction

The development of peripheral arteriolar vasoconstriction in response to hypovolemia is generally independent of cardiac preload and cardiac output and primarily regulated by the autonomic nervous system and activity of vasoactive hormones.

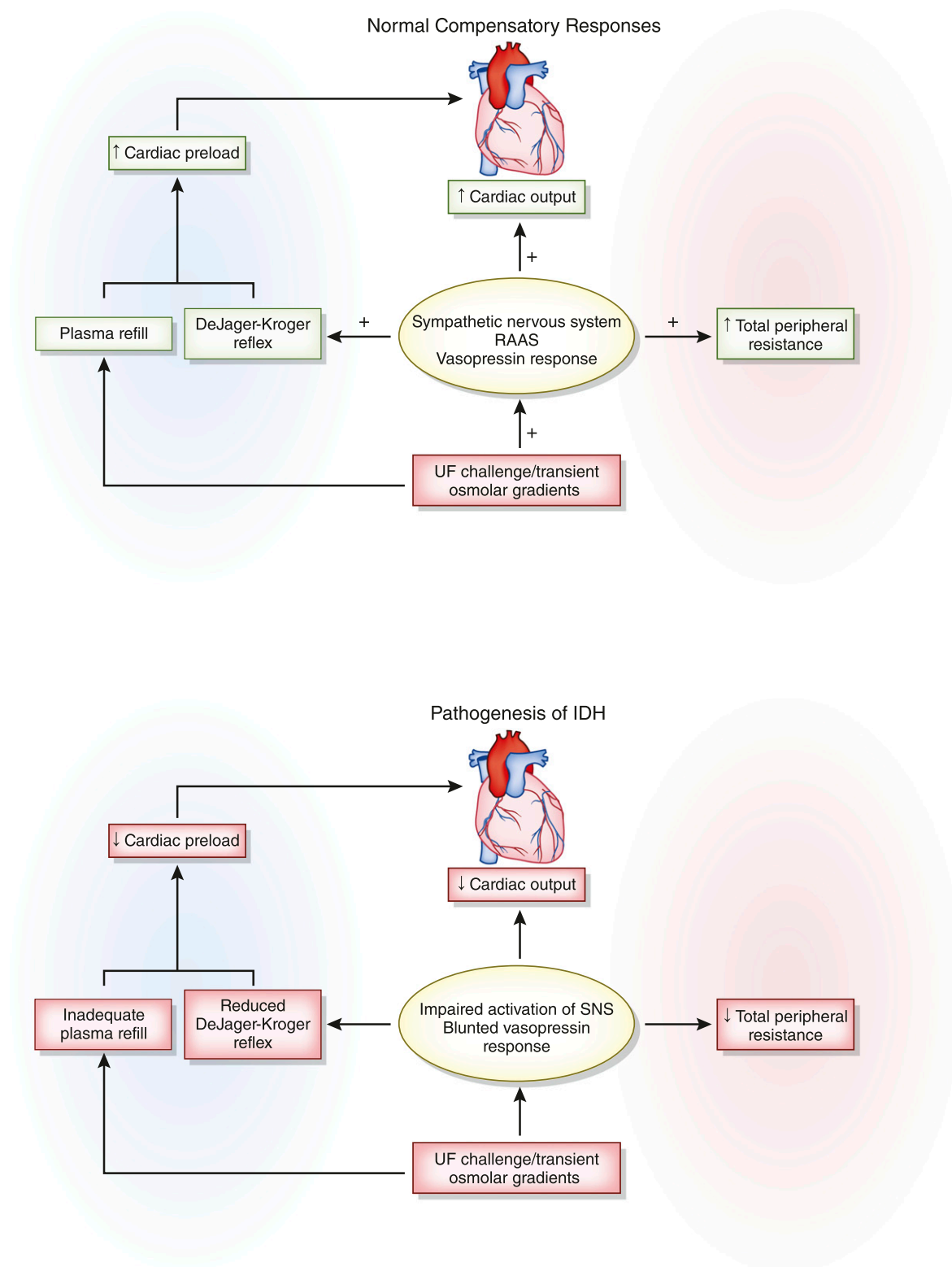


Figure 1. | Schematic demonstrating normal and inadequate compensatory mechanisms to maintain BP in response to hemodialysis with ultrafiltration (blue background denotes venous circulation; red background denotes arterial circulation). Top: Normal compensatory responses involve activation of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS) and possibly increased vasopressin release, in addition to adequate plasma refill. Together these facilitate maintenance of BP via increased venous return and cardiac preload, increased cardiac output, and arteriolar vasoconstriction. **Bottom:** When any aspect of the normal compensatory response is impaired, the maintenance of adequate perfusion pressure may be compromised, leading to intradialytic hypotension. UF, ultrafiltration.

Table 1. Summary of management strategies for treatment and prevention of intradialytic hypotension

Management Strategies	Proposed Physiologic Mechanism to Counteract IDH
Immediate management (excluding acute medical emergencies)	
Stop ultrafiltration	Optimize plasma refill/augment preload
Trendelenburg position	Augment venous return/preload
Saline or albumin infusion	Augment venous return/preload
Consider reduction in blood flow (Qb) and dialysate flow (Qd)	Optimize plasma refill (minimize osmolar gradients)
First-line preventive measures	
Reassess estimated dry weight	Optimize plasma refill/augment preload
Reassess ultrafiltration rate	Optimize plasma refill/augment preload
Counsel about dietary sodium and fluid goals	Optimize plasma refill/augment preload
Avoid food ingestion during hemodialysis	Promote arteriolar vasoconstriction
Review antihypertensive regimen	Promote arteriolar vasoconstriction/optimize cardiac function
Review dialysate composition (Ca ²⁺ , Mg ²⁺ , Na ⁺ , HCO ₃ [−])	Promote arteriolar vasoconstriction/optimize cardiac function
Second-line preventive measures	
Prescribe dialysate cooling	Promote arteriolar vasoconstriction/optimize cardiac function
Evaluate for undiagnosed cardiac disease	Promote arteriolar vasoconstriction/optimize cardiac function
Increase dialysis treatment time	Optimize plasma refill/augment preload
Third-line preventive measures	
Initiate midodrine before hemodialysis	Promote arteriolar vasoconstriction/optimize cardiac function
Change dialysis modality	

Adapted from European Best Practice Guidelines (50).

Autonomic Nervous System. The presence of hypovolemia activates cardiopulmonary and baroreceptors, resulting in release of the tonic inhibition of sympathetic nervous system outflow to the peripheral vasculature. Initially this leads to skeletal muscle and cutaneous arteriolar constriction, and eventually to increased heart rate and contractility (42). In some patients with ESKD there appears to be a paradoxical decrease in sympathetic nervous system activity before the development of sudden IDH, which some hypothesize to be related to heightened sensitivity of the Bezold–Jarisch reflex. This reflex is initiated when myocardial mechanoreceptor activation in response to ventricular under filling leads to vagal afferent inhibition of the medullary cardiovascular center, resulting in a dramatic decrease in sympathetic nervous system activity and consequent arteriolar vasodilation, bradycardia, and IDH. To date, there is limited evidence to support therapeutic approaches to ameliorate IDH related to autonomic dysfunction. However, results from prior small studies using sertraline (43), postulated to act through augmentation of central serotonergic pathways, suggest this may represent an interesting area for further investigation.

Vasopressor Hormones. Inappropriate basal levels or inadequate increases in vasoconstrictor hormones in response to hypovolemia have also been implicated in IDH. Of particular interest is arginine vasopressin, which has potent vasoconstrictor effects *via* its action on V1a receptors in the vasculature. Under normal conditions arginine vasopressin is stimulated by increases in plasma osmolality and significant hypovolemia; however, these responses appear to be blunted in hypotension-prone patients on hemodialysis (44). Indeed, we previously reported that higher predialysis calculated osmolality is associated with greater decline in intradialytic BP (4), whereas others have reported on the benefit of infusing vasopressin for the prevention of IDH (44).

Plasma Refill. The combination of ultrafiltration and hemodialysis clearly presents a unique hemodynamic challenge. The vast majority of interdialytic weight gain

is related to a net positive fluid balance, resulting in hypervolemia and its attendant sequelae. One of the goals of therapy is to safely remove this excess volume in pursuit of the elusive “dry weight.” As ultrafiltrate is removed from the intravascular compartment, “refilling” from interstitial and intracellular compartments ensues in order to maintain BP, and appears to be dependent, in part, on dynamic oncotic and hydrostatic gradients (45).

The performance of hemodialysis alone (*i.e.*, without ultrafiltration) results in diffusive clearance of waste products (*e.g.*, urea), and can potentially lead to the generation of temporary osmotic gradients between the plasma and intracellular compartments. Consequently, plasma refill may be enhanced with the use of albumin or with hyperosmolar solutions (*e.g.*, mannitol, glucose, higher dialysate sodium) that act to increase intravascular osmotic pressure, facilitating movement of water into the intravascular compartment (46). However, there are of course potential drawbacks, particularly in relation to concerns of thirst, interdialytic weight gain, and hypertension with higher dialysate sodium solutions (47). Other strategies proposed to reduce the rate of change in plasma osmolality include lowering of the blood and dialysate flow rates.

On the other hand, isolated ultrafiltration results in the removal of fluid that is isotonic to plasma, resulting in minimal change to plasma osmolality and potentially helping to explain some reports of less IDH with this modality (46). However, others report limited benefit from the use of sequential isolated ultrafiltration followed by hemodialysis, and in clinical practice it is more common to have both hemodialysis and ultrafiltration occurring simultaneously (with greater risk of IDH). Potentially more important than the volume of ultrafiltration, greater ultrafiltration rates are associated with a higher likelihood of IDH (48), but also with greater cardiovascular and all-cause mortality (49). The clinical implications of these observations in response to IDH relate to the immediate actions of stopping/reducing ultrafiltration,

and the administration of fluids to resuscitate intravascular volume. Longer-term strategies involve the need for accurate determination of dry weight, dietary sodium and fluid restriction, and lengthening of the dialysis treatment time. Of course, these “simple” concepts are much harder to achieve in real-life settings, both from a patient perspective and from logistic limitations within the confines of outpatient providers and reimbursement.

Of note, the United States Centers for Medicare and Medicaid Services ESKD Quality Incentive Program recently proposed a quality measure to limit ultrafiltration rates (<13 ml/hr per kilogram) for outpatient hemodialysis treatments. Although the intention is noble (to minimize IDH and reduce cardiovascular risk), it must be remembered that this proposal is on the basis of observational data, without evidence from prospective trials. Therefore, some authorities have raised concerns, highlighting the potential downsides that include progressive hypervolemia and its associated adverse clinical outcomes (50).

Conclusion

In summary, IDH is common and is clearly associated with significant adverse clinical outcomes. The preponderance of available evidence suggests that strategies to limit the frequency and magnitude of IDH is worthwhile. Although general guidelines for the prevention of IDH are available (51), for treating physicians, a thorough understanding of the underlying pathophysiology may guide institution of targeted treatment plans for individual patients. In Table 1 we review some potential strategies and highlight their pathophysiologic basis. It must be noted that many of these suggestions lack robust prospective evidence. Therefore, the prevention and treatment of IDH is a ripe area for clinical investigation and lends itself to the execution of well designed clinical trials that will definitively answer how we should best treat and prevent excessive BP decline during hemodialysis.

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Disclosures

None.

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