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Why is Intradialytic Hypotension the Commonest Complication of Outpatient Dialysis Treatments?

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Intradialytic hypotension (IDH) is the most frequent complication of hemodialysis (HD) treatments with a frequency of 10% to 12% for patients with chronic kidney disease attending for outpatient treatments and is associated with both temporary ischemic stress to vital organs, including the heart and brain, and increased patient mortality. Although there have been many different definitions of IDH over the years, an absolute nadir systolic blood pressure (SBP) has the strongest association with patient outcomes. The unifying pathophysiology is one of reduced effective blood volume, resulting in lower plasma tonicity, and if this cannot be adequately compensated for by activation of neurohumeral systems, then arteriolar tone and blood pressure fall. The risk factors for developing IDH are numerous, ranging from patient-related factors, including age and comorbidity with reduced cardiac reserve, to patient compliance with dietary and lifestyle advice, to reactions with the extracorporeal circuit and medications, choice of dialysate composition and temperature, setting of postdialysis target weight, ultrafiltration rate, and profiling. Advances in dialysis machine technology by providing real time estimates of the effective circulating volume and adjusting dialysate composition to maintain vascular tonicity are being developed, but currently require more sophisticated biofeedback loops to be clinically effective in preventing IDH. While awaiting advances in artificial intelligence, the clinician continues to rely on patient education to limit interdialytic weight gains, frequent assessment of the postdialysis target weight, adjusting dialysate composition and temperature, introducing convective therapies to increase thermal losses, and altering dialysis session duration and frequency to reduce ultrafiltration rate requirements.

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Hypotension is the most commonly reported complication of routine outpatient HD treatments.[1] The incidence of IDH has been reported to range from 0.5% to 40% of all treatments, although more recent studies have suggested a prevalence of approximately 11%.[2] In part, this variation is because of the numerous definitions of IDH that have been used, ranging from symptomatic hypotension requiring active management to symptomatic or asymptomatic absolute or percentage fall in SBP, or mean arterial blood pressure, or an absolute nadir SBP. In 2005 the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines in 2005 defined IDH as either a decrease in SBP ≥20 mm Hg or mean arterial blood pressure ≥10 mm Hg in conjunction with symptoms of hypotension.[3] This was followed by the European Best Practice Guidelines, which defined IDH as a decrease in SBP ≥20 mm Hg in combination with associated clinical and nursing interventions.[4] Other national and clinical guideline groups essentially adopted similar definitions based on the Kidney Foundation Kidney Disease Outcomes Quality Initiative or European Best Practice Guidelines definitions, with some variations including a fall in SBP of ≥30 mm Hg.[5,6] Studies investigating the association between IDH and mortality reported that a nadir SBP had a stronger association with mortality, with a nadir of <100 mm Hg for patients starting dialysis with a SBP ≥160 mm Hg, and <90 mm Hg for those with a predialysis SBP of <160 mm Hg.[6]

Physiological Response to Hypovolemia

Venous Return

Most HD patients gain weight between dialysis sessions, and as such fluid removal and returning patients to a postdialysis target weight is a key objective of the dialysis treatment. Because veins can distend more than

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the arteries, approximately 70% of the blood volume is normally distributed in the venous system. Increased resistance to the vessels supplying a compliant vascular bed reduces inflow and distending pressure, resulting in a passive recoil of the venous bed and translocation of blood pooled in the venous bed back into the central circulation, thereby increasing right atrial filling pressure (DeJager-Krogh effect).[7]

Increased sympathetic drive and elevated plasma catecholamines predominantly increase cardiac venous return by reducing venous capacitance in the splanchnic and cutaneous circulations. Although the capacity of other vascular beds, such as muscle and kidney are also reduced, these only have a minor effect in supporting the central circulation. Studies in HD patients have demonstrated initial pooling of radiolabeled red blood cells in the splanchnic circulation, and when ultrafiltration was applied, these transferred to the systemic circulation, and bioimpedance measurements demonstrated a preferential initial movement of extracellular fluid to the splanchnic circulation.[8,9] Similarly, intravital microscopy and doppler studies have demonstrated a reduction in skin and mucosal blood flow during HD in response to ultrafiltration.[10-13]

Cardiovascular Response

The cardiovascular response to hypovolemia includes changes in heart rate, contractility, and peripheral vascular resistance. Heart rate initially increases, however, it reduces toward baseline as other compensatory mechanisms get activated. However, in severe cases of refractory hypovolemia the heart rate may slow because of the Bezold-Jarisch reflex. Although heart rate is thought to have only a relatively minor effect on the response to hypovolemia,[13] many HD patients have diastolic dysfunction, estimated between 50% to 75%, and are therefore more vulnerable to a reduction in cardiac venous return if they cannot increase their heart rate response.[14,15] Similarly, increased contractility by increasing cardiac output could potentially provide some degree of compensation for hypovolemia. However, magnetic resonance imaging studies conducted during HD have noted a reduction in myocardial blood flow by approximately 13% during the first 30 minutes when minimal fluid has been removed.[16] Other magnetic resonance imaging studies have reported a 25% reduction in myocardial blood flow at the end of a dialysis session following 2.5 liter fluid removal, with both a reduction in ventricular volumes and left ventricular muscle mass, because of removal of intracardiac muscle water.[16,17] Echocardiography studies have observed that these changes in myocardial blood flow can induce stress related segmental left ventricular dysfunction.[18] Echocardiographic studies have suggested that approximately 6% of incident HD patients may have an ejection fraction of <25%.[15] However, correcting volume overload often leads to an improvement in left ventricular function;[19] even so, many dialysis patients have left ventricular hypertrophy[20] because of chronic volume overload and hypertension.[20-22]

Thus, the response to hypovolemia for HD patients with normal cardiac function or diastolic dysfunction is predominantly dependent on sustaining venous return. However, patients with left ventricular dysfunction will be at greater risk of decompensation if cardiac return cannot be maintained.

Autonomic Response

Hypovolemia triggers cardiopulmonary receptors in atria and main pulmonary veins, and the baroreceptors in the aortic arch and carotid sinuses, resulting in neurohumeral activation of the sympathetic nervous system, followed by nonosmotic vasopressin and renin release. This leads to reduced blood flow to the skin and skeletal muscles, redistribution of blood from venous capacitance vessels with increased peripheral vascular resistance, and increased heart rate and contractility, designed to preserve blood flow for vital organs. Circulating catecholamines and aldosterone then increase with progressive hypovolemia.

There has been debate as to whether uremia *per se* causes autonomic dysfunction, because autonomic dysfunction increases with age, and comorbidities including diabetes, hypertension, and heart failure. Studies in HD patients have reported variable findings with some observing deterioration in autonomic function over time, whereas others noted improvement.[23] Many HD patients have some degree of autonomic impairment, and greater autonomic dysfunction is associated with increased mortality.[23] Sympathetic nervous system activity is increased in patients with chronic kidney disease,[24] and this had generated a hypothesis that chronic overstimulation results in a down regulation of the sympathetic nervous system response.[25] Although reports vary, majority have noted an increase in plasma catecholamines in keeping with chronic overactivation.[23,26]

Renin seems to have little effect in the acute response to hypovolemia in HD patients. Similarly, although vasopressin levels are increased, consequent on the increased plasma osmolality of HD patients, vasopressin levels do not rise during HD in response to hypotension[27] because vasopressin is cleared.[28]

Hypotension During HD Sessions

Ultrafiltration and IDH

Most HD patients gain weight between dialysis sessions, and the fluid gained needs to be removed during

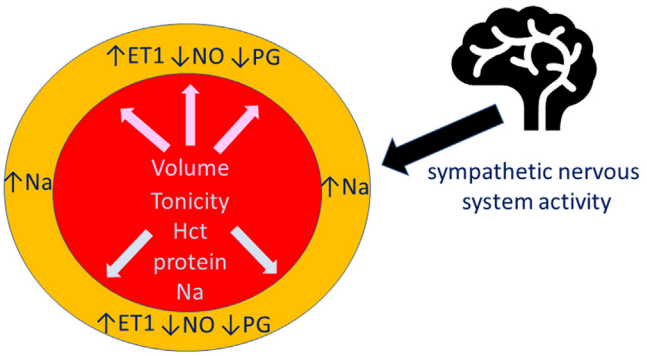

Figure 1. Blood pressure is a measure of arterial tone, which reflects internal outward pressure on vessel wall by the circulating volume, plasma tonicity (Hct, total protein-protein and sodium) and vascular smooth muscle tone (sodium content vascular smooth muscle, balance of local vasoconstrictors (ET1) and vasodilators NO, PDG) and sympathetic nerve activity. ET1, endothelin; Hct, hematorcrit; Na, sodium; NO, nitric oxide; PDG, prostanoids.

HD to return the patient to their post-HD target weight, because persistent volume overload increases left ventricular hypertrophy and reduces survival.[29] Fluid is removed during passage through the dialyzer by applying a transmembrane pressure to generate an ultrafiltrate. Most fluid gained between dialysis sessions is intracellular and extracellular, with only a modest increase in plasma volume.[30] If the rate of fluid removal from plasma volume exceeds the rate at which fluid can be mobilized from the intracellular compartment and extracellular extravascular volume, termed plasma refill rate, plasma volume will be reduced and the patient becomes hypotensive unless compensated for by neurohumeral responses. Blood pressure is a measure of vascular tone. Tonicity in the vessel wall depends upon the internal pressure from the blood volume and viscosity, and the tone in the media of the arterial wall (Figure 1). Hematocrit has the greatest effect on blood rheology, followed by protein and then sodium concentration. This effect of anemia on vascular changes has been shown by studies demonstrating increasing orthostatic hypotension with greater severity of anemia in patients with chronic kidney disease.[31] Similarly, observational reports have highlighted that hypoalbuminemia is a risk factor for IDH.[32] Studies in HD patients have shown that vasopressin levels, a potent constrictor of the splanchnic circulation, do not increase in response to ultrafiltration during HD.[33,34] Similarly, catecholamines, dopamine, norepinephrine, or epinephrine do not increase during HD.[33,35] Over time, more older patients and those with diabetes and other comorbidities are now treated by HD, thereby increasing the number of patients with potentially impaired autonomic responses to hypotension (Table 1).

Determining Target Weight and Ultrafiltration

One of the differences between adult and pediatric practice is the number of children with sodium-losing nephropathies. Therefore, many children may have minimal interdialytic weight gains, and IDH is much more common in pediatric HD units.[36] Similarly, adult patients attending for dialysis with minimal extracellular water overload are more likely to suffer IDH,[37] and report more intradialytic symptoms.[38,39] Therefore, it is important to determine and regularly review target weight for patients. Most dialysis centers use clinical assessment aided by laboratory and other investigations (Table 2).[40] Although serial measurements of brain natriuretic peptides, cancer antigen 125, inferior vena cava diameter, lung ultrasound comets, and extracellular water by bioimpedance provide important information as to whether volume overload is increasing or decreasing, they have not been shown to reduce the risk of IDH.[41-46] Advances in dialysis machine technology have led to the integration of relative blood volume (RBV) monitoring or adding measurements of venous oxygenation.[47] RBV monitoring measures hematocrit or blood density of blood density entering the dialyzer, on the basis that contraction of the plasma volume leads to an increase in hematocrit and density. Although multicenter trials of RBV did not show that this technology reduced IDH,[48] they did not have nurses continuously monitoring the trends. Several patterns of RBV monitoring have been described (Figure 1) as follows: no change in RBV when patients are very volume overloaded; a gradual fall with ultrafiltration, suggesting that plasma refill is compensating for ultrafiltration losses, an initial fall at the start of HD; and a steep decline suggesting that the

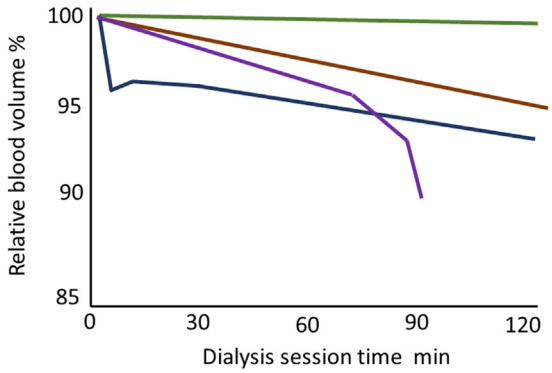

Figure 2. Relative blood volume patterns Linear flat line in a patient who is substantially volume overloaded and no change with ultrafiltration (Green line). Patient with stable downward trend so plasma refill is being compensated during ultrafiltration (Brown line). Initial fall in relative blood volume because of reaction with dialyzer, and then stabilization (Black line). Patient decompensating as sudden steep fall in relative blood volume, as plasma refill does not keep pace with ultrafiltration (Purple line).

Table 1. Patient factors which potentially increase the risk of intradialytic hypotension

Risk factors	Pathology	At risk groups
Normal plasma volume	Pulmonary hypertension	Chronic lung disease
		High flow A-V shunt
	Pericardial effusion	Cardiac tamponade
	Right ventricular dysfunction	Inferior myocardial infarction
	Heart failure with preserved ejection fraction	Diastolic dysfunction
	Cardiac conduction defect	Complete heart block
	Infiltrative cardiomyopathy	Amyloid
Reduced plasma volume	Hemorrhage	Acute blood loss
	Diarrhea	Gastroenteritis
	Vomiting	Gastric outflow obstruction
	Sodium losing nephropathy	Posterior urethral valves
Reduced effective plasma volume	Systemic sepsis	Bacterial infection
	Liver failure	Acute on chronic liver failure
	Anemia	Chronic kidney disease
	Hypoalbuminemia	Malnutrition & sepsis
Cardiac afterload	Heart failure with reduced ejection fraction	Ischemic heat disease
		Cardiomyopathy
	Valvular heart disease	Aortic stenosis
Autonomic dysfunction	Age	Elderly
	Endocrine/metabolic	Diabetes
		Thyroid disease
		Porphyria
	Autoimmune	Systemic lupus erythematosus
		Sjogrens syndrome
		Coeliac disease
	Infiltrative	Amyloid
	Neurologic	Parkinson's disease
	Life style	Alcohol
	Malignancy	Paraneoplastic
		Bortezomib
		Doxorubicin
	Sympathetic denervation	Cardiac transplant
		Artificial heart
	Medications	Atenolol/metoprolol/ propranolol/timolol
		Methyl dopa
		Alpha blockers

A-V, arterio-venous.
Predominantly because of reduced cardiac reserve to repond to a reduction in cardiac filling pressures and autonomic dysfunction AV shunt.

Table 2. Postdialysis target weight needs to be regularly assessed because an inappropriately low target increases the risk of intradialytic hypotension

Assessment	Volume overload	Volume depleted
History	↑Dietary salt intake	↓Appetite
	↑Dyspnea	Diarrhea/vomiting
Examination	No postural hypotension	Postural hypotension
	↑Blood pressure	↓Blood pressure
	↑Weight trend	↓Weight trend
	↑Neck veins	↓Neck veins
	↑Peripheral edema	No edema
Laboratory	Low albumin	↑Albumin
	↑Natriuretic peptides	↓Natriuretic peptides
	↑Serum CA125	Normal serum CA125
Imaging chest X ray	↑CTR	Normal/↓CTR
	Septal lines	
	Kerley B lines	
Lung ultrasound	>10 B lines	<5 B lines
Abdominal ultrasound	<50% collapse IVC	>50% IVC collapse
Bioimpedance	↑ECW/ICW	↓ECW/ICW
Dialysis session RBV	Flat line	Rapid decline
Dialysis session VO_2	Stable O_2 saturation	↓O_2 saturation

CA125, cancer antigen 125; CTR, cardio-thoracic ratio; ECW, extracellular water, ICW, intracellular water; RBV, relative blood volume; VO_2, venous oxygen saturation.

ultrafiltration rate exceeds the plasma refill rate.[49,50] As patients approach their target weight, pulses of ultrafiltration lead to increasingly steeper slopes, and longer recovery[50] (Figure 2). However, there are several confounders to consider with RBV monitoring, including setting the starting point and the Fahraeus effect, because hematocrit varies in different organ circulations so that changes in RBV may lag behind real time changes in the circulating volume. Attempts to add biofeedback control to respond to changes in RBV monitoring have not yet been successful in preventing IDH.[51] There is no absolute critical threshold that predicts IDH, and not only is there marked variation in patient responses to ultrafiltration, but also different responses within the same patient during different dialysis sessions.[52] Central venous oxygen saturation can be measured in patients dialyzing with catheters,[53] and as with RBV monitoring there is a heterogenous patient response to ultrafiltration, with an overall trend for a fall in oxygenation in patients with IDH.[54] However, studies using RBV monitoring did show that different prescriptions of ultrafiltration were associated with different risks of IDH. A linear constant fluid removal rate reduced the risk of IDH compared with intermittent periods of ultrafiltration, and the pattern with the least risk of IDH was one starting a little higher than the linear pattern and then slowly decreasing over the course of the dialysis session.[55]

Multiple observational studies have reported an association between high ultrafiltration rates >10 to >13 ml/h/kg, mortality, and increased IDH.[56,57] Therefore, ultrafiltration by removing excess fluid improves cardiac performance and venous oxygen saturation in HD patients,[53,58] whereas excessive ultrafiltration rates risk myocardial and other organ ischemia.[18] In addition, excessive fluid removal can lead to postdialysis thirst, with increased interdialytic weight gains, thereby setting up a vicious cycle. Such patients require appropriate dietary advice, and if possible, longer or more frequent of more frequent dialysis sessions to control volume overload. Because weight naturally varies, applying a "soft" target

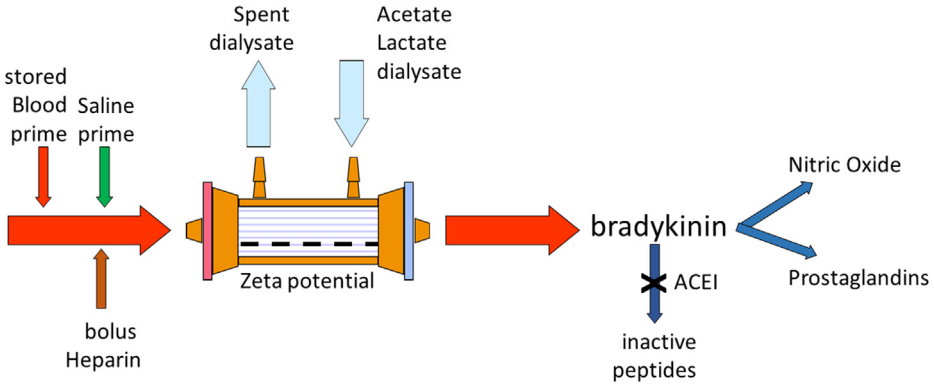

Figure 3. Negative electrical charges in priming fluids (chloride in 0.9% saline, citate in stored blood) and heparin combine with negatively charged dialyzer membrane (negative zeta potential) combine to increase bradykinin and nitric oxide generation by inflammatory cells. angiotensin converting enzyme inhibitor reduces bradykinin breakdown to inactive peptides. ACEI, angiotensin converting enzyme inhibitor.

weight, so that the target weight does not have to be achieved with every session, particularly after the longer interdialytic interval allows the development of a protocol which is less likely to cause patients to have greater interdialytic weight gains.[59]

Hypotension Unrelated to Ultrafiltration

Anaphylactoid Reactions

The extracorporeal circuit consists of plastic tubing and the dialyzer. Plastics are formed from a basic polymer to which other compounds are added, and the capillary fibers are assembled in a dialyzer casing that contains additional organic compounds. As blood flows through the extracorporeal circuit, the circuit has to be sterilized and anticoagulants administered to prevent clotting. Therefore, patients may develop profound hypotension within the first few minutes of starting dialysis because of an anaphylactoid reaction to some of these compounds. In the 1980s, a number of serious anaphylactoid reactions were reported because of the use of ethylene oxide (EtO) as a sterilant for dialyzers. EtO formed a complex with albumin resulting in the formation of IgG antibodies to the EtO-albumin complex.[60] Today, very few dialyzers are sterilized with EtO, but some blood lines may still be sterilized with EtO.

If dialyzers and tubing are not thoroughly rinsed before connection, a series of potentially toxic hydrocarbons and halocarbons can be released from the dialyzer and tubing set and be detected in the exhaled breath of HD patients.[61] Hypotensive anaphylactoid reactions were reported from several countries when patients were dialyzed with polysulfone and polyethersulfone dialyzers from different manufacturers.[62-64] Some patients demonstrated histamine release from mast cells, reacting to polyvinylpyrrolidone, and others to substances released on rinsing the dialyzers.[62,64] Some of the most severe hypotensive anaphylactoid reactions, sometimes fatal, have been due to anticoagulants. These include heparin-induced thrombocytopenia with antibodies generated against heparin-platelet factor 4 complexes,[65] and reactions to the serine protease inhibitor nafamostat maleate.[66] Heparin contaminated with chondroitin sulfate, termed over-sulfated heparin, was also reported to cause severe hypotension.[67,68] Other reactions causing early onset hypotension have been reported with the use of acetate containing bicarbonate dialysate during both HD and hemodiafiltration (HDF),[69] and topical preparations of chlorhexidine used to cleanse the skin around central venous access catheters.[70]

Inflammatory Reactions to the Extracorporeal Circuit

During the 1980s and 1990s, a variety of polymers were used in the manufacture of capillary dialyzers. One of the main differences in polymer composition was the surface charge, or zeta potential. Reports of severe hypotension soon after starting HD appeared in the pediatric literature. Because the volume of the extracorporeal circuit is relatively larger than that of an infant or small child, circuits were typically primed with whole blood. Blood is anticoagulated with approximately 40 mmol/l of citrate, which is quite negatively charged, and the amount of negative charge is increased with storage and cold temperature. The combination of negative charges from blood, saline, and heparin coupled with a negatively charged dialyzer membrane could potentially increase bradykinin and nitric oxide generation in the circuit, resulting in profound vasodilation and hypotension (Figure 3).[71,72] This response was also dependent on patient factors in terms of activation of the acute inflammatory system, which is more common in patients with sepsis and liver failure.[73,74] In addition, because nitric oxide can be scavenged by hemoglobin, anemic patients are at greater risk of IDH with these reactions.[75]

Even with the modern day dialyzer, leukocytes, monocytes, platelets, and complement are activated in

the extracorporeal circuit, with initial leukocyte sequestration in the lung,[76] and increased alveolar capillary permeability.[77] As such, a substantial number of patients have an initial fall in RBV and blood pressure during the first 30 minutes of dialysis, at a time when there has been minimal ultrafiltration (Figure 1).[78] Nitric oxide is generated by the activation of inflammatory cells, and although there is some clearance during dialysis, the rate of change supports ongoing production,[33] and some studies have reported greater nitric oxide production in those patients with IDH.[79]

Dialysate Composition and Temperature

Historically, acetate was used for the buffer base for dialysate solutions, and acetate accumulation was linked to hypotension, particularly for patients with impaired cardiac function.[80] Current bicarbonate dialysates contain a small amount of acetate (3−4 mmol/l), but even some studies have shown an early reduction in vascular tone, measured with aortic pulse wave velocity, in patients using a standard bicarbonate dialysate.[81] Acetate-free biofiltration is a form of dialysis available in Europe, which uses no acetate, and observational studies have reported less IDH with acetate-free biofiltration compared with standard dialysis with a standard bicarbonate and low acetate dialysate.[82,83] Acetate free dialysates are now becoming available for HD, replacing 3 mmol/l acetate with 1 mmol/l of citrate, and preliminary studies have reported a reduction in IDH with the acetate-free citrate dialysate.[84]

Sodium is important in maintaining plasma tonicity and vascular refilling. Single or dual center studies have demonstrated that using a high dialysate sodium leads to increased interdialytic weight gains and hypertension but less IDH, whereas a lower dialysate sodium reduces interdialytic weight gains, but increases IDH.[85] The effects of dialysate sodium are also affected by patient factors, and meta-analysis particularly of multicenter studies failed to demonstrate an overall effect of different dialysate sodium concentrations.[86,87] However, a number of studies have reported that the prescribed dialysate sodium and delivered sodium may differ, in which case this may have been a confounder in the results from the multicenter studies.[88,89]

During the first hour of HD, plasma urea concentrations and osmolality rapidly fall. To modify this fall in plasma tonicity, centers used a varying dialysate sodium, starting with a higher dialysate sodium and ending with a lower sodium,[90] with reports that this practice reduced the incidence of IDH in the short term.[91] Other studies have shown a marginal reduction in the fall of SBP during the first hour of dialysis when starting with a higher dialysate sodium, which was associated with a greater vasopressin response.[33] However, as patients consume different amounts of sodium and have different interdialytic weight gains, this has led to the concept of an individual osmostat.[92,93] Individualizing the dialysate sodium concentration according to the plasma sodium, so that delivering an iso-natric dialysate has been reported to reduce the incidence of IDH, but this technology requires further refinement and clinical testing.[94]

Plasma potassium declines rapidly during the early phase of dialysis, predominantly by diffusion and then plateaus. Choosing a lower dialysate potassium to maximize potassium removal potentially risks inducing hypokalemic intradialytic and postdialytic arrhythmias.[95] Although the rapid change of intracellular and extracellular potassium concentrations may potentially alter cardiac conduction, this may be exacerbated when using a lower dialysate magnesium and high bicarbonate.[47] However, there are no studies demonstrating an effect of dialysate potassium concentration and the prevalence of IDH.[96]

Following the introduction of active forms of Vitamin D3, the concentration of calcium in dialysates has been reduced from 1.75 mmol/l to much lower concentrations because of concerns over calciphylaxis. One major US dialysis provider reduced dialysate calcium to 1.0 and 1.125 mmol/L and observed an increased prevalence of IDH.[97] Other studies reported a reduction in IDH when calcium dialysate was increased from 1.25 to 1.5 mmol/l.[98] The differences in IDH with different calcium dialysate concentrations are typically reported during the latter phase of the dialysis session, when volume has been lost because of ultrafiltration. Though calcium can affect nerve transmission and muscle contraction, several short term interventional studies have reported that a reduction in dialysate calcium, from 1.75 to 1.5 mmol/l, or comparison between 1.75 to 1.25 mmol/l and 1.37 versus 1.12 mmol/l, led to a reduction in vascular stiffness, as measured by pulse wave velocity.[99-101] However, longer term observational studies did not demonstrate a difference in the change in PWV over time.[102] Most centers use a fixed dialysate calcium, but dialysate calcium profiling starting with a lower dialysate calcium of 1.25 mmol/l and then increasing to 1.75 mmol/l,was reported to cause less IDH than when dialyzing with 1.5 mmol/l.[103] This is most likely because of calcium induced vasoconstriction.

Traditionally, dialysates have had a low magnesium concentration to prevent magnesium accumulation in dialysis patients.[104] Magnesium has an important role in generating cardiac myocyte action potentials and

muscle contraction.[105] Observational reports noted an association between the fall in intradialytic magnesium and an increased incidence of IDH.[106] Prospective studies demonstrated that IDH was reduced following an increase in dialysate from 0.25 to 0.75 mmol/l when combined with a calcium dialysate of 1.35 mmol/l.[107] Whereas another study investigating the effects of different dialysate magnesium and calcium concentrations reported that the combination with fewest episodes of IDH was one of magnesium 0.75 mmol/l and calcium 1.25 mmol/l.[106] Other studies have observed lower postdialysis serum magnesium when using acetate compared with bicarbonate dialysates,[107] and also with Citrasate (bicarbonate with citrate and acetate) (Health Tec Medical Ltd).[108] However, studies using citrate as an anticoagulant have not shown any reduction in IHD.[109]

Despite warming the dialysate, there are thermal losses as blood flows through the extracorporeal circuit, which leads to a reduction in blood flow to the skin microvasculature and redistribution to the larger venous capacitance vessels.[110,111] This leads to an increase in the central core temperature and coupled with additional thermal energy gain from the inflammatory reaction with the extracorporeal circuit. If the rise is too great, this will cause reflex vasodilatation and increased blood flow to the skin.[110] Reports of the effects of thermal energy losses and IDH date back some 40 years.[112,113] Since then, there have been many studies confirming these early reports, such that a meta-analysis of 26 randomized controlled trials, including 484 patients, reported that reducing the dialysate temperature significantly reduces the rate of IDH by 70% and increased intradialytic mean arterial blood pressure by 12 mm Hg.[114] Although, another systematic review of 25 randomized controlled trials, including 712 patients, concluded that the prevention of IDH by cooled dialysate temperature was less certain, confounded by differences in study design and potential bias.[115] A fixed reduction of dialysate temperature reduced IDH (rate ratio 0.52, 95% confidence interval 0.34–0.80), but potentially increased patient discomfort (rate ratio 8.31, 95% confidence interval 1.86–37.12) although the studies reporting were rated low as to certainty of evidence reported, and larger studies have not demonstrated an effect of dialysate temperature and self-reported symptoms.[116,117] Thus, both international and national clinical guideline committees have recommended the use of cooled dialysate to prevent episodes of IDH.[4,5] However, the practice of cooling dialysate varies between centers from simply reducing the dialysate temperature to a fixed lower temperature, or individualizing the temperature to 0.5 to 1.0 °C below the patient's core temperature, or using dialysis machine technology to deliver isothermic (no change in temperature), or thermoneutral (no increase in thermal energy), or a prescribed negative thermal energy target.[118] One study has demonstrated an advantage for isothermic compared with thermoneutral HD.[119] However, cooled dialysate has a greater protective effect on IDH than increased dialysate sodium concentrations.[120]

HD Modes

IDH became an increasingly recognized problem as HD provision expanded. In the late 1970s, dialysis machines did not have the accurate volumetric pumps of today, and studies reported greater cardiovascular stability with isolated ultrafiltration compared with HD with ultrafiltration.[121] The greater number of IDH with HD was variously ascribed to the use of acetate dialysate and fall in osmolality with changes in vessel tonicity. However, the advantage for ultrafiltration was primarily because of starting before HD, when patients were most volume overloaded and to experience greater peripheral vasoconstriction and venous tone to better support cardiac filling pressures, with a smaller rise in core temperature.[122] Because ultrafiltration is a convective process, studies of hemofiltration similarly reported less IDH compared with comparable high-flux HD sessions.[123] Initially, this was thought to be due to the removal of a cardio-depressant factor, or because of differences in sodium balance, if a higher dialysate sodium was used as the replacement fluid for convective volume losses.[124] Similarly, HDF, in particular, high-volume postdilutional HDF was observed to cause fewer IDH episodes than high-flux HD.[125] However, a series of interventional studies demonstrated that the reduction in IDH was related to the greater thermal losses with postdilutional HDF, and predilutional HDF, so that when HD treatments used cooled dialysate and thermal losses were comparable, blood pressure profiles were not different between modes.[112,126,127] *In-vitro* studies demonstrated that cooled dialysates reduced endothelial nitric oxide production.[128]

Unusual Causes of Hypotension Unrelated to Ultrafiltration

Although ultrasound techniques have noted microembolic signals in the extracorporeal circuit that may derive from clots or gas embolies, it is very unusual for a sufficiently sized air embolus not to be detected and allowed to pass into the patient causing hypotension and cardiac arrest. Most fatal reports relate to central venous access catheters when tubing has not been adequately clamped, thereby allowing air entry and then faulty or silenced machine alarms, which have often been over-ridden.[129] Clot emboli from venous

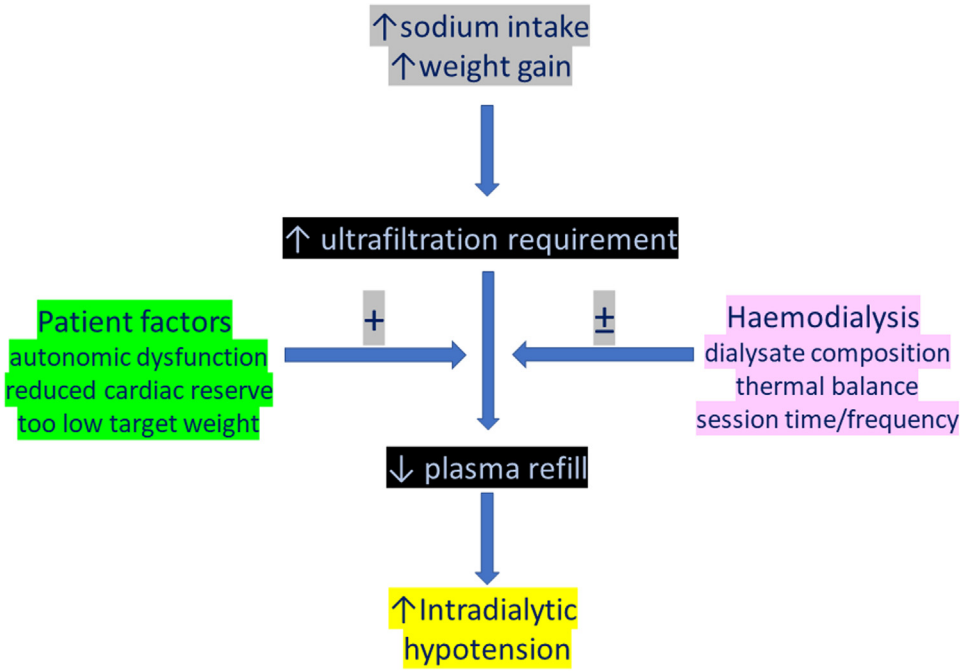

Figure 4. Increased interdialytic weight gains driven by dietary sodium increase ultrafiltration requirements, and the risk of intradialytic hypotension is then potentially increased by patient comorbidities, and inappropriately low postdialysis target weight, but risk could be modified by adjusting dialysate composition and increasing thermal losses and altering dialysis session time and frequency of treatments.

catheters may occasionally be large enough to cause pleuritic pain and hypotension. Some years ago, dialyzers were tested for potential blood leaks in the capillary fibers with liquid perfluorocarbons. If these compounds were not fully removed during sterilization, they would transform to a gas at body temperature as warm blood flowed through the dialyzer, and result in a gas embolus.[130]

In extreme cases, exsanguination can occur during dialysis. The blood pump will automatically stop the dialysis machine alarm, if there is a disconnection with the arterial access. Whereas the dialysis blood pump will continue to pump blood, the machine would not alarm if there is disconnection or faulty venous needle or catheter connection, resulting in rapid exsanguination.[131]

Blood Pressure Targets and Medications

HD patients are at increased risk of stroke, and in the general population, stroke risk is associated with increased SBP.[132] In an attempt to reduce stroke risk guideline targets for predialysis and postdialysis blood pressure control were introduced, but IDH rates were far greater for those dialysis centers with higher achievement of blood pressure targets.[133] Further studies demonstrated that pre-HD and post-HD sessional measurements of blood pressure do not accurately reflect interdialytic blood pressures,[134] and so peridialytic targets were discontinued.

There is a debate about antihypertensive medications for HD patients, with reports showing no advantage for angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and a possible cardioprotective effect with β-blockers.[135] However, some drugs are cleared by HD, including water soluble β-blockers and some of the angiotensin converting enzyme inhibitors. Carvedilol is not cleared by dialysis,[136] and carvedilol has been reported to improve outcomes for HD patients with heart failure.[137] However, an observational study compared carvedilol with metoprolol, which is cleared during dialysis,[136] and reported a greater number of IDH episodes with carvedilol.[138] This would suggest that carvedilol potentially reduces any increase in heart rate to compensate for volume shifts. Although logical not to administer potent vasodilatory antihypertensive medications before a HD session, there are few reports and the PanThames review did not demonstrate a difference in IDH between those centers which advised patients not to take antihypertensive medications and those which did, although IDH was more frequent in those prescribed antihypertensives.[133]

Eating and Exercise During Dialysis Sessions

HD patients are at increased risk of sarcopenia,[139] and unlike fat, there is no body protein store. Many

patients spend time traveling to and from dialysis centers, and as such the "dialysis" day can be a long one, and postdialysis recovery times are variable, so patients may consume less food on the day of dialysis.[140] There is a risk of peridialysis hypoglycemia, whether food is offered or not.[141,142] However, providing patients with a large meal to eat during the HD session potentially risks IDH, because blood is diverted to the gut.[143,144] Not all studies have demonstrated an increase in IDH,[145] and many centers continue to provide patients with hot food and sandwiches, especially with the increasing number of diabetics. If however, patients develop IDH while eating during dialysis, then cold food could be provided after the session has been completed.[146]

Most reports on exercise during dialysis have used cycling or bands, and exercise that started during the early phase of dialysis before significant ultrafiltration has occurred, but only when patients have been cardiovascularly stable and for only a short duration. Coupled with patient selection, it is currently unclear as to whether exercise has a neutral or beneficial effect on IDH.[147-149]

Conclusion

Despite numerous advances in dialysis practice, IDH remains the most common complication associated with dialysis sessions. IDH leads to episodes of transitory organ ischemia, and repetitive episodes lead to permanent organ damage. Although most episodes of IDH occur during the latter phase of the dialysis session with increasing ultrafiltration volumes (Figure 4), increased patient mortality is associated with IDH both during the early and later phases of the dialysis session.[56,57,150]

Different clinical guideline groups and researchers have used different definitions of IDH and this has hampered research and advances in the prevention and treatment of IDH by the lack of a unifying definition, although the strongest association with mortality appears to be the nadir SBP.

The fundamental pathogenesis of IDH is a reduction in vascular tone, primarily because of a fall in the effective circulating volume without an effective compensatory neurohumeral response. The etiology is wide ranging from patient-related factors to the extracorporeal circuit and dialysis prescription.

Until artificial intelligence biofeedback systems can be developed to institute changes during dialysis, the clinician is reliant on patient compliance to limit interdialytic weight gains, reviewing postdialysis target weight, achieving isothermic or negative thermal energy losses, and adjusting dialysis session times and frequency to reduce ultrafiltration rate requirements.

DISCLOSURE

The author decalred no competing interests.

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