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Pathophysiology and Implications of Intradialytic Hypertension

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Abstract

Purpose of Review—Intradialytic hypertension occurs regularly in 10–15% of hemodialysis patients. A large observational study recently showed that intradialytic hypertension of any magnitude increased mortality risk comparable to the most severe degrees of intradialytic hypotension. This review discusses the most recent evidence underlying the pathophysiology of intradialytic hypertension and implications for its management.

Recent Findings—Patients with intradialytic hypertension typically have small interdialytic weight gains, but bioimpedance spectroscopy shows these patients have significant chronic extracellular volume excess. Intradialytic hypertension patients have lower albumin and pre-dialysis urea nitrogen levels, which may contribute to small reductions in osmolarity that prevents blood pressure decreases. Intradialytic vascular resistance surges remain implicated as the driving force for blood pressure increases, but mediators other than endothelin-1 may be responsible. Beyond dry weight reduction, the only controlled intervention shown to interrupt the blood pressure increase is lowering dialysate sodium.

Summary—Patients with recurrent intradialytic hypertension should be identified as high risk patients. Dry weight should be re-evaluated, even if patients do not clinically appear volume overloaded. Antihypertensive drugs should be prescribed due to the persistently elevated ambulatory blood pressure. Dialysate sodium reduction should be considered, although the long term effects of this intervention are uncertain.

Keywords

Intradialytic hypertension; extracellular volume overload; vascular resistance; dialysate sodium; endothelial cell dysfunction

INTRODUCTION

The dialysis procedure aids in hypertension management in most hemodialysis patients, inducing blood pressure decreases from beginning to end. The phenomenon of intradialytic hypertension (IH), where blood pressure increases throughout dialysis, has intrigued nephrologists for years due to its deviation from the expected response to dialysis and the

evidence that patients with recurrent IH have higher risk for long term complications. Initial research in IH focused on potential biologic mechanisms to explain the acute rise in blood pressure, particularly the role of endothelin-1 (ET-1). More recent research has generated an in-depth characterization of the patient phenotype from epidemiologic studies, and smaller case control studies have explored new mechanisms. There is strong evidence that extracellular volume excess is a consistent phenotype in IH patients. While the role of ET-1 continues to be revisited, other mechanisms including the role of dialysate sodium and extracellular osmolality have been explored. This review aims to provide the most recent findings on the pathophysiology of IH and implications for its management.

EPIDEMIOLOGY

There is presently no standardized definition of IH. Intradialytic hypertension broadly refers to blood pressure increases from pre- to post-dialysis or during dialysis, but there remains heterogeneity in how IH patients are classified in the literature. Most epidemiologic studies focusing on hard clinical outcomes defined IH by an *average* change in systolic blood pressure (increases of 5–10 mmHg) from pre- to post-dialysis during periods ranging from 1 week to 3 months. Most smaller case-control studies focusing on mechanistic associations used definitions including an increase in systolic (>10 mmHg) or mean arterial pressure (>15 mmHg) from pre- to post-dialysis *occurring in the majority of treatments* during periods ranging from 2–12 weeks. Observing the blood pressure pattern over several treatments is critically important to minimize misclassification risk as IH occurs in a single treatment in almost any hemodialysis patient sporadically. Among all treatments in all hemodialysis patients in various sample populations, about 20% of treatments are associated systolic blood pressure increases ≥ 10 mmHg[1, 2]. However, using various definitions of IH above, approximately 9–15% of patients have *recurrent* IH.

Cohort studies consistently show that systolic blood pressure increases of 5 or 10 mmHg from pre- to post-dialysis are associated with increased mortality. The largest single study looking at intradialytic blood pressure changes (>100,000 patients in the Davita system[3]) established that mortality risk started with systolic blood pressure increases of *any magnitude*, and the risk increases further with larger increases in blood pressure. In this review, IH broadly refers to patients who frequently experience any increase in blood pressure from pre- to post-dialysis.

PROPOSED PATHOPHYSIOLOGY

The dialysis procedure introduces two unique challenges to a patient's physiology: 1) a reduction in intravascular volume from ultrafiltration and 2) a reduction in extracellular osmolality as solutes diffuse down concentration gradients from blood to dialysate. Both factors contribute to the decrease in blood pressure experienced by most patients, but individual patients may respond differently by activating various paracrine and neurohormonal systems aimed at minimizing hemodynamic instability. The cumulative effects of the hemodialysis procedure and the compensatory mechanisms on cardiac output and vascular resistance ultimately determine the overall blood pressure pattern. Observing IH should invoke two questions: 1) why does blood pressure *not go down* during dialysis

and 2) why does blood pressure *go up* during dialysis? The former question is likely related to the presence of covert chronic extracellular volume overload in patients that are not undergoing adequate ultrafiltration. The latter is likely related to exaggerated hemodynamic responses resulting in vascular resistance increases. Figure 1 summarizes the interplay between some of these proposed mechanisms. Further details on epidemiology and pathophysiology of blood pressure patterns other than IH are reviewed elsewhere[4, 5].

Why does blood pressure not go down?

Extracellular Volume Overload—Removing a volume of fluid during dialysis equivalent to the interdialytic weight gain ensures fluid *balance* but does not necessarily eliminate extracellular volume *excess*. Compared to most hemodialysis patients, IH patients weigh less, have smaller interdialytic weight gains, and have lower pre-dialysis blood pressure[3]. In short, they do not appear to have acute extracellular volume expansion and are subsequently prescribed less ultrafiltration than other patients. There is an association between ultrafiltration volume/rate and intradialytic blood pressure decrease where patients with smaller ultrafiltration volumes have less steep declines in blood pressure. Because IH patients have slower ultrafiltration rates, it is not unexpected that they do not experience large decreases in blood pressure.

Intradialytic blood pressure response is also impacted by chronic extracellular volume excess. In the Dry Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial, Agarwal showed that intensive ultrafiltration for several weeks steepened the intradialytic blood pressure decrease[6, 7] suggesting that flatter intradialytic slopes are consistent with chronic extracellular volume excess. The objective evidence for chronic extracellular volume excess in IH patients has accumulated over the past several years. Using bioimpedance spectroscopy, Nongnuch et al. showed that IH patients (based on one treatment) had a higher ratio of post-dialysis extracellular water to total body water[2]. Two other case-control studies including patients with *recurrent* IH have also recently used bioimpedance spectroscopy to demonstrate post-dialysis extracellular volume excess in IH patients[8, 9]. The ambulatory blood pressure patterns of IH patients are also consistent with a chronically volume expanded state. Not only is ambulatory blood pressure higher in IH patients compared to other hemodialysis patients[10], but it does not increase for up to 24 hours post-dialysis[11] compared the expected rapid increases in blood pressure that more euvolemic patients manifest as they gradually gain weight between treatments.

Osmolarity Changes—Intradialytic osmolar changes also contribute to blood pressure changes. Both higher pre-dialysis calculated serum osmolarity and prescribed dialysis dose are associated with larger intradialytic blood pressure decreases, even when adjusting for ultrafiltration rate[12, 13]. There is some evidence that IH patients have smaller changes in measured plasma osmolarity during dialysis related to lower pre-dialysis osmolarity compared to other hemodialysis patients[8]. The IH patients had lower pre-dialysis blood urea nitrogen which, along with other evidence of lower pre-dialysis serum creatinine, serum phosphorus, albumin, PNA, body weight, interdialytic weight gain in another study [3], characterizes IH patients as individuals with relatively little dietary protein and fluid intake between treatments.

Plasma sodium levels were similar in the study above[8], but there has been investigation into the role of dialysate sodium modification. Whether through intracellular-extracellular fluid shifts or osmotic release of vasopressin, the gradient between plasma and dialysate sodium can influence intradialytic blood pressure[14]. One observational study confirmed a strong correlation between the sodium concentration gradient and change in intradialytic blood pressure with a higher gradient in IH patients[15]. In a prospective crossover trial randomizing patients with recurrent IH to periods of low and high dialysate sodium[16], blood pressure increased with high dialysate sodium and decreased with low dialysate sodium. The mechanisms remain unclear, but there are strong implications to consider dialysate prescription modification from a management standpoint.

In summary, the stimuli that typically cause intradialytic blood pressure decline, ultrafiltration-induced intravascular volume depletion and rapid osmolar changes, are blunted in IH patients. A unifying feature is the small interdialytic weight gain despite chronic extracellular volume overload. This results in slow ultrafiltration rates allowing extracellular volume overload to persist. This also reflects a sicker patient profile with poor dietary intake. Based on these findings, it is not unexpected that such patients do not have substantial intradialytic blood pressure decreases. However, the remaining question is what actually drives the increase in blood pressure.

Why does blood pressure go up?

Hemodynamic Changes and Patient Comorbidities—The association of extracellular volume overload with IH does not establish any causal mechanism. If there is a causal relationship, however, it does not appear to be related to increasing cardiac output during dialysis. Chou et al, using echocardiograms to measure cardiac output and vascular resistance, were the first to show that IH was associated with increasing vascular resistance but no significant change in cardiac output compared to controls[17]. Another study using echocardiograms to measure cardiac output recently replicated these findings based where IH was defined in a single hemodialysis treatment[18]. More recently, in a case control study involving patients with recurrent IH, non-invasive cardiac output monitors showed that IH patients experienced significant increases in total peripheral resistance, but not cardiac output, compared to other hypertensive hemodialysis controls[8]. Overall, the finding that vascular resistance is the driving force behind IH is strong and consistent.

This vascular resistance increase is likely related to an acute response to the dialysis procedure itself, and recent epidemiologic data show some interesting unifying features of IH patients related to chronic comorbidities. Ischemic heart disease, congestive heart failure, stroke, and peripheral vascular disease are all more common in IH patients than other hemodialysis patients[3]. One small study also found elevated aortic stiffness attributed to accelerated arteriosclerosis to be common in IH[19]. In addition to higher ambulatory blood pressure already discussed, IH patients have a greater degree of chronic endothelial cell dysfunction compared to hemodialysis controls. It is likely that any acute hemodynamic changes stem from some predisposition related to an underlying chronic comorbidity. The relationship between IH and endothelial cell dysfunction remains at the heart of this controversy.

Endothelial Cell Dysfunction—Endothelial cell dysfunction in IH has been studied for more than a decade directed at changes and imbalances in known endothelial cell-derived vasoconstrictors (endothelin-1 [ET-1], asymmetric dimethylarginine [ADMA]) and vasodilators (nitric oxide [NO]). The earliest case-control studies investigating this mechanism found that ET-1 rose or fell during dialysis in accordance with blood pressure[17, 20, 21]. More recent studies show mixed results. Two small case-control studies supported the ET-1 hypothesis showing IH patients having a higher post-dialysis ET-1 in both and a lower NO/ET-1 ratio in one, although neither study specified the nature of the between group change in ET-1 during dialysis[18, 22]. Conversely, two other case control studies failed to show any significant between-group difference in the change in ET-1 or ADMA in IH patients or hypertensive hemodialysis controls from pre to post-dialysis[8, 11]. In one study, the intradialytic increase in ET-1 was statistically significant, but did not significantly differ from the rise seen in controls[11]. In the crossover trial using high vs. low dialysate sodium mentioned above[16], there were no significant differences in pre, post or change in ET-1 or NO with the different prescriptions despite the drastic differences in intradialytic blood pressure. Consequently, the benefit of this intervention likely resides in different amounts of vasopressin release (not measured in the study) or transcellular fluid shifts.

Amidst these conflicting results, there is one uncontrolled pilot study that explored the effects of the beta adrenergic antagonist carvedilol on intradialytic ET-1 levels in IH patients[23]. The intradialytic ET-1 increase was blunted after several weeks of carvedilol, and IH was less common during that period. However, this occurred in the absence of a comparator group and the presence of significant improvements in ambulatory blood pressure and flow mediated vasodilation that might have confounded the results. Due to the relatively small nature and heterogeneity of definition of IH in most of the above mechanistic studies (summarized in Table 1), it is difficult to conclude how large a role ET-1 plays in intradialytic increases in vascular resistance and IH. It should not be disregarded as a mechanism, but other potential mechanisms should continue to be explored.

Sympathetic Nervous System—In the Chou study[17] showing differences in vascular resistance, there was no evidence to support sympathetic nervous system activation as a causative mechanism. Plasma epinephrine and norepinephrine were similar between groups pre-dialysis, and norepinephrine was actually higher in the controls post-dialysis. A more recent study suggested that intradialytic blood pressure surges occur in the immediate context of increased heart rate and suppressed baroreflex activity indicating a primary surge in adrenergic activity. Limitations to both studies include the lack of a gold standard metric of sympathetic nervous system activity. The results of a pilot study using carvedilol to resolve intradialytic hypertension remains limited by the absence of a control group[23]. This remains an area that would be enhanced with more formal evaluation of sympathetic nervous system activity.

Other potential mechanisms—There are other hypotheses that remain unexplored or unproven. Two small case control studies have failed to demonstrate any convincing evidence of renin-angiotensin-aldosterone system hyperactivation [8, 17]. High dialysate

calcium has been shown to increase intradialytic blood pressure, but the evidence supports increases in cardiac output, not vascular resistance as the responsible mechanism. Dialyzability of antihypertensive medications also remains formally unproven as a contributing factor.

IMPLICATIONS OF INTRADIALYTIC HYPERTENSION

The strongest and most consistent associations in IH patients are that compared to other hemodialysis patients, they are older, have more comorbidities, and have significant chronic extracellular volume overload. Observing recurrent IH should first prompt recognition that the patient is at high risk for short-term and long-term morbidity and mortality. Dry weight should be thoroughly re-evaluated and probed as tolerated from the standpoint of intradialytic symptoms. Dialysate sodium reduction shifts the intradialytic blood pressure pattern from an increase to a decrease in IH patients. It is unknown whether this results in any other short term (reduction in ambulatory blood pressure) or long term benefits (reduction in hospitalizations or mortality). Chronic management of other underlying comorbidities should be optimized, and patients referred to appropriate specialists as necessary.

The presence of recurrent IH should prompt recognition that the blood pressure elevation in the dialysis unit is related to vasoconstriction, and it is expected that blood pressure will be highest for many hours following the treatment. While volume management will address one of the long term causes of high blood pressure, vasodilating medications will likely be necessary. Due to the conflicting studies on the role of ET-1 in the pathophysiology of IH, it is not necessary that this pathway be specifically targeted. Calcium channel blocker and angiotensin receptor blockers (less dialyzable than angiotensin converting enzyme inhibitors) are appropriate, and carvedilol did have beneficial effects in a pilot study. No medication, including carvedilol, is FDA approved to treat IH. Most episodes of IH are not severe or symptomatic, but it may be necessary in some cases to administer short acting medications during dialysis. Patients should monitor blood pressure at home or at least record measurements obtained outside the unit to confirm blood pressure is improving.

CONCLUSION

Intradialytic hypertension occurs regularly in at least 10% of hemodialysis patients. The association with extracellular volume overload has been confirmed in multiple studies, and these patients should receive appropriate fluid management to minimize the long-term effects of this. There is no consensus on what triggers the vascular resistance surges associated with the intradialytic blood pressure surge, and it may vary between patients with IH who all share in common extracellular volume overload. Treatment of underlying comorbidities is appropriate and vasodilating antihypertensives are appropriate pharmacologic therapy. Dialysate sodium reduction remains the only intervention shown to change the intradialytic blood pressure increase among recurrent IH patients in an uncontrolled study. While the pathophysiology behind IH is becoming more clear, further research is necessary to establish that any management decisions will definitively modify the overall prognosis.

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Key Points

1. Patients with recurrent intradialytic hypertension have been characterized as patients with lower baseline weight and small interdialytic weight gain that may result in masked chronic extracellular volume excess.
2. Multiple studies using bioimpedance spectroscopy have demonstrated a consistent association between intradialytic hypertension and extracellular volume excess after dialysis.
3. There is new evidence in observational studies and prospective studies that dietary sodium reduction can be useful in preventing intradialytic hypertension, but there is no data on further end points with this intervention.
4. While the evidence supporting vascular resistance increases in intradialytic hypertension is consistent, the role of endothelin-1 in this hemodynamic change remains controversial.

Figure 1.

The proposed pathophysiology of intradialytic hypertension involves factors that either prevent blood pressure from decreasing during dialysis or directly cause blood pressure to increase during dialysis (bottom of figure). There are several baseline characteristics of patients with recurrent intradialytic hypertension related to chronic underlying medical comorbidities (top of figure) that may provide a unifying explanation for how this blood pressure pattern occurs.

Patients with recurrent intradialytic hypertension gain less weight between treatments. This results in prescription of a smaller amount of ultrafiltration. The slower ultrafiltration rates prevent the intravascular volume depletion that typically promotes an intradialytic blood pressure decrease. Furthermore, because these patients may not overtly appear volume overloaded, the state of chronic extracellular volume excess persists if fluid challenges are not implemented. These factors contribute to preservation of intravascular fluid volume during dialysis that prevents a large decrease in blood pressure during dialysis.

Patients with intradialytic hypertension have been shown to have smaller changes in osmolarity from pre to post-dialysis compared to other hemodialysis patients that may be due to poor dietary intake and nutrition in general (supported by low serum albumin, urea nitrogen body weight). A relatively lower pre-dialysis plasma sodium and higher dialysate-plasma sodium gradient may also contribute to this. Though evidence for the exact mechanisms is lacking, this could influence intradialytic blood pressure change by minimizing intracellular fluid shifts caused by acute reduction in extracellular osmolarity

(preservation of intravascular volume) or prevent vasopressin levels from decreasing due the blunted reduction in osmolarity (increased vascular resistance).

Chronic endothelial cell dysfunction has been shown in intradialytic hypertension patients. There is some evidence supporting endothelin-1 directly or an imbalance between endothelin-1 and other endothelial cell derived vasoregulators as a mechanism responsible for increased vascular resistance.

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Table 1**Studies Evaluating Endothelin-1 in Intradialytic Hypertension**

Author	Subjects	Intradialytic Hypertension Definition	Intradialytic Hypertension Patients	Controls
Van Buren et al. (11)	n=36	SBP increase >10 mmHg in 4/6 treatments	ET-1 (pg/mL): Pre-HD: 2.1 Post-HD: 2.18	ET-1 (pg/mL) Pre-HD: 1.9 Post-HD: 2.05 Between Group Difference in Intradialytic Change: p=0.6
Van Buren et al(19)	n=49	SBP increase >10 mmHg in 4/6 treatments	ET-1 (pg/mL) Pre-HD: 4.97 Post-HD: 5.98	ET-1 (pg/mL) Pre-HD: 5.10 Post-HD: 5.59 Between Group Difference in Intradialytic Change: p=0.4
Gutierrez et al(27)	n=21	SBP increase during a single HD treatment	ET-1 (pg/mL) Pre-HD: 10.8 pg/mL Post-HD 25.9 pg/mL	ET-1 (pg/mL) Pre-HD: 11.1pg/mL Post-HD: 13.3 pg/mL Between Group Difference (post- HD): p<0.001
Teng et al(29)	n=34	SBP increase >10 mmHg averaged over 4 treatments	ET-1 (pg/mL) Pre-HD: 3.92 Post-HD 4.09 NO/ET-1 Ratio Pre HD: 20.32 Post HD: 17.79	ET-1 (pg/mL) Pre-HD 3.51 Post-HD 2.75 Difference (post – HD): p=0.03 NO/ET-1 Ratio Pre HD: 27.28 Post HD: 24.78 Difference (post- HD): p=0.04
El-Shafey(7)	n=45	MAP increase >15 mmHg in a single HD treatment	ET-1 (pg/mL) Pre-HD: 11.93 Post-HD: 16.39 Within group p<0.001	Group 1: stable blood pressure ET-1 (pg/mL) Pre-HD: 14.49 Post-HD: 14.33 Within group NS Group 2: blood pressure decrease ET-1 (pg/mL) Pre-HD: 11.75 Post-HD: 8.56 Within group p<0.001
Chou(6)	n=60	MAP increase >15 mmHg in >8/12 treatments	ET-1 (pg/mL) Pre-HD: 346 Post-HD: 511 Within group p<0.005 Between group: p<0.05 NO/ET-1 Pre-HD: 0.869 Post-HD: 0.018 Within group p<0.005 Betewen group: p<0.05	ET-1 (pg/mL) Pre-HD: 287 Post-HD: 276 NO/ET-1 Pre-HD: 0.129 Post-HD: 0.034 Within group p<0.005
Raj(5)	n=27	MAP increase >15 mmHg at least once a week for 3 months	ET-1 (pg/mL) Pre-HD: 12.8 Post-HD: 16.8 Within group change: p=0.06	Group 1: no change in blood pressure ET-1 (pg/mL) Pre-HD:14.3 Post-HD: 14.8 Within group change NS Group 2: blood pressure decrease

Author	Subjects	Intradialytic Hypertension Definition	Intradialytic Hypertension Patients	Controls
				ET-1 (pg/mL) Pre-HD: 12 Post-HD: 7.9 Within group change $p < 0.05$

SBP=systolic blood pressure; ET-1=Endothelin-1; HD=Hemodialysis; MAP=Mean Arterial Pressure