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Review Article

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Intradialytic Hypertension: Pathogenesis and Treatment Update; Review

Elmukhtar Habas[1], Ala Habas[2], Almehdi Errayes[3], Eshrak Habas[2], Kalifa Farfar[4], Aml Habas[5], Amnna Rayani[6]

[1]Department of Nephrology, Open Libyan University, Tripoli, Libya
[2]Department of Internal Medicine, Tripoli Central Hospital, University of Tripoli, Tripoli, Libya
[3]Department of Internal Medicine, Hamad General Hospital, Qatar University, Doha,Qatar
[4]Department of Internal Medicine, Alwakra General Hospital, Qatar University, Alwakra, Qatar
[5]Tripoli Children Hospital, University of Tripoli, Tripoli, Libya
[6]Department of Pediatric Medicine, Tripoli Children Hospital, University of Tripoli, Tripoli, Libya

ABSTRACT

Hypertension that occurs during or after a hemodialysis (HD) session is called intradialytic hypertension (ID-HTN). Intradialytic hypertension affects 15% of HD patients, more often in older adults with lower dry weights, using antihypertensive medications, and with lower blood creatinine. Intradialytic hypertension independently increases hospitalization and death rates. Fluid overload, excessive sympathetic activity, concentration of dialysate components, renin-angiotensin system activation, inflammatory processes, and endothelial cell dysfunction are possible risk factors and mechanisms that may cause ID-HTN. Dry weight control, avoiding dialyzable antihypertensive drugs, restricting high-calcium dialysate usage, sodium solute elimination, and renin-angiotensin-aldosterone system inhibitors or endothelin 1 antagonists during HD sessions are preventive and therapeutic approaches. Scopus, Google Scholar, PubMed, and Google for articles published during the last 3 decades were searched for epidemiology, prognostic implications, plausible causes, preventative tactics, and therapies. Keywords and texts such as HD complications, blood pressure variations during HD, intradialytic hypertension, antihypertensive medication and HD, dry weight, and HD blood pressure variability were used were searched. Intradialytic hypertension should be taken more seriously since it can be avoided and treated because it affects patients' life quality and survival. Further studies are required to understand its pathogenesis, therapy, and whether treating ID-HTN improves patient outcomes.

Keywords: Intradialytic hypertension, ID-HTN, HTN, dialysis-induced HTN, hemodialysis

Corresponding author: Elmukhtar Habas ✉ Habas1962@gmail.com

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PLAIN LANGUAGE SUMMARY

High blood pressure during or after hemodialysis (HD) is known as intradialytic hypertension (ID-HTN). Intradialytic hypertension affects 10%-15% of HD patients. It happens more often in older adults who are lighter, take blood pressure (BP) medicine, and have lower blood creatinine. Intradialytic hypertension raises the risks of hospitalization and death on its own. Intradialytic hypertension may be caused by a number of factors, including too much fluid in the body, excessive nervous activity, high concentrations of dialysate components, activation of the renin-angiotensin system, inflammation, and problems with endothelial cells. Avoiding dialyzable hypertension drugs, limiting the use of high-calcium dialysate, getting rid of sodium solutes, and taking renin-angiotensin-aldosterone system inhibitors or endothelin 1 blockers may prevent and treat HD. Scopus, Google Scholar, PubMed, and Google were searched for papers written in the last 30 years that discussed statistics, predictive consequences, probable causes, ways to avoid the disease, and treatments. Keywords like HD complications, BP changes during HD, intradialytic hypertension, antihypertensive medicine and HD, dry weight, and HD blood pressure changes were searched for. People with ID-HTN should be treated and prevented more carefully because it lowers the

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quality of life and shortens the duration of life. More research is needed to learn more about how ID-HTN happens, how to treat it, and whether treating it improves patient outcomes.

INTRODUCTION

It is well documented that hypertension (HTN) is significantly prevalent in chronic kidney disease and end-stage kidney disease (ESKD) dialysis-dependent patients.[1] Blood pressure (BP) variation before, during, and following hemodialysis (HD) affects cardiovascular-related morbidity and mortality.[2] Studies showed that individuals who experienced intradialytic hypertension (ID-HTN) have a systolic BP of 19 mmHg higher during HD than those without ID-HTN. Patients who exhibit ID-HTN tend to be older, have lower dry weights, use more antihypertensives, and exhibit lower serum creatinine. Analysis of 32 295 hemodialysis (HD) sessions revealed that older patients and African Americans were more prone to systolic BP upsurges from pre to post-HD despite similar ultrafiltration (UF) volumes.[3] In an investigation of 1748 new HD patients, 12.2% had >10 mmHg upsurges in systolic BP during HD. The 12.2% of patients had a low body mass index, decreased dry weight, and lower interdialytic weight gain than the rest of the participants, with no increase in systolic BP during HD. Interestingly, the patients with raised ID-systolic BP reported low serum albumin, phosphate, and creatinine. The authors attributed the reported increase of systolic BP during the HD in this group to undetermined independent factors that require further exploration, undetected comorbidities, or hidden undetected intradialytic body-weight gain/fluid retention. Another possible reported mechanism is endothelial cell dysfunction. The intradialytic increased body weight might be due to improved cardiac contractility.[4] The same study reported that increased systolic BP is associated with a higher mortality rate.[4] Intradialytic hypertension appears more prevalent in older patients with reduced dry weight and those with reduced serum creatinine or albumin levels. The decreased albumin and pre-dialysis urea nitrogen levels can cause low osmolarity and prevent BP drops. This is also associated with spiking intradialytic vascular resistance, which may cause BP to rise. Furthermore, there was speculation about the vascular endothelin-1 effect, but experts deferred it. Moreover, patients with ID-HTN seem to be prescribed antihypertensive medications more than needed, although the impact of specific agents remains unclear. A detailed search was conducted for articles published in Scopus, Google Scholar, PubMed, or Google over the last 3 decades. The relevant articles were downloaded and reviewed for definitions, epidemiology, pathophysiology, prevention, and therapy of ID-HTN.

MAIN POINTS

- Blood pressure fluctuates during dialysis, with low- and high-pressure occurrences during and after the procedure.
- The pathophysiology of intradialytic hypertension remains poorly understood; however, proposed mechanisms include activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, excess fluid intake and retention during dialysis, increased arterial stiffness, and alterations in sodium body content.
- Intradialytic hypertension is a common condition in patients undergoing hemodialysis, and its prevention reduces hospitalization rates and mortality.
- Volume management involves reducing interdialytic fluid intake, decreasing sympathetic and RAAS overactivity, avoiding high dialysate sodium, and regulating dialysate and body temperature to minimize the risk of intradialytic hypertension in certain patients.

DEFINITION OF INTRADIALYTIC HYPERTENSION

Hemodialysis typically reduces BP in hypertensive ESD patients; D patients; however, some individuals experience an unexpected increase in BP during HD or immediately after HD. This phenomenon, known as ID-HTN, has been described for several decades.[5] Despite its long-standing recognition, ID-HTN lacks a standardized definition, is commonly overlooked, has unclear pathophysiology, and its clinical implications have only recently become the subject of investigation.[4,6] Although understudied, previous clinical research has defined ID-HTN in various ways: A) an elevation in mean arterial BP (MAP) ≥ 15 mmHg during or immediately following HD,[7] B) an increase in systolic BP (SBP) >10 mmHg from pre to post-dialysis,[4,6] C) high BP during the second or third hour of HD after substantial UF has occurred,[7] D) a BP increase that resists UF,[5] or E) the worsening of existing HTN or the development of new HTN with erythropoietin-stimulating agents.[8] Given the absence of a unified diagnostic criterion for ID-HTN, this review concentrates on BP that rises during or immediately after HD, which leads to ID-HTN as defined by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative [KDOQI]: post-dialysis BP ≥130/80 mmHg.

EPIDEMIOLOGY

Intradialytic hypertension is reported in patients having regular HD in a range of 3%-30%.[7,9] Another report found that 13.2% experienced an increased systolic BP that exceeded 10 mmHg from pre- to post-dialysis.[6] Similarly, an examination of 1748 new HD patients in the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Wave II cohort revealed that 12% showed systolic BP increases > 10 mmHg from pre- to post-dialysis.[4] Another researcher noted that 5%-15% of HD patients have HTN that does not respond to UF.[10] It was reported that 8% of HD patients over 2 weeks were associated with a rise in MAP exceeding 15 mmHg immediately following or during HD.[11] Although intradialytic BP increases typically result in post-dialysis HTN, they may also occur in patients without HTN. In a group of participants in the Crit-Line Intradialytic Monitoring Benefit [CLIMB] study study, 94% of those with intradialytic systolic BP increases > 10 mmHg exhibited post-dialysis HTN. Likewise, 93% of the USRDS Wave II patients with intradialytic systolic BP increases exceeding 10 mmHg showed post-dialysis

HTN.[7] Consequently, intradialytic BP elevations are relatively frequent and generally lead to post-dialysis HTN.

PATHOPHYSIOLOGY OF INTRADIALYTIC HYPERTENSION

Despite extensive research on its mechanism and pathophysiology, the exact cause of ID-HTN remains unclear. Multiple factors have been proposed as potential contributors to this condition. The implicated factors or mechanisms include overactivity of the sympathetic nervous system (SNS), activation of the renin-angiotensin-aldosterone system (RAAS) (neurohormonal), impaired endothelial cell function, excess fluid retention, increased sodium retention, ionized calcium levels, introduction of new medications, erythropoietin therapy, dialysis-related factors, arterial stiffness, and alterations or discontinuation of antihypertensive medications.

NEUROHORMONAL MECHANISM OF INTRADIALYTIC HYPERTENSION

Sympathetic Over-Activity

Intradialytic hypertension occurs when peripheral resistance increases inappropriately during HD, accompanied by increased stroke volume and/or peripheral resistance because of vasoconstriction. It is plausible that activation of the SNS plays a role in its onset. Moreover, it is well-established that HD patients demonstrate excessive SNS activity, as shown through microneurography studies.[12] However, research revealed that the elevated peripheral resistance in ID-HTN patients could not be attributed to increased plasma epinephrine or norepinephrine levels during HD.[13] Nonetheless, it is imperative to note that circulating catecholamine levels do not always correlate with BP changes, and no microneurography studies have been conducted to examine the differences between patients who had and did not have ID-HTN.

Renin-Angiotensin-Aldosterone System

Alternative justifications for ID-HTN include overstimulation of the RAAS and a decrease in intravascular volume. However, responses to RAAS activation and volume depletion are not uniform. Two studies showed that the percentage of blood volume change was similar for subjects with and without HD-responsive BP, suggesting that BP responses to HD and UF were not linked to blood volume alterations during HD.[14] Nonetheless, a comparison of 30 ID-HTN patients with 30 controls revealed that the percentage rise in blood volume (measured by Hct change) was smaller in ID-HTN patients despite comparable UF volumes and fluid removal rates.[13] A small interventional study involving 6 ID-HTN patients examined whether ACE inhibitor (captopril) treatment improved BP management during HD, supporting the hypothesis that RAAS may mediate ID-HTN.[15] Administering 50 mg captopril before HD enhanced BP control in patients with high and normal plasma renin levels, with plasma renin increasing in 4 out of 6 patients. However, a study reported no increase in renin, nitric oxide, catecholamine, or endothelin-1 plasma levels from pre- to post-HD in ID-HTN patients.[13]

ENDOTHELIAL CELL DYSFUNCTION

Studies have suggested that endothelial cell dysfunction influences hemodynamic changes during HD.[13,16] Endothelial cells produce and secrete hormonal factors that help maintain BP homeostasis in response to various stimuli during UF. Imbalances in endothelial-produced hormones, such as nitric oxide (NO), which dilates smooth muscle, and endothelin 1(Et1), a vasoconstrictor, lead to intradialytic hypertension (ID-HTN). Three investigations explored the equilibrium of endothelial-produced factors in patients with ID-HTN.

A study involving 27 patients examined the fractional exhaled nitric oxide levels, asymmetric dimethyl arginine (ADMA, l-arginine, serum nitrite/nitrate), and endothelin-1 (ET1, encoded by the EDN1 gene) before and after dialysis. The participants included 9 patients with ID-HTN, 9 with IDH, and 9 with stable BP during HD sessions.[16] Pre-dialysis fractional expiration of NO was lowest in patients with stable or increased BP during HD compared to those experiencing IDH. No significant differences were observed in l-arginine, nitrite/nitrate, or ADMA levels among the groups. However, ET1 levels increased from pre- to post-dialysis in 9 ID-HTN patients. In 60 patients, imbalances in endothelial-derived BP regulators were identified between subjects with and without ID-HTN.[13] Compared to patients without ID-HTN, patients with ID-HTN showed a significant upsurge in ET1 from pre- to post-dialysis. Furthermore, the NO/ET1 ratio, which decreased in both groups after dialysis, was notably lower in patients with ID-HTN. In a study of 45 HD patients, pre- to post-dialysis, ET1 concentrations increased in ID-HTN patients, decreased in those with IDH, and remained almost the same in patients with stable BP during HD.[17] These 3 studies collectively suggest that ID-HTN may result from a peculiar endothelial cell response to HD, characterized by excessive ET1 production and insufficient NO levels.

Further research focused on endothelial cell dysfunction in ID-HTN due to evidence that vascular constriction may be the main mechanism and ET-1 may be a mediator. Intradialytic hypertension was associated with lower flow-mediated vasodilation than hypertensive HD controls, with BP decreases.[18] Intradialytic hypertension patients had fewer endothelial progenitor cells than controls. Lower endothelial progenitor cell numbers indicate increased cardiovascular risk.[19] These were assessed before HD to avoid HD-induced changes. However, a study found no difference in ET-1 pre- and post-HD between ID-HTN patients and controls.[18] Endothelial cell dysfunction is higher in ID-HTN patients; however, current studies focus on how endothelial dysfunction affects BP.

FLUID OVERLOAD

Volume imbalance is crucial in developing poorly controlled BP in HD. Previous studies suggested that excess volume may be essential to ID-HTN pathogenesis. Research involving 11 patients showed significant cardiac enlargement on echocardiography and elevated BP during HD that did not

respond to antihypertensive drugs. After intensive UF and dry weight reduction, most patients experienced improvements in echocardiographic volume parameters and normalized BP response to HD.[20] Another study of 6 ID-HTN patients found minimal UF increased mean arterial pressure and enhanced cardiac output.[21] The initial mean arterial pressure increases during HD and UF in these patients were likely due to substantial volume excess, as evidenced by the decreased cardiac index and mean arterial BP following more aggressive UF. However, a different study did not detect echo-specific volume excess or cardiac dysfunction in ID-HTN patients compared to controls.[13] Thus, while volume excess may explain BP elevations during HD in certain hypervolemic patient subgroups, it does not fully account for the increase in ID-HTN in all HD patients. Other factors, such as primary HTN, decreased vascular response to BP variation as in the elderly, RAAS and nervous system activation, endothelin-1, and inter- or intradialytic fluid retention.

DIALYSIS FACTORS

Dialysate composition is a known effector on intradialytic hemodynamics.[22] As sodium is the main determinant of serum osmolarity, sodium dialysate may cause intradialytic HTN. Previous studies show that sodium dialysate and increased osmolarity may affect the intravascular fluid flow. Low sodium dialysate content (7% less than serum) induces intradialytic low BP with extracellular volume reduction exceeding HD fluid removal, as estimated by dilutional methods.[23] Fluids moving from the lower sodium extracellular compartment to the higher sodium intracellular compartment cause extracellular fluid loss. This presumably increases the risk of symptomatic hypotension. High sodium dialysate removes fluid from intracellular and extracellular regions, reducing extracellular fluid significantly less than hypotonic or isotonic dialysates. A later whole-body bioimpedance spectroscopy research established a connection between the dialysate and plasma sodium gradient and decreased intracellular volume.[24] According to previous research, maintaining an appropriate plasma volume during HD might stabilize BP and prevent clinical cardiac output decreases. High-sodium dialysate may promote vasoconstriction by increasing vasopressin due to serum osmolarity; however, this has yet to be well studied. Sodium dialysate modification is usually used to prevent severe IDH, but it is unclear whether higher sodium levels cause HTN.[25]

Randomized crossover research examined how sodium dialysate adjustment affects BP in recurrent IC-HTN patients.[26] Higher serum sodium and BP were observed after an HD session in patients exposed to high sodium dialysate (pre-dialysis serum sodium + 5 mmol/L) than in those exposed to low sodium (pre-dialysis serum sodium – 5 mmol/L). This study also examined the effect of sodium gradients on endothelial cell activity. Following endothelial cell culture findings that high sodium concentration in the extracellular compartment reduces NO release,[27] it was expected that patients exposed to high sodium dialysate would have decreased NO production and greater ET-1. It was observed that there was no great difference in NO or ET-1 levels based on sodium dialysate; however, subjects who received high sodium dialysate as the initial intervention had a substantial increase in ET-1 and reduction of NO levels over the study time, suggesting a long-term effect.

Utilizing a high sodium dialysate concentration has been a strategy for maintaining hemodynamic stability during HD. However, this approach may result in sodium retention, potentially leading to increased thirst, weight gain between and during dialysis sessions, and hypertension between dialysis treatments.[28] A study involving 11 patients compared various sodium dialysate profiles and found that higher sodium dialysate concentrations (147 vs. 138 or 140 mmol/L) during HD resulted in elevated 24-hour ambulatory BP, including systolic (approximately 10 mmHg), diastolic BP, pre-, and post-load.[29] Furthermore, using standard sodium dialysate (e.g., 140 mmol/L) for patients with pre-dialysis sodium levels < 140 mmol/L can create an intradialytic sodium burden, possibly contributing to ID-HTN. Despite the potential impact of inadequate sodium removal on overall BP control, no reported study has specifically examined the relationship between dialysate sodium concentration and ID-HTN development.

The impact of dialysate potassium on intradialytic BP remains unclear, although low serum potassium levels can cause vasoconstriction. An earlier study reported that low dialysate potassium (1, 2, and 3 mmol/L concentrations) reduced the BP during HD at all potassium concentrations. A recent study concluded that potassium dialysate containing 2 or 3 mmol/l did not affect the ID-HTN rate in patients who frequently developed ID-HTN. However, patients receiving 1 mmol/L and 2 mmol/L potassium dialysate experienced a significant BP increase 1 hour after the end of the HD session.[30] This suggests that hypokalemia from low potassium dialysate might cause post-HD rebound HTN; it is doubtful that low potassium dialysate significantly contributes to ID-HTN, as previous studies have observed ID-HTN in patients irrespective of the given potassium during the HD session.[13]

It is well-established that a sudden rise in ionized calcium can enhance myocardial contractility, boost cardiac output, and improve hemodynamic stability during HD.[31,32] Other studies have explored using high calcium dialysate to address hemodynamic instability in patients with hypotension or impaired cardiac function without significantly affecting ID-HTN with different dialysate calcium concentrations.[31] High calcium dialysate was shown to increase arterial stiffness, decrease arterial compliance, and result in a less pronounced reduction in systolic BP during HD. Although increasing calcium in the dialysate stabilizes BP during HD, the role of high calcium dialysate in ID-HTN pathophysiology remains understudied, and patients still develop ID-HTN even with standard calcium dialysate.[31]

Body temperature affects BP. It was reported that ID-HTN is linked with heat gain during HD sessions.[32] Furthermore, the ID-HTN incidence declined when dialyzed at the isothermic temperature.[32] Another report declared that a lower dialysate temperature below body temperature increases intradialytic BP.[33]

VASCULAR TONE AND STIFFNESS

Studies have shown that arterial stiffness is associated with HD patients' negative cardiovascular (CV) outcomes.[34] In a study by Mourad et al, pulse wave velocity was compared between HD patients with responsive BP and those with unresponsive BP. This study included 47 HD patients without known CV diseases. Responsive BP was defined as a decline in mean arterial BP > 5% during HD, whereas unresponsive BP was characterized by a failure to achieve this decrease. Results showed that 45% of patients with responsive BP experienced a 17% reduction in mean arterial BP during HD, whereas the unresponsive group experienced a 6% increase in mean arterial BP. Notably, patients with unresponsive BP exhibited higher pulse wave velocity (12.9 vs. 10.8 m/s), supporting the theory that undetected arteriosclerosis may play a role in ID-HTN development.[35]

One case-control study by Chou et al[13] contradicted Gunal[21] and Cirit's[20] uncontrolled experiments showing that cardiac output alterations cause ID-HTN. In ID-HTN patients, cardiac output assessed from BP and echocardiogram evaluations before and after HD showed a substantial increase in vascular resistance compared to those whose BP had not increased. No noteworthy cardiac output variations or pre- or post-dialysis measures existed between groups. The study endeavored to uncover endogenous vasopressors related to mediating the BP increase. A spike in SNS activity (assessed via plasma catecholamine changes) or RAAS activity (evaluated by plasma renin activity) could not explain the rise in vascular resistance in the Chou study.[13] After the HD session, ID-HTN patients exhibited abnormalities in endothelial-1 (ET-1) cell-derived mediators. High amounts of ET-1 and low ratios of NO: ET-1 were observed. Other research on ET-1 alterations during HD in ID-HTN showed suggestive but inconclusive results. ET-1 reductions and ET-1 elevations were reported in ID-HTN patients but no significant difference from controls,[36] and there were reductions in hypotension-prone individuals and potential increases in ID-HTN patients.[16]

ANTIHYPERTENSIVE MEDICATIONS REMOVAL

The onset of ID-HTN can be triggered by the elimination of various BP medications during dialysis treatment. The dialysis process is known to remove certain antihypertensive drugs, including angiotensin-converting enzyme inhibitors (ACEi) (except fosinopril) and beta-blockers (specifically metoprolol and atenolol).[37] Eliminating these medications during HD should be considered a potential factor in ID-HTN cases. Still, research has not yet determined whether this plays a crucial role in developing ID-HTN. Furthermore, a previous study showed that ID-HTN occurred even in patients who were not taking antihypertensive medications.[13]

Dry Weight and Extracellular Volume

The early literature on ID-HTN suggested that the paradoxical BP increase might be due to dynamic variations in cardiac output during HD.[38] Despite small sample sizes and no control groups, studies concluded that reducing end-diastolic volume through ultrafiltration allowed for increased BP and cardiac output. The Dry-weight reduction in hypertensive hemodialysis patients (DRIP) study retrospective analysis found that probing dry weight over several weeks reduced ambulatory BP and changed the intradialytic BP slope.[39] Surprisingly, the patients who had not reduced their dry weight lost the most post-HD weight and transitioned from stable intradialytic BP gradients at baseline to a sharp decline by the study's end. The study concluded that adjusting dry weight over time could alter the ID-HTN phenotype without cardiac output measurement. The relationship between ID-HTN and extracellular volume overload remains to be explored using advanced in vivo fluid volume measurement methods. A recent cross-sectional study using multifrequency bioimpedance spectroscopy compared the body composition of HD patients with different intradialytic BP schemes during a single treatment.[9] The study's large sample size was a strength despite measurements reflecting only one treatment. The results displayed that patients with increased BP during HD sessions had higher extracellular water-to-total body water ratios. Collectively, these studies support reassessing dry weight as the initial approach for patients with ID-HTN. The factors and possible mechanisms of ID-HTN are summarized in Figure 1.

TREATMENT OF INTRADIALYTIC HYPERTENSION

Attention should be directed to the previously listed potential etiologies in individuals with ID-HTN. In some cases, the trigger is evident; for example, a patient who has skipped many HD sessions or drinks extra fluid, increasing interdialytic dry weight, has ID-HTN. After many HD sessions to return them to their original dry weight, ID-HTN often subsides. In some cases, the cause and therapy may not be explicit, and the subsequent therapeutic alternatives should be evaluated for hypertensive individuals experiencing ID-HTN.

VOLUME MANAGEMENT

Given that 2 small studies indicated an enhancement in ID-HTN by gradually reducing dry weight in certain people, an effort to decrease dry weight must be undertaken in patients experiencing ID-HTN.[40] Additionally, patients must be advised to restrict salt and fluid consumption between HD treatments. Nevertheless, while a reduction in dry weight may alleviate ID-HTN in many individuals, it is improbable that this can rectify the situation universally.

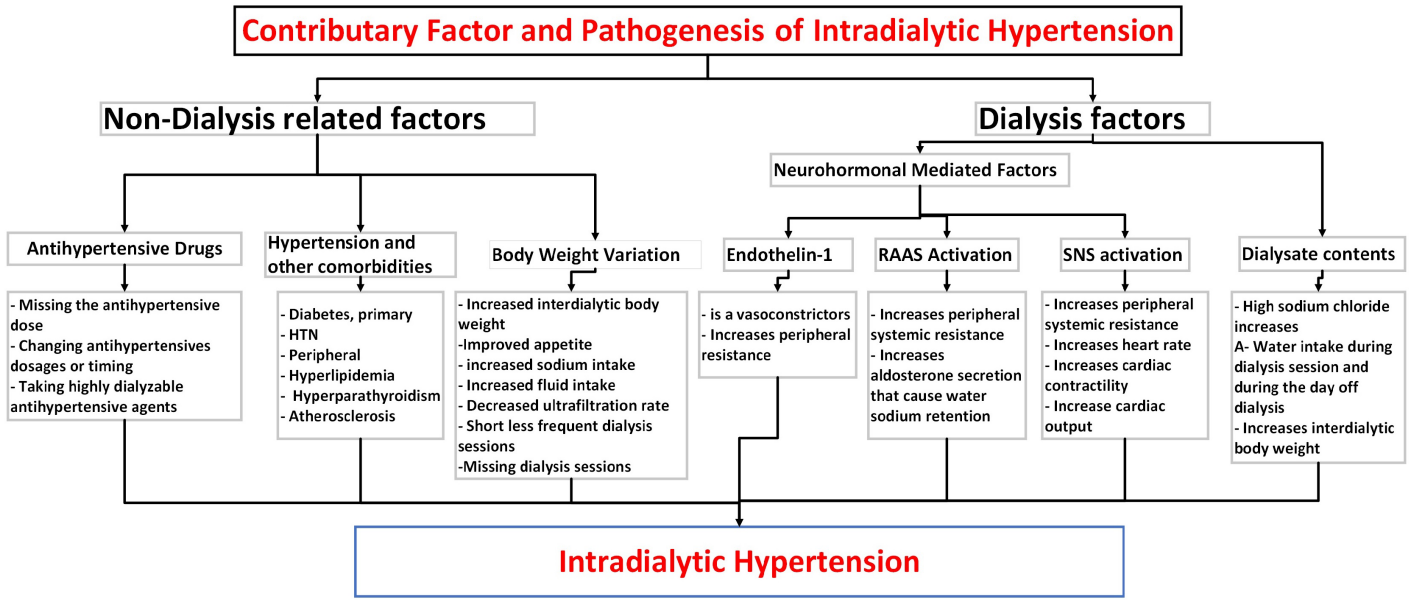

Figure 1. Factors and mechanisms of intradialytic hypertension: renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS).

SUPPRESSION OF THE SNS SYSTEM

The contribution of sympathetic overactivity to ID-HTN needs to be more adequately defined. Patients with renal illness have SNS activity that normalizes after nephrectomy.[12] The development of ID-HTN in individuals who have both kidneys excised remains uncertain; nonetheless, it cannot be regularly recommended as a method to manage BP. Adrenergic antagonists, including alpha- and beta-blockers, must be considered therapeutic alternatives for managing BP. Since HD does not substantially eliminate them, carvedilol and labetalol, which provide simultaneous alpha and beta-adrenergic inhibition, should be explored. However, their use has shown better BP control.[41]

SUPPRESSION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Renin-angiotensin-aldosterone system activation of the system by UF during HD may lead to ID-HTN, and suppressing RAAS might be a viable therapeutic approach. A short trial involving 6 individuals who had hypertensive crises during HD demonstrated that captopril treatment effectively controlled BP.[15] Recent long-acting ACE inhibitors and angiotensin receptor blockers (ARBs) may enhance the management of ID-HTN, especially since specific RAAS inhibitors might suppress ET1 production; however, these have yet to be explored.

PHARMACOLOGICAL INHIBITION OF ENDOTHELIN-1

Three studies have shown increased post-HD ET1 plasma concentration in ID-HTN patients; nevertheless, it remains uncertain if pharmacological suppression of ET1 will eliminate ID-HTN. Particular ET1 antagonists (avosentan) may be useful if their safety in HD populations can be established. Instead, nonspecific ET1 inhibitors, RAAS inhibitors, or carvedilol may enhance ID-HTN by suppressing ET1 release.[42] There is an ongoing pilot trial evaluating the effectiveness of carvedilol for treating ID-HTN and endothelial cell malfunction.

ANTIHYPERTENSIVE TREATMENT PROTOCOL

In a prospective analysis of 48 young HD patients, carvedilol reduced pre-HD, intradialytic, and post-HD high BP more than metoprolol.[43] A randomized, cross-over trial of 38 ID-HTN patients treated with nebivolol and irbesartan found that beta-blockers were better than RAAS blockers because SNS overdrive may be a key pathophysiologic reason.[44] Nebivolol had comparable effects on post-HD and 24-hour central systolic BP.[45] ID-HTN has also been treated with cilnidipine. Cilnidipine is an L/N-type calcium channel blocker that limits noradrenaline release from SNS terminals by blocking N-type calcium channels and widens sympathetically innervated efferent and afferent arterioles, lowering intraglomerular BP, and has a prolonged action.[46]

In individuals with ID-HTN, the class of antihypertensive medications, along with timing and dose, should be reassessed. Since HD eliminates certain beta-blockers and ACE inhibitors, these drugs should be substituted with non-dialyzable antihypertensives. Patients must be advised about withholding BP drugs before HD. Captopril administration has shown efficacy in alleviating ID-HTN crises; however, alternate medications may be more advantageous due to their short-acting nature and removal during HD.[15] Administer a short-acting antihypertensive medication before the HD session, such as hydralazine and captopril, which have rapid offset and onset, making them suitable for preventing ID-HTN without inducing hypotension during the interdialytic period,[15] and additionally, electing antihypertensive agents with reduced dialyzability. Except for fosinopril, ACE inhibitors have high dialyzability,

whereas all angiotensin receptor blockers are characterized by non-dialyzability. Widely used beta-blockers, like metoprolol and atenolol, have high dialyzability, while bisoprolol has intermediate dialyzability, and carvedilol is characterized by little dialyzability.[47] Nebivolol, a non-dialyzable beta-blocker, and irbesartan have effectively mitigated ID-HTN in a randomized experiment.[48] In summary, HD does not remove angiotensin receptor blockers and calcium channel blockers. Dialysis removes certain angiotensin-converting enzyme inhibitors and beta-blockers but not others (fosinopril, propranolol, pindolol, esmolol, bisoprolol, carvedilol, acebutolol). Table 1 lists a summary of common antihypertensive medications.

ERYTHROPOIETIN

Intravenous erythropoietin or its analogs may elevate BP in some people, which is less with the subcutaneous route.[49] In patients with ID-HTN, exploring a shift to subcutaneous erythropoiesis-stimulating agents is advisable, especially if the patient necessitates substantial erythropoiesis-stimulating agents (ESA) dosages.

MODIFICATION OF DIALYSATE COMPOSITION

Insufficient sodium solute elimination may lead to excessive fluid consumption and hypertension; hence, HD prescriptions must be customized to attain a net negative sodium solute balance. Prescriptions incorporating a programmed variable content of sodium dialysate have demonstrated efficacy in reducing sodium load during HD, potentially leading to lower post-HD BP, especially in patients with serum sodium levels below 140 mmol/L, who may experience sodium loading with standard sodium dialysate.[50] A recent study reported that in ID-HTN patients, low dialysate sodium substantially decreases post-HD BP drop and ID-HTN attack frequency compared with higher sodium-containing dialysate.[51] Moreover, a low sodium dialysate concentration markedly decreased 48-hour ambulatory BP in IDH patients compared to conventional dialysate sodium. These results support reduced dialysate sodium as a significant non-pharmacologic strategy for BP control in individuals with intradialytic hypotension.[51] Hence, presumably, increasing sodium in the dialysate can lead to ID-HTN.

Elevated calcium dialysate enhances cardiac contractility and output, potentially worsening hypertension during HD. Therefore, high calcium dialysate is not advisable in patients with ID-HTN. Additional modifications to the HD regimen that may enhance the patient's condition include extended HD duration, increased frequency of HD, and nighttime HD. These alternative HD modalities have been shown to enhance BP control and potentially ameliorate endothelial cell dysfunction. However, they have yet to be explicitly studied, and they can be used for patients with refractory, challenging ID-HTN. A correlation between reduced calcium dialysate and decreased post-HD systolic BP is that a low-calcium dialysate is sometimes advised for managing ID-HTN.[52] However, robust data is not widely available, and this method may lead to a detrimental calcium balance and heightened risk of cardiac arrhythmias,[53] increasing CV-related deaths.

DIALYSATE AND BODY TEMPERATURE

The body and dialysate temperature are significant factors that may influence BP maintenance during BP. Reports indicate that reducing the dialysate temperature to less than the core temperature elevates intradialytic BP, while elevated dialysate temperatures correlate with lower BP.[32,33]

PREVENTION OF INTRADIALYTIC HYPERTENSION

Various circumstances may lead to the onset of ID-HTN, and several strategies exist to mitigate its incidence. Patients exhibiting reduced blood creatinine, diminished dry weights, and decreased serum albumin levels are more predisposed to ID-HTN, possibly due to inaccurate dry weight assessment. Consequently, monitoring changes in a patient's dietary consumption and nutritional condition is essential to guarantee that patients achieve their optimal dry weight. The

Table 1. Dialyzable and Minimally or Non-Dialyzable Commonly Used Antihypertensive Drugs

Drug Group	Highly Dialyzable	Minimally Or Not Dialyzable
ACEi	Enalapril, lisinopril, captopril ramipril, and perindopril	Fosinopril
ARB	None	Candesartan, Telmisartan, irbesartan, and losartan
CCB	None	Nifedipine, amlodipine, diltiazem, felodipine, and verapamil
Alpha/beta blockade		Labetalol, terazosin, prazosin
Beta blockade	Metoprolol, nadolol, and atenolol	Propranolol, acebutolol, esmolol, bisoprolol, nebivolol, and carvedilol
Vasodilators	Diazoxide, nitroprusside, and minoxidil	Hydralazine
Sympatholytic	Methyldopa	Guanabenz, clonidine

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers.

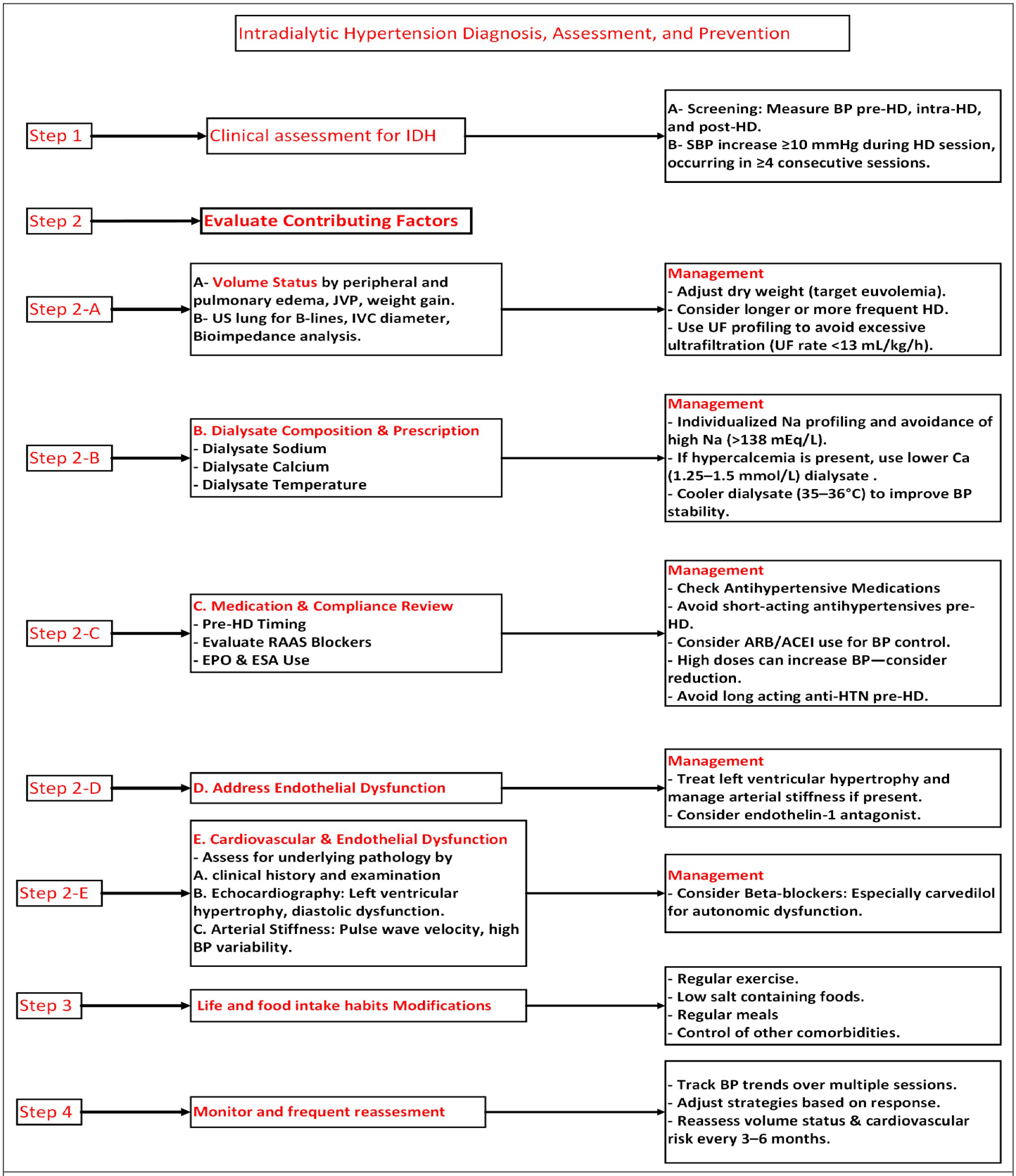

Figure 2. Intradialytic assessment, diagnosis, and prevention. HTN, Hypertension; RAAS, Renin angiotensin aldosterone system; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; EPO, Erythropoietin; JVP, Jugular venous pressure; US, ultrasound; ESA, erythropoiesis-stimulating agents; Na, sodium; UF, ultrafiltration; IVC, inferior vena cava; BP, blood pressure; HD, hemodialysis.

antihypertensive dose must be customized for each patient. Routine suspension of BP drugs before HD should be avoided except in ID-HTN patients.

Furthermore, antihypertensive medications that are not easily removed by hemodialysis should be favored. The dialysis prescription must be tailored to provide sufficient solute elimination, and regular high-calcium-containing dialysate must not be prescribed unless clinically warranted. Ultimately, while the function of ESA drugs in ID-HTN remains ambiguous, the minimal effective dosage should be administered. In patients exhibiting signs of ID-HTN, subcutaneous administration should be contemplated. The prevention and therapeutic options are summarized in Figure 2.

PROSPECTIVE

Recurrent ID-HTN patients had lower baseline weight and little interdialytic weight increase, which may hide persistent extracellular volume excess, leading to ID-HTN. Further studies are needed to assess this prospect.

Numerous bioimpedance spectroscopy investigations have linked ID-HTN to extracellular volume surplus following dialysis. If this theory is correct, every HD patient should have ID-HTN, which is not the case. Hence, further studies are needed to explore the possibility of undetected mechanisms to prevent further attacks of ID-HTN and reduce the associated mortality.

Recent observational and prospective studies showed that dietary salt reduction and stepwise dialysate sodium reduction may reduce ID-HTN, but there are no data on additional end goals. Therefore, further study projects are needed to assess the effect of interdialysis sodium intake on BP variability during HD sessions.

There is consistent evidence that ID-HT increases vascular resistance. Although this increase may be due to endothelin-1 excess release, RAAS, and SNS activation, other unknown mechanisms are mostly involved. Endothelin-1 antagonists, at least in animal studies, decrease BP. Human studies are required to determine the effects of endothelin-1 and its antagonists on ID-HTN control and prevention. Furthermore, more studies are required to investigate the clinical impact of RAAS and SNS activation blockers in ID-HTN prevention.

Moreover, research has also studied pharmacological therapies. Beta-blockers, especially vasodilators, may target SNS overactivity and endothelial dysfunction, decreasing intradialytic and ambulatory BP. Other medication classes have been considered for IDH treatment, but further study is required to determine their effectiveness.

A small sample size, lack of randomization, brief duration, and various IDH definitions are drawbacks of most published research on pharmacological and non-pharmacological measures in IDH-HTN. Furthermore, most of these studies have only measured BP during HD inside the dialysis unit and are usually intermittent. For the benefit of these patients with such a negative hypertensive phenotype, future studies with suitable design randomized trials using 24- or 48-hour ambulatory BP monitoring should further investigate the long-term effectiveness and safety of these novel treatment strategies.

CONCLUSION

Intradialytic hypertension has been acknowledged for some time; nevertheless, current studies have begun detailing its incidence, underlying pathophysiology, and correlation with negative clinical consequences. However, a universally accepted definition is lacking. Persistent BP increases during HD that culminate in a post-dialysis BP over 130/80 mmHg must be considered intradialytic hypertension.

Intradialytic hypertension has a higher prevalence among older individuals, those with lower dry weights, and those on several multitherapy antihypertension agents. In hypertensive individuals, intradialytic hypertension is individually is linked to more than 2.5-fold increased hospitalization or mortality rate within 6 months.

The pathophysiology of intradialytic hypertension is likely multifactorial; thus, treatment should be tailored to the individual patient. This includes reducing dry weight, transitioning to non-dialyzable antihypertensive therapies that inhibit the RAAS or decrease endothelin-1, contemplating a switch of erythropoiesis-stimulating agents from intravenous to subcutaneous, and modifying the dialysis prescription. Future research on managing intradialytic hypertension should evaluate the effectiveness of various therapeutic strategies, and larger trials are necessary to ascertain if therapy may enhance clinical outcomes.

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