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Hypertension and hemodialysis: pathophysiology and outcomes in adult and pediatric populations

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Abstract

Hypertension is prevalent in adult and pediatric end-stage renal disease patients on hemodialysis. Volume overload is a primary factor contributing to hypertension, and attaining true dry weight remains a priority for nephrologists. Other contributing factors to hypertension include activation of the sympathetic and renin–angiotensin–aldosterone systems, endothelial cell dysfunction, arterial stiffness, exposure to hypertensinogenic drugs, and electrolyte imbalances during hemodialysis. Epidemiologic studies in adults show that uncontrolled hypertension results in cardiovascular morbidity, but reveal increased mortality risk at low blood pressure, so that it remains unclear what the target blood pressure should be. Despite the lack of a definitive BP target, gradual dry weight reduction should be the first intervention for BP control. Renin–angiotensin–aldosterone system inhibitors have been shown to improve cardiovascular morbidity and mortality and are recommended as the initial pharmacologic therapy for hypertensive hemodialysis patients. Short-daily or nocturnal hemodialysis are also good therapeutic options for these patients. It is already established that hypertension in pediatric hemodialysis patients is associated with adverse cardiovascular outcomes, and there is emerging evidence that the mechanisms causing hypertension are similar to adults. Hypertension in adult and pediatric hemodialysis patients warrants aggressive management, although clinical trial evidence of a target BP that improves mortality does not currently exist.

Keywords

Hemodialysis; Hypertension; Renin–angiotensin–aldosterone system; Cardiovascular outcomes; Pediatrics

Introduction

Hypertension (HTN) is the second leading cause of end-stage renal disease (ESRD) in the United States, and is present in up to 90% of ESRD patients irrespective of the etiology of kidney disease [1]. HTN is recognized as an important modifiable risk factor for progression of chronic kidney disease (CKD) to ESRD and overall cardiovascular morbidity and mortality. The mechanisms responsible for HTN in ESRD patients include increased extracellular volume, increased sympathetic and renin–angiotensin–aldosterone system (RAAS) activation, abnormalities in properties of the vasculature such as endothelial cell

dysfunction, increased oxidative stress, arterial stiffness, and exposure to exogenous mediators such as erythropoiesis-stimulating agents (ESA) and dialysate.

The primary renal diseases leading to ESRD in the pediatric population are different from adults, and pediatric ESRD patients also lack comorbidities that commonly coexist in adults. However, HTN remains an important consequence of ESRD in the pediatric population. The purpose of this article is to summarize the various mechanisms and consequences of HTN in adult ESRD patients and review available data in the pediatric ESRD population.

Epidemiology

Adult population

HTN is both a cause and consequence of CKD and ESRD in adults, and its incidence increases with each stage of CKD. The prevalence of uncontrolled HTN in hemodialysis (HD) patients, defined based on Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations to achieve a pre-HD SBP <140 mmHg and a post-HD SBP <130 mmHg, [2] is as high as 80–90% [3]. An early prospective cohort study showed that elevated pre-HD systolic BP was associated with the occurrence of de novo cardiac failure and left ventricular hypertrophy (LVH), while actually lower systolic BP was associated with increased mortality [4]. It has since been shown that a “U”-shaped curve exists where low and extremely high systolic BP are associated with increased mortality in this population [5]. A recent secondary analysis of more than 16,000 incident HD subjects with median follow-up of 1.5 years has further characterized some of the factors associated with this relationship [6]. The overall findings from this study confirmed previous observational evidence that low SBP is associated with increased mortality. However, it also identified that while SBP <140 mmHg was associated with increased mortality in subjects > 50 years of age, SBP >160 mmHg was associated with increased mortality in subjects <50 years of age. The presence of diabetes accentuated the mortality risk from low BP in older subjects. Of importance in defining the relationship between BP and outcomes, recent studies have identified changes in BP during HD to be significant predictors of clinical outcomes [3, 7, 8]. Intradialytic hypertension, defined as 10 mmHg increase in systolic BP from pre to post-HD, which occurs in up to 15% of the HD population, is associated with increased morbidity and mortality [3, 7]. A comprehensive review provides further details on this topic [9].

It has recently been emphasized that *individual* BP measurements taken in the HD-unit may not be as prognostically useful as measurements taken between dialysis treatments. HD-unit BP measurements have poor agreement with home and ambulatory BP measurements taken during the interdialytic period. These interdialytic BP measurements are better predictors of mortality than HD-unit measurements [10]. In a cohort of 326 maintenance HD patients, increased home and ambulatory systolic BP were predictive of higher all-cause mortality, with the best outcomes associated with a home systolic BP of 120–130 mmHg and an ambulatory systolic BP of 110–120 mmHg [11].

Pediatric population

Compared to adults, where essential or primary HTN is common, the presence of HTN in the pediatric population is usually associated with a secondary form of HTN with CKD being the most common. In pediatric patients, HTN is defined as BP measurements exceeding the 95th percentile at a given height, age, and sex, with the 90th–95th percentile (not requiring antihypertensive therapy) representing the pre-hypertensive range [12]. A cross-sectional study of more than 600 chronic HD patients younger than 18 years of age has shown that the overall prevalence of HTN is 75–85% [13]. Multivariate logistic regression identified an acquired primary cause of ESRD as an independent risk factor for HTN, while

a longer duration on HD (either 3–6 years or ≥ 7 years) was associated with decreased prevalence of HTN. Although 62% of the subjects were receiving antihypertensives, BP remained uncontrolled in 74% of them. A larger cohort study inclusive of 3,743 pediatric HD and peritoneal dialysis patients (67% were on peritoneal dialysis) found the prevalence of baseline HTN or use of antihypertensive at initiation of renal replacement therapy to be 76.6% [14]. BP decreased significantly during the first year of dialysis in these subjects, but most subjects remained hypertensive, and no further significant changes in BP occurred after the first year of follow-up. Overall, independent risk factors for HTN on follow-up included baseline HTN or use of an antihypertensive, black race, age <12 years, hemodialysis as renal replacement modality, and acquired cause of ESRD. As these studies utilized HD-unit BP measurements, it should be acknowledged that similar to the adult population, ambulatory BP measurements among pediatric ESRD patients have poor agreement with HD-unit measurements [15].

As in adults, the presence of end-organ damage from HTN in the pediatric population can manifest as LVH. Because of the relatively small population of pediatric ESRD patients and the higher incidence of patients receiving renal transplants compared to adults, it is difficult to conduct long-term studies in this population with mortality as an outcome. Alternatively, LVH is a useful surrogate marker for assessing adverse outcomes related to HTN in pediatric ESRD patients. Even pediatric subjects with masked HTN (i.e., an elevated ambulatory BP measurement despite normal clinic BP measurements) and either normal renal function or CKD have increased prevalence of LVH [16, 17]. In pediatric subjects with pre-ESRD CKD, elevated nocturnal systolic BP load is an independent risk factor for the development of incident LVH [18]. For pediatric ESRD patients, the absence of other age- and lifestyle-related comorbidities commonly seen in adults allows for less confounded assessments of the association between HTN and LVH. The prevalence of LVH is high among pediatric patients who progress to ESRD, and an elevated systolic BP remains an independent predictor of LVH [19]. Furthermore, cumulative long-term increases in systolic BP following the initiation of HD result in LVH progression [20].

Pathophysiology

Volume overload

The inability to excrete sodium and water via the kidneys contributes to increased extracellular volume, increased cardiac output, and increased BP in HD patients. Although other factors related to increased peripheral vascular resistance are involved in HTN, targeting each patient's dry weight remains a major goal of adult and pediatric nephrologists. Limiting interdialytic salt ingestion and adhering to strict fluid restriction can be challenging for HD patients, and recent technologic advancements utilized in HD machines may enable nephrologists to better ascertain each patient's dry weight while minimizing significant hemodynamic changes during the HD procedure. A summary of human studies documenting the effects of extracellular volume on BP in HD patients using standard HD prescriptions is provided in Table 1.

Adult population—The percentage of interdialytic weight gain (overall weight gain/estimated dry weight $\times 100$) predicts increased pre-HD systolic BP and greater *reduction* in systolic BP from pre to post-HD, particularly in non-diabetics, younger patients, and those with greater estimated dry weight [21]. In one large observational study, increased interdialytic weight gain was associated with increased mortality [22]. In contrast, another study demonstrated improved 5-year survival with greater interdialytic weight gain, possibly explained by effects of improved nutrition from dietary intake (serum albumin was also higher in those with higher interdialytic weight gain) on long-term survival [23].

Conceptually, slow reductions in estimated dry weight over time with little change in interdialytic weight gain could lower BP without imposing excessive dietary restrictions on patients. Gradual dry weight reduction leads to improved ambulatory BP in hypertensive HD patients [24]. Techniques that monitor blood volume during dialysis may offer the opportunity to better estimate dry weight in HD patients. One study looking at the potential long-term effects of volume status, as assessed by relative plasma volume slope (flatter indicating volume overload) during 1 HD treatment, showed volume overload to be associated with increased mortality independent of ultrafiltration [25]. However, a randomized trial of blood-volume monitoring found higher mortality rates and hospitalization with continuous relative plasma volume monitoring [26].

Pediatric population—In pediatric ESRD patients, age-related differences in growth and weight can complicate the clinical assessment of volume status. In an uncontrolled study, guided ultrafiltration using non-invasive monitoring of the hematocrit (NIVM) reduced ambulatory BP and the number of antihypertensive medications [27]. In another uncontrolled study, this technique decreased ambulatory daytime BP and antihypertensive use, but not ultrafiltration or estimated dry weight [28]. However, in this 6-month study “true weight gain” that might be expected in adolescents and children of other ages may have confounded the assessment of overall volume status. While no study to date has demonstrated the use of non-invasive assessments for management of extracellular volume and attainment of dry weight may improve outcomes in the pediatric population, the above studies suggest a benefit in this population where dry weight assessment based on clinical evaluation alone can be confounded by expected weight changes over time. Current KDOQI recommendations are to limit sodium intake to 2 g/day and arrange dietary education every 3 months to ensure optimal nutrition [2].

Dialysate sodium and extracellular volume

In addition to the convective sodium losses prescribed through ultrafiltration during HD, sodium exchange is also achieved through diffusion determined by the dialysate to plasma sodium concentration gradient. Historically, dialysate sodium concentrations lower than typical pre-HD plasma sodium concentrations were used to optimize sodium and volume removal via diffusion. However, low dialysate sodium concentrations are no longer used since ultrafiltration is directly programmable. Over the past few decades, higher dialysate sodium has become commonly prescribed to reduce hemodynamic and osmotically induced disequilibrium complications that arise when high-flux dialyzers are used. Exposure to large dialysate to plasma sodium gradients that favor diffusion of sodium into the patient may increase patient vulnerability to hypertension through mechanisms both related and unrelated to extracellular volume. One crossover study with HD patients prone to intradialytic hypotension found increased 24-h ambulatory systolic BP with time-averaged dialysate sodium concentrations set to 147 mEq/l compared to 138 mEq/l [29]. Furthermore, compared to standard dialysate sodium concentrations, which typically exceed the patients pre-HD plasma sodium, the use of individualized sodium concentrations aimed at maintaining a stable pre-HD plasma concentration results in decreased thirst and interdialytic weight gain as well as better control of pre-HD BP [30]. It is also possible that exposure to elevated sodium concentration itself triggers abnormal endothelial cell responses resulting in vasoconstriction [31]. Beyond the responsibilities that a HD patient has to limit dietary salt intake, it must also be considered that a high dialysate-to-plasma-sodium gradient may impose an additional obstacle in maintaining dry weight by increasing thirst and interdialytic weight gain. A recent review includes further details on the various small studies aimed to assess changes in BP based on dialysate sodium changes [32].

Renin–angiotensin–aldosterone system

The renin–angiotensin–aldosterone system (RAAS) has long been implicated in the etiology of HTN in HD patients. In a study of 51 HD patients, there were significant differences in the plasma renin activity (PRA) between normotensive subjects ($n=9$), hypertensive subjects whose BP was controlled by ultrafiltration and dietary sodium restriction ($n=24$), and subjects with persistent hypertension ($n=18$). [33] PRA was lowest in the normotensive group, significantly higher in the group with controlled HTN, and highest in the persistently hypertensive group where all values except 1 fell outside the reference range for healthy individuals. In 17 of the 18 persistently hypertensive subjects, bilateral nephrectomy resulted in significant reductions in BP. Post-nephrectomy PRA was measured in 12 subjects, and was significantly lower (undetectable in seven), suggesting that elevated baseline PRA may have contributed to the poorly controlled hypertension. Angiotensin II (Ang II) and aldosterone, which are primary mediators of RAAS, both contribute to LVH and endothelial cell dysfunction independent of BP. Drugs that inhibit RAAS are recognized as first-line therapy in the pharmacologic management of HTN in HD patients.

A recent cross-sectional study among pediatric subjects investigated differences in RAAS between healthy controls, normotensive CKD subjects, hypertensive CKD subjects, and hypertensive ESRD subjects. [34] Increases in angiotensin 1 (Ang 1), and angiotensin 1–7 (Ang 1–7) were seen with severity of renal disease and with HTN. However, Ang II levels were similar and PRA measurements were in fact lower in hypertensive ESRD compared to hypertensive CKD pediatric subjects. This study also demonstrated that Ang II is poorly suppressed by angiotensin-converting enzyme inhibitors (ACE inhibitors) in ESRD compared to normotensive or hypertensive CKD pediatric subjects. The significance of the different levels of Ang II and Ang 1–7 is not clear, but the study authors suggested that the RAAS pathway may be altered in pediatric ESRD subjects, exhibiting a preferential conversion to Ang 1–7.

Sympathetic nervous system activity

It has been shown that ESRD patients have higher sympathetic nervous system (SNS) activity (using skeletal muscle sympathetic nerve activity [MSNA]), mean arterial BP, and vascular resistance than healthy controls or ESRD patients who have had bilateral nephrectomies [35]. Furthermore, in a small cohort of renal transplant recipients, MSNA remained elevated following renal transplant but subsequently decreased following native kidney nephrectomy suggesting that it is not uremia, but rather signaling from diseased kidneys that results in elevated MSNA and HTN [36]. However, while the initial trigger for increased SNS activity is likely renal ischemia with a consequential increase in renal afferent nerve activation, effects from other mediators that are also affected by ESRD such as nitric oxide, angiotensin II, and superoxide may further modify the overall SNS response. Abnormal autonomic sympathetic nervous activity can manifest as an absence of a nocturnal dip in BP. Nocturnal or diurnal dipping in BP is frequently absent in both CKD and ESRD populations and is associated with adverse outcomes [37].

There is evidence that more frequent HD, whether through increased removal of uremic toxins or improvement in volume status, can lower SNS activity. In a study of stable non-diabetic adult HD patients whose BP was controlled with or without antihypertensives, conversion from standard thrice weekly HD (12 h/week total HD time) to HD six times a week (12 h/week total HD time) resulted in significant reduction in ambulatory BP (systolic and diastolic) and MSNA. The subjects who had studies repeated following conversion back to standard HD regimen (7/11 subjects) demonstrated an increase in MSNA back to baseline values [38]. Evidence of SNS activation in the pediatric population is limited to observations

that plasma catecholamines increase significantly during HD (concomitant with decreased BP and increased heart rate), although the pre-HD levels are similar to controls [39].

Renalase—A recent area of investigation has focused on the role of renalase in HTN, including in ESRD patients. Renalase is a protein secreted by the kidneys that is responsible for the degradation of catecholamines. Its role in HTN is suggested by the findings that renalase knockout animal models develop HTN and that recombinant renalase infusion reduces BP in Sprague-Dawley rats [40]. Renalase is almost undetectable in the plasma of HD patients, and it is conceivable that its absence contributes to HTN via catecholamine excess. This promising protein continues to be explored, but has not yet been studied in the pediatric population.

Endothelial cell dysfunction

Nitric oxide and endothelin-1—Endothelial cell-derived nitric oxide (NO) and endothelin-1 (ET-1) cause vasodilatation and vasoconstriction, respectively, upon binding to vascular smooth muscle cell receptors. Endothelial cell dysfunction (ECD) involves disrupted balance of these mediators, with increased vasoconstriction being one of the consequences. Furthermore, NO release can be reduced by the actions of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of endothelial NO synthase. ET-1 levels have been found to be elevated in hypertensive compared to normotensive HD patients [41], although this finding alone may not explain the differences in BP. However, in the context of the “perfect storm” of mediators where there is impaired release/action of NO and increased Ang II-mediated vasoconstriction from increased PRA, the cumulative effect may result in elevated BP. ADMA levels in partial nephrectomy rats correlate with increased systolic BP and suggest a mechanistic link between ADMA and BP [42]. Increases in ADMA have been found in adult HD patients [43], and are associated with increased cardiovascular and all cause mortality in this population [44].

Oxidative stress—Oxidative stress and ECD have been mechanistically linked in animal and adult CKD studies. Reactive oxygen species (ROS) can interfere with NO synthesis and availability. Furthermore, oxidative stress impairs the ADMA inhibitor, dimethylarginine diaminohydrolase (DDAH), leading to accumulation of ADMA. Animal experiments have demonstrated that administration of an antioxidant and plasma peroxidation inhibitor to 5/6 nephrectomy rats with increased plasma markers of oxidative stress partially attenuates HTN, and that HTN recurs in the absence of the inhibitor [45]. Pediatric ESRD patients have increased levels of plasma markers of oxidative stress compared to healthy controls, which is consistent with findings in adults [46]. There is no data demonstrating the relationship between ROS and BP in the pediatric ESRD population.

Arterial stiffness

Arterial stiffness is a pathogenetic process that occurs naturally with aging, but is accentuated in disease states such as HTN, diabetes, and ESRD. Changes in the elastance properties of the walls of large arteries cause arterial stiffness. Healthy arteries are capable of accommodating the volume from each ventricular systolic ejection so that pressure waveforms reflected backwards from the peripheral circulation do not interfere with the forward transmission of another wave. However, stiffened, non-compliant arteries quickly transmit each ejected wave so that the timing of the reflected peripheral wave occurs while systole is still in progress. The ultimate consequence is increased systolic BP and pulse pressure, which contribute to LVH. The reader is referred to an earlier review for details on these mechanisms [47]. In adult ESRD patients, elevations in pulse wave velocity (PWV), a measure of arterial stiffness, are associated with increased mortality [48].

A case-control study including 11 pediatric HD subjects and 133 healthy controls younger than 23 years showed that pediatric ESRD subjects have elevated PWV compared to age-, height-, and weight-matched controls [49]. In this study, the ESRD subjects were either normotensive at baseline or had BP well controlled on antihypertensives so that a clear relationship between standardized BP and PWV could not be made. Regardless, the elevated PWV in pediatric ESRD subjects persisted despite the use of vasodilatory medications. Another study used aortic distensibility as a measurement of arterial stiffness in pediatric ESRD subjects [50]. Aortic distensibility was lower (more arterial stiffness) in both HD and PD subjects compared to controls, and HD subjects had more impairment than PD subjects. Arterial stiffness correlated with a diagnosis of HTN and pre-HD systolic BP, but not with average systolic BP. A final study measuring arterial stiffness with diastolic pulse wave analysis determination of large and small vessel elasticity index confirmed decreased elasticity in hypertensive and normotensive HD subjects [51]. Overall, the small sample sizes and enrollment of normotensive subjects or subjects with controlled HTN limit the direct conclusions that can be made regarding the association of these findings with BP in the pediatric ESRD population. However, extrapolating evidence from the adult ESRD population allows for a valid argument that arterial stiffness contributes to (or is a consequence of) the overwhelming prevalence of HTN in the pediatric ESRD population.

Hyperparathyroidism

It has previously been proposed that secondary hyperparathyroidism that accompanies CKD may contribute to the high prevalence of HTN. Early evidence stemmed from a retrospective study in non-ESRD CKD adults demonstrating that systolic and diastolic BP were significantly increased in subjects with elevated parathyroid hormone (PTH) [52]. Furthermore, a possible mechanism was suggested by the finding of increased platelet cytosolic calcium in the group with elevated PTH. Mean BP correlated highly with cytosolic calcium and PTH (except in subjects taking nifedipine). Treatment with vitamin D (alfacalcidol) significantly lowered cytosolic calcium, PTH, and mean BP. The potential antihypertensive effect of vitamin D has since been investigated in numerous clinical scenarios and a recent meta-analysis of the effects of vitamin D supplementation on CV health among healthy individuals identified trends towards improved systolic BP [53]. A randomized trial in subjects with diabetic nephropathy (median glomerular filtration rate 37–38 ml/min) where albuminuria reduction was the primary endpoint demonstrated a significant reduction in systolic BP with paricalcitol when the higher dose (2 µg) was used [54]. Unfortunately, there is a paucity of studies among HD patients describing the relationship between hyperparathyroidism and BP and of the effects of active vitamin D on BP.

Erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents (ESA) used to correct the anemia associated with ESRD are also suspected of causing increases in BP [55]. The proposed mechanisms specific to HD patients include increased ET-1 release and increased sensitivity to Ang II and adrenergic stimuli. The effect on BP is dependent on dose, but not necessarily the pre-treatment BP as both previously normotensive and hypertensive patients can have BP elevations. Further details on this topic are beyond the scope of this review, but may be found in a previous review on the subject [56]. HTN has also been confirmed as being a common side-effect in pediatric HD patients receiving ESA [57].

Management

Adult population

Annual mortality in adult ESRD patients is nearly 20% with CV deaths being the leading cause [58]. As mentioned earlier, epidemiologic data shows that higher systolic BP is associated with LVH, congestive heart failure, and coronary artery disease, while low and extremely high systolic BP are associated with increased mortality risk. As the relationship between systolic BP and outcomes is derived from observational studies, it is important to know how pharmacologic and non-pharmacologic management impacts outcomes.

Treatment with antihypertensives—Although a specific BP target has not yet been determined, certain antihypertensive medications are associated with improved outcomes in ESRD patients. The current recommendation according to the Kidney Disease Quality Outcomes Initiative is to employ a RAAS-blocking drug as the first-line agent in patients on HD [2]. This evidence is meant to supplement the findings discussed above that attention to dry weight, interdialytic sodium intake, and interdialytic weight gain are essential in HTN management.

Initial evidence for the benefit of ACE inhibitors came from observational data. One retrospective study in HD subjects showed that subjects treated with ACE inhibitors had decreased mortality compared to those receiving non-ACE-inhibitor antihypertensives, with the majority of the benefit coming from a reduction in CV deaths [59]. The prevalence of calcium channel blocker and beta-blocker use was similar between groups, and the 52% relative risk reduction in mortality with ACE inhibitors occurred in the context of increased baseline prevalence of LVH in the ACE-inhibitor group. ACE-inhibitor use has since been tested in a randomized clinical trial (Table 2). In the Fosinopril in Dialysis (FOSIDIAL) study, 397 HD patients were randomized to fosinopril plus conventional therapy vs. placebo plus conventional therapy [60]. Despite reductions in systolic BP with fosinopril (statistically significant in *hypertensive* subjects), there was a non-significant 8% reduced incidence in the primary composite outcome of death and CV events. Limitations of the study include significantly greater baseline LV mass index in the fosinopril group and a lower-than-expected number of primary outcomes, limiting the power to identify differences between groups. However, ACE inhibitors remain a recommended first-line therapy in treating HTN in ESRD patients, and evidence that ACE-inhibitors improve LVH and pulse wave velocity in other studies support additional benefits of their use [61, 62].

The benefit of ARBs has also been studied in HD patients. One recent study from Japan randomized 366 HD patients to receive an ARB (valsartan, candesartan, or losartan) or to continue with current management. In this prospective controlled randomized open-label trial, the primary end point of fatal and nonfatal CV events was lower in the ARB arm with a trend towards improved overall mortality with an ARB. The baseline and achieved BP were not different between arms so that despite demonstrating a benefit of ARB therapy, no clear target BP was established [63]. Another small study in adult HD patients found improved survival and decreased CV events in subjects randomized to candesartan vs. control (14% of all subjects were already taking ACE inhibitors) despite similar baseline and achieved BP [64]. A summary of the findings from outcomes studies using ACE inhibitors or ARB is provided in Table 2.

Additional antihypertensive agents are frequently needed for persistent HTN, and calcium channel blockers and beta-blockers are some of the next recommended therapies [2]. Calcium channel blockers are effective in reducing BP in HD patients, with additional evidence that they may improve CV outcomes as well. In one randomized placebo-controlled trial of 251 hypertensive HD patients, amlodipine 10 mg daily resulted in a non-

significant reduction in mortality [65]. Limitations to this study include smaller-than-anticipated sample size and lower-than-expected mortality in the placebo arm. However, secondary analysis did show a significant reduction in the composite endpoint of mortality and non-fatal cardiovascular events. Coexistent comorbidities should dictate further antihypertensive therapies, and the use of the combined alpha and beta-blocker carvedilol has been shown to improve survival in HD patients with cardiomyopathy [66]. Alpha-blockers (alone or as a combination alpha/beta-blocker), centrally acting sympathetic agonists (such as clonidine) and direct vasodilators remain as options for patients whose BP is still uncontrolled. Other considerations in individualizing anti-hypertensive therapy include choosing agents with simple dosing regimens to enhance patient compliance (i.e., once-a-day formulations) and choosing agents with low side-effect profiles. A more comprehensive review on choice of antihypertensive agents has recently been published [67].

Regardless of the agent selected, it appears that antihypertensive treatment in general has a protective benefit, and two recent meta-analyses in ESRD patients demonstrated that treatment with antihypertensive agents was associated with improved CV events and mortality. Subjects in these studies had varying comorbidities and had been randomized to a variety of antihypertensive drugs including ACE inhibitors, ARB, calcium channel blockers, and beta-blockers [68, 69].

Changes in hemodialysis frequency

Beyond the effects seen from gradual dry weight reduction during individual HD treatments, the utilization of more frequent or longer HD treatments may offer benefits that cannot be accomplished with standard thrice-weekly HD. The Frequent Hemodialysis Network (FHN) Daily Trial recently addressed this in a randomized controlled clinical trial [70]. In this study, 245 adult HD patients were randomized to conventional HD treatments (three times weekly with a target equilibrated Kt/V_{urea} of 1.1 per treatment) or frequent HD (goal of six treatments per week with target Kt/V of 0.9 per treatment). After 12 months of follow-up, the weekly Kt/V , amount of time on HD per week, and weekly ultrafiltration volumes were higher in the frequent HD group, although corresponding values for each individual treatment were lower than in the conventional HD group. The frequent HD group had a significantly lower hazard ratio for the co-primary composite outcomes of death and increase in left ventricular mass as well as death and change in physical health outcome score. Furthermore, the frequent HD group had significantly greater reductions in pre-HD systolic BP and number of antihypertensive medications used. These benefits were seen at the cost of more access-related interventions in the frequent HD group. The lack of interdialytic ambulatory BP measurements limits the conclusions regarding reduction in overall BP burden, but the significant reduction in LV mass found with frequent HD suggests that the current standard of thrice-weekly HD may be sub-optimal for achieving adequate BP control and preventing HTN-related complications.

Nocturnal HD is another option suggested to improve outcomes in HD patients by offering increased dialysis time and reducing the large fluctuations in fluid shifts that occur with conventional HD. A prospective observational study compared 28 adult HD patients converted to nocturnal HD (8–10 h every night with mean 3.4 years follow-up) to 13 patients continuing home care conventional HD (4-h treatments three times a week with mean 2.8 years follow-up) using LV mass index and BP as outcomes. The nocturnal HD group, while having no change in post-HD extracellular volume measured by bioelectrical impedance analysis, showed improvements in BP (systolic, diastolic, and mean arterial pressure) and LV mass index, while the conventional HD subjects did not [71]. Presently, two randomized trials studying nocturnal HD have been conducted. In one trial, 52 adult HD

patients were randomized to nocturnal HD (5–6 times per week with at least 6 h per treatment) vs. conventional HD (three times per week) with the primary outcome of change in LV mass measured by cardiovascular magnetic resonance imaging. Both groups had their BP managed by nephrologists with the target post-HD SBP of 130 mmHg. After 6-month follow-up, the nocturnal HD group experienced significantly greater reduction in LV mass. There was also significant improvement in the pre-HD systolic BP in the HD group when adjusted for baseline BP, and more subjects receiving nocturnal HD were able to discontinue or decrease the dose of antihypertensive medications compared to the conventional HD group [72]. The FHN Nocturnal Study [73] is a larger randomized trial with the same co-primary composite outcomes as the FHN Daily Study [70]. In this study, patients were randomized to either conventional thrice-weekly HD (2.5 h/treatment) or six nocturnal HD treatments per week (6–8 h/treatment). After 12 months of follow-up, there were no significant differences between groups in the co-primary composite outcomes, but the nocturnal HD group did experience improved control of hypertension and hyperphosphatemia [74].

Pediatric population

The consequences of HTN in pediatric CKD patients are also unfavorable. Children with CKD and ESRD have an enormously increased risk of CV death compared to age-matched controls. At least 25% of deaths in pediatric ESRD patients are attributable to CV disease [75]. This risk is higher in African American patients compared to white patients and is reduced in all pediatric ESRD patients following renal transplantation. Uncontrolled HTN in pediatric CKD patients results in progression of CKD towards ESRD, increased incidence of LVH, and the progression of LVH following initiation of HD [19, 20, 76, 77]. There is currently evidence supporting the benefits of strict BP control in the pediatric CKD population. The Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) trial randomized pediatric CKD patients (stages II–IV) whose BP was controlled with or without antihypertensive management to either conventional BP management (target 50–90th percentile) or intensified BP management (target below 50th percentile) with the primary outcome being 50% reduction in glomerular filtration rate or progression to ESRD [78]. During the study period where all subjects received ramipril, the intensive BP control group demonstrated lower mean arterial BP and decreased incidence of the primary outcome. Evidence from that study supports the current recommendation to optimize renoprotection in pediatric patients with non-ESRD CKD by targeting SBP <75th percentile in the absence of proteinuria and <50th percentile in the presence of proteinuria [79]. Despite these recommendations and the recommendation to target SBP <90th percentile in the general pediatric population, there is no ideal SBP specific for pediatric ESRD patients.

There is a lack of data to determine the optimal antihypertensive medications in pediatric ESRD patients. Most agents commonly used in adults are safe and well tolerated in pediatric patients as well, including beta-blockers, diuretics, calcium channel blockers, ACE inhibitors, and ARB [12]. A recent survey distributed to pediatric nephrologists showed that calcium channel blockers and ACE inhibitors were the antihypertensives most frequently prescribed to HD patients [80]. The survey responses in general showed great diversity in the factors that determine choice of drug including dry weight, end-organ damage, underlying diseases, and interdialytic BP. Other antihypertensives that were used include ARB, beta-blockers, alpha blockers, clonidine, and the vasodilators hydralazine and minoxidil.

Daily and nocturnal HD have also been considered in the pediatric HD population to investigate the effects of a more physiologic balance of toxins and extracellular volume. In a small observational study, five non-compliant pediatric HD patients with significant

cardiovascular comorbidities were converted from thrice-weekly hemodiafiltration (4 h/treatment) to hemodiafiltration six times per week (3 h/treatment) [81]. The total duration of weekly dialysis increased from 675 to 990 min per week. There were reductions in systolic BP, diastolic BP, and the number of antihypertensive medications. The latter findings were confirmed in another observational study of 12 pediatric HD patients switched to hemodiafiltration 5–6 times weekly [82]. A prospective observational study in pediatric HD patients utilizing nocturnal HD (three-weekly 8-h in-center treatments) also demonstrated reduction in pre-HD mean arterial BP and the requirement for antihypertensive agents even in the context of liberalized fluid intake [83]. While the use of daily HD or nocturnal HD for pediatric patients has not been investigated in a randomized study, considering the recent trial evidence in adults, more frequent HD likely represents a good therapeutic option for BP control in pediatric ESRD patients.

Conclusions

Hypertension is highly prevalent in both adult and pediatric HD patients. Though observational studies fail to consistently show a direct association with HTN and mortality, HTN clearly is associated with CV disease, the leading cause of mortality in HD patients. The etiology of HTN in these patients is complex with extracellular volume playing a major role in addition to increased vascular constriction. The evidence for these mechanisms mainly stems from studies in adult patients, but it is suspected that there is similar pathophysiology in the pediatric population. Management of HTN in adult and pediatric HD patients should include the establishment and maintenance of the appropriate dry weight through limitation of interdialytic sodium/fluid intake and adequate removal of these substances during HD. Pharmacologic therapy should include ACE inhibitors or ARB as first-line agents. In addition to their beneficial effect on BP, RAAS inhibitors also appear to improve left ventricular hypertrophy and pulse wave velocity. It is likely that increased dialysis time through either daily or nocturnal HD allows for better control of BP, but the implementation of this practice requires further confirmation from randomization studies and studies assessing the cost–benefit ratio. Although there is no firm evidence to base what BP target should be achieved, the current recommendations are to achieve systolic BP < 140 mmHg pre-HD or <130 mmHg post-HD in adults and at least a BP <90th percentile of the age, sex, and height appropriate level in the pediatric population.

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Table 1

Studies demonstrating effects of extracellular volume on blood pressure in adult and pediatric hemodialysis patients using conventional hemodialysis

Study	Study design/population	Primary analysis	Conclusion
Inrig 2007 [21]	Secondary analysis of a prospective cohort <i>n</i> =442 adult prevalent HD subjects	Relationship between interdialytic weight gain % and pre-HD SBP and intradialytic Δ SBP during 6 months of follow-up	1% interdialytic weight gain associated with 1 mmHg increase in pre-HD SBP, <i>p</i> <0.0001 1% interdialytic weight gain associated with 1.08 mmHg Δ SBP, <i>p</i> <0.0001
Agarwal 2009 [24]	Randomized controlled trial <i>n</i> =150 adult prevalent HD subjects 100 randomized to additional ultrafiltration 50 randomized to control (regular ultrafiltration)	Change in 44-h ambulatory SBP from baseline to study end	Δ ASBP of -6.6 mmHg between groups at 8 weeks, <i>p</i> <0.021
Agarwal 2010 [25]	Cohort <i>n</i> =308 adult prevalent HD subjects (separated by > or < median relative plasma volume)	Survival between groups (30-month median follow-up)	Greater survival for steeper relative plasma volume slope (less volume overloaded), <i>p</i> =0.011
Candan 2009 [27]	Uncontrolled trial <i>n</i> =9 pediatric prevalent HD subjects Blood Volume Monitoring used to reduce dry weight	Change in ambulatory systolic BP from baseline to study end (4 weeks)	44-h ASBP: 129.3 (baseline) vs. 122.6 mmHg (following BVM protocol), <i>p</i> = .034
Patel 2007 [28]	Uncontrolled trial <i>n</i> =20 pediatric prevalent HD subjects Non-invasive monitoring of hematocrit guided ultrafiltration algorithm used to reduce dry weight and guide ultrafiltration	Change in ambulatory systolic BP from baseline to study end (6 months)	Daytime ASBP Index 0.97 (baseline) vs. 0.87 (6-month follow-up), <i>p</i> =0.05 Daytime ADBP index 0.94 (baseline) vs. 0.79 (6-month follow-up), <i>p</i> =0.05 Nighttime index comparisons were not significant, <i>p</i> =0.09 for SBP and 0.10 for DBP
Reddan 2005 [26]	Randomized controlled trial <i>n</i> =443 adult prevalent HD subjects 227 randomized to Non-invasive monitoring of hematocrit guided ultrafiltration (encouraged, not mandated algorithm) 216 randomized to conventional management	Change in pre and post-HD SBP and DBP following 6 months of follow-up (secondary analysis)	No significant difference in pre and post-HD SBP and DBP

HD Hemodialysis; SBP Systolic blood pressure; DBP Diastolic blood pressure; ASBP Ambulatory systolic blood pressure; BVM Blood volume monitoring

Table 2

Studies using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers to treat hypertension in patients with end-stage renal disease on hemodialysis

Study	Study design/population	Primary analysis	Conclusion
Efrati 2002 [59]	Retrospective cohort <i>n</i> =126 adult prevalent HD subjects 66 prescribed ACE inhibitor 60 not prescribed ACE inhibitor	Survival between groups (mean follow-up 59 months)	RR for mortality in ACE inhibitor group: 0.482, <i>p</i> <0.0019 Mean follow-up SBP: 143 (ACE inhibitor) vs. 132.5 mmHg (no ACE inhibitor), <i>p</i> <0.013
Zannad 2006 [60]	Randomized controlled trial <i>n</i> =397 adult (50-80 years) prevalent HD subjects with baseline LVH 196 randomized to fosinopril 201 randomized to placebo	Survival between groups at 2 years	RR for mortality in fosinopril group: 0.929, <i>p</i> =0.35 24 month mean BP: 139/76 (fosinopril) vs. 143/74 mmHg (placebo), <i>p</i> =0.07/0.08
Suzuki 2008 [63]	Randomized controlled trial <i>n</i> =366 hypertensive adult prevalent HD subjects 183 randomized to ARB (losartan, candesartan, or valsartan at the discretion of treating nephrologists) 183 randomized to control	Cardiovascular event-free survival between groups at 3 years	Greater event-free survival with ARB <i>p</i> =0.001 RR for fatal and non-fatal CV events in ARB group 0.51, <i>p</i> =0.002 3-year achieved BP: 140/80 (ARB) vs. 140/78 mmHg (control), <i>p</i> value not significant
Takahashi 2006 [64]	Randomized controlled trial <i>n</i> =80 adult prevalent HD subjects at established dry weight 43 randomized to candesartan 4–8 mg daily 37 randomized to control	Cardiovascular event-free survival between groups (mean follow-up 19.4 months)	Greater event free rate with candesartan, <i>p</i> =0.007 Mean follow-up BP: 153/83 (candesartan) vs. 149/80 (control), <i>p</i> =0.21/0.18

HD Hemodialysis; RR Relative risk; ACE Angiotensin-converting enzyme; ARB Angiotensin receptor blocker; LVH Left ventricular hypertrophy; BP Blood pressure, SBP Systolic blood pressure