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IN-DEPTH REVIEW

Hemodialysis-Associated Hypertension: Pathophysiology and Therapy

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● **The majority of end-stage renal disease (ESRD) patients are hypertensive. Hypertension in the hemodialysis patient population is multifactorial. Further, hypertension is associated with an increased risk for left ventricular hypertrophy, coronary artery disease, congestive heart failure, cerebrovascular complications, and mortality. Antihypertensive medications alone do not adequately control blood pressure (BP) in hemodialysis patients. There are, however, several therapeutic options available to normalize BP in these patients, often without the need for additional drug therapy (eg, long, slow hemodialysis; short, daily hemodialysis; nocturnal hemodialysis; or, most effectively, dietary salt and fluid restriction in combination with reduction of dialysate sodium concentration). Optimal BP in dialysis patients is not different from recommendations for the general population, even though definite evidence is not yet available. Predialysis systolic and diastolic BPs are of particular importance. Left ventricular mass correlates with predialysis systolic BP. Survival is better in hemodialysis patients with a mean arterial pressure below 99 mm Hg as compared with those with higher BP. Low predialysis systolic BP (<110 mm Hg) and low predialysis diastolic BP (<70 mm Hg) are associated with increased mortality, primarily because of severe congestive heart failure or coronary artery disease. Patients that experience repeated intradialytic hypotensive episodes should also be viewed with caution, and predialytic BP values should be reevaluated. A possible treatment option for these patients may be slow, long hemodialysis; short, daily hemodialysis; or nocturnal hemodialysis. Among the antihypertensive agents currently available, angiotensin-converting enzyme (ACE) inhibitors appear to have the greatest ability to reduce left ventricular mass. Pressure load can be satisfactorily determined by using the average value of predialysis BP measurements over 1 month. In selected hemodialysis patients, interdialytic ambulatory blood pressure monitoring (ABPM) may help to determine if the patient is in fact hypertensive. In addition, ABPM provides important information about the change in BP between day and night. Regular home BP monitoring, yearly echocardiography, and treatment of traditional risk factors for cardiovascular disease are recommended.**

INDEX WORDS: Hemodialysis (HD); hypertension; left ventricular hypertrophy; erythropoietin (EPO); sodium restriction; dialysis regimen; angiotensin-converting enzyme (ACE) inhibitors.

HYPERTENSION is very common in patients undergoing regular conventional hemodialysis treatment.[1-6] Between 50% and 90% of dialysis patients have a blood pressure (BP) greater than 140/90 mm Hg, whereas only a minority has adequate BP control.[7] Hypertension is independently correlated with morbidity and mortality in the hemodialysis population.[2,8] Charra et al[9] have found reduced survival in hemodialysis patients when predialysis mean arterial pressure was greater than 99 mm Hg. In contrast, Salem and Bower[10] and Salem[11] reported that hyperten-

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sion did not have an adverse effect on 1-year and 2-year mortality in a cohort of 649 hemodialysis patients. Hemodialysis patients often do not have the normal decrease in nocturnal BP,[7,12-14] thereby exposing them to the development of left ventricular hypertrophy.[15-18] Left ventricular hypertrophy is an independent predictor of cardiovascular disease and significantly reduces the life expectancy of hemodialysis patients.[19,20] Left ventricular dysfunction is present in approximately 80% of end-stage renal disease (ESRD) patients and highly predictive of future ischemic heart disease, cardiac failure, and death.[21] Cardiac disease is the single most important risk factor among long-term dialysis patients, accounting for almost 50% of deaths in the United States.[22] Data from the Canadian Organ Replacement Register indicate that in 1995, 45% of the deaths among patients on renal replacement therapy were related to cardiovascular disease.[23] Foley et al[24] found that each 10 mm Hg rise in mean arterial BP was independently associated with a progressive increase of concentric left ventricular hypertrophy, the development of de novo cardiac failure, and de novo ischemic heart disease. Very high correlations were found between both the degree of cerebral atrophy and predialytic BP values, as well as cerebral atrophy and the duration of hypertension in hemodialysis patients.[25] These data suggest that long-term hypertension is not a harmless condition but rather a major risk factor for cardiovascular events in the general population and particularly in ESRD patients. It is well known that it takes several years for hypertension-associated complications to become manifest.

The aims of this overview were not only to underline the importance of hypertension as a cardiovascular risk factor for hemodialysis patients, but also to define how to monitor and treat hypertension in this patient population, and, finally, to evaluate the pathophysiologic factors involved in the manifestation of high BP in hemodialysis patients.

HOW TO MONITOR BLOOD PRESSURE?

Manual home BP monitoring is recommended. Agarwal[26] compared daily home BP monitoring in chronic hemodialysis patients with the 44-hour interdialytic ambulatory blood pressures (ABPs) by using a Spacelab 90207 ABP monitor (SpaceLabs Medical Inc, Redmond, WA). Ambulatory blood pressure monitoring (ABPM) showed a progressive BP decrease after dialysis and during the first night. BP rapidly reached predialysis levels by the next morning and did not decrease during the second night (Fig 1). The investigator found an excellent correlation between average systolic and diastolic ABP and respective home BPs. Predialysis diastolic (prediastolic) BPs more than predialysis systolic (presystolic) BPs were a good reflection of the respective ABPs. Studies using ABPM in patients undergoing regular hemodialysis therapy have shown that casual BP measurements either under-

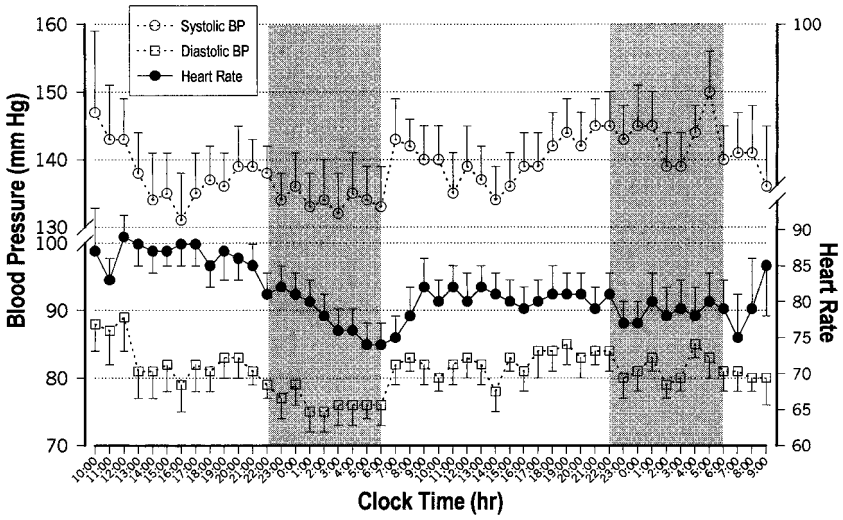

Fig 1. The average heart rate and systolic BP with ABP monitoring during the 44-hour interval. The error bars are the standard error of the mean and the shaded columns represent the hours of 10 PM to 6 AM defined as night for the purpose of analysis of ABP. Reprinted with permission from Agarwal.[26]

estimate or overestimate the degree of hypertension during the interdialytic period.[4,7,27-29]

Sorof et al[30] measured interdialytic BP by ABPM during in-patient fluid restriction in 12 children receiving chronic hemodialysis. The investigators found that sleep BP decreased from daytime BP by 6% for systolic and 11% for diastolic BP. One patient had a normal dip (≥10%) in systolic BP and 7 children had a normal dip in diastolic BP. Sleep loads (defined as the percentage of BPs greater than the 95th percentile) were significantly greater than daytime loads for systolic BP (53% versus 28%) and diastolic BP (57% versus 27%). Casual BP correlated poorly with ABPM.[30]

Conlon et al[31] found no difference between daytime and nighttime ABP in adult hemodialysis patients; however, they observed a strong correlation between systolic ABP and presystolic BP. Postdiastolic BP correlated better with diastolic ABP than did prediastolic BP. In this group of hemodialysis patients on stable antihypertensive medications and with stable hematocrit values, left ventricular mass correlated with systolic ABP and presystolic BP (Fig 2). Zoccali et al[32] concluded that the pressure load can be satisfactorily approached by using the average value of 12 predialysis BP measurements over 1 month.

Normal nocturnal decline of BP in healthy individuals results in a 15% reduction in systolic and a 20% reduction in diastolic BP.[33] ABP over a 24-hour period correlates with end-organ damage.[34,35] The prevalence of nondipping increases with declining renal function. Abnormal diurnal BP is found in approximately 80% of the dialysis patients, in approximately 75% of the patients with plasma creatinine greater than 6.8 mg/dL, and in renal transplant recipients.[36] The association of altered nycthemeral BP rhythm and an increased pulse pressure plays a major role in the cardiovascular prognosis of ESRD patients. Pulse-wave velocity is significantly higher in nondippers than in dippers.[37]

WHAT IS THE TARGET BLOOD PRESSURE IN HYPERTENSIVE DIALYSIS PATIENTS?

The target BP in hypertensive patients should not be different than that recommended for the general population.[38] Several studies, however, have shown that low presystolic BP is associated with increased mortality in hemodialysis patients.[39-44] The risk of mortality is U shaped, being higher among patients who are markedly hypertensive (presystolic BP >180 mm Hg) or markedly hypotensive (presystolic BP <110 mm Hg) before dialysis or markedly hypotensive after dialysis. The mortality risk was lowest for patients with presystolic BP between 150 and 159 mm Hg.[42] Cardiovascular complications may contribute to this high mortality risk. Hemodialysis patients with low presystolic BP also have congestive heart failure and/or coronary artery disease.[42,44] Therefore, low predialytic BP is a marker of severe congestive heart failure rather

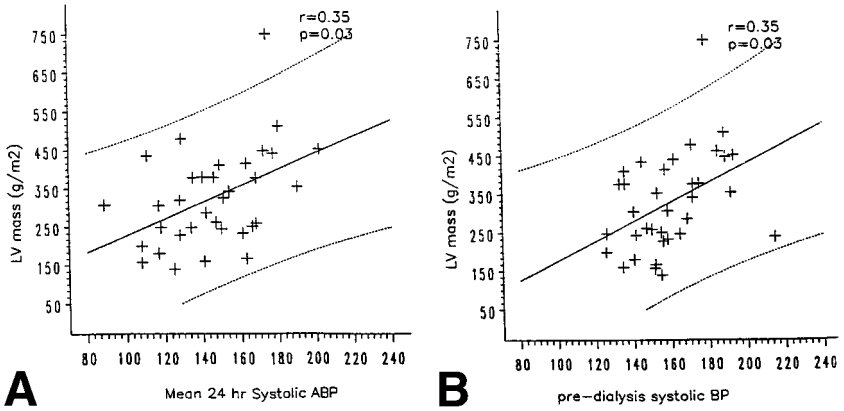

Fig 2. (A) Relationship between mean predialysis systolic BP and left ventricular mass. (B) Relationship between mean 24-hour systolic ABP and left ventricular mass. Straight line is regression line, and dotted line is 95% confidence interval of regression line. Reprinted with permission from Conlon et al, "Predialysis systolic blood pressure correlates strongly with mean 24-hour systolic blood pressure and left ventricular mass in stable hemodialysis patients." J Am Soc Nephrol 7(12):2658-2663, 1996.[31]

than a causal risk factor for cardiovascular mortality in ESRD patients.[45]

Presystolic hypertension is associated with left ventricular hypertrophy,[31] a main mortality risk factor not only in ESRD patients but also in the general population. In hemodialysis patients without intradialytic hypotension, BP should not differ from recommendations made for the general population.[46] In the study by Port et al,[43] the presystolic BP of the reference group was between 120 and 149 mm Hg. These investigators found an association between low presystolic BP and an elevated adjusted mortality risk (Fig 3). No association was observed between mortality risk and presystolic hypertension, except for an elevated risk for cerebrovascular deaths. Therefore, low predialysis BP must to be viewed with great concern.[43] London[47] recommends an optimum predialysis BP of less than 140/90 mm Hg for hemodialysis patients with classic systolic-diastolic hypertension. For patients with isolated systolic hypertension (commonly observed in elderly people), he recommends presystolic BP values of 150 to 160 mm Hg ("my personal opinion"[47]), but adequate controlled studies are not available. In the study by Grekas et al,[6] only 4.5% of the hemodialysis patients had isolated systolic hypertension. Iseki et al[48] found a crude death rate of 40% in a cohort of chronic hemodialysis patients when the diastolic BP was less than 70 mm Hg, of 35.0% at 70 to 79 mm Hg, of 25.0% at 80 to 89 mm Hg and 90 to 100 mm Hg, and of 13.0% at greater than 100 mm Hg. Low diastolic BP may be a manifestation of malnutrition and/or cardiovascular disease in chronic hemodialysis patients. Therefore, the investigators recommended higher target diastolic BP levels in chronic hemodialysis patients than in the general population. On the other hand, there was a significant correlation between diastolic BP and both interdialytic weight gain and percent weight gain.[49] Mazzuchi et al[50] found that lower predialytic BP values were predictive of death during short observation periods. Mortality in long-term observations was, however, less in hemodialysis patients with normal BP as compared with those with hypertension.

WHICH BLOOD PRESSURE SHOULD BE TREATED: PREDIALYSIS OR POSTDIALYSIS?

Mittal et al[5] defined hypertension for the hemodialysis patient population as BP greater than 150/90 mm Hg. These investigators found presystolic hypertension in 112 patients (58.9%), prediastolic hypertension in 49 patients (25.8%), postsystolic hypertension in 61 patients (32.1%), and postdiastolic hypertension in 26 patients (13.7%). Kooman et al[13] also included hypotensive patients in their analysis and found that the postdialysis BP was more representative of the average interdialytic BP in hemodialysis patients than the predialysis BP values. On the second day, however, predialysis systolic BP was more representative of the average ABP. Systolic BP is more strongly linked to cardiovascular risk than either the diastolic BP or the mean arterial pressure.[51,52] According to Conlon et al,[31] it is essential to control presystolic BP in hemodialysis patients.

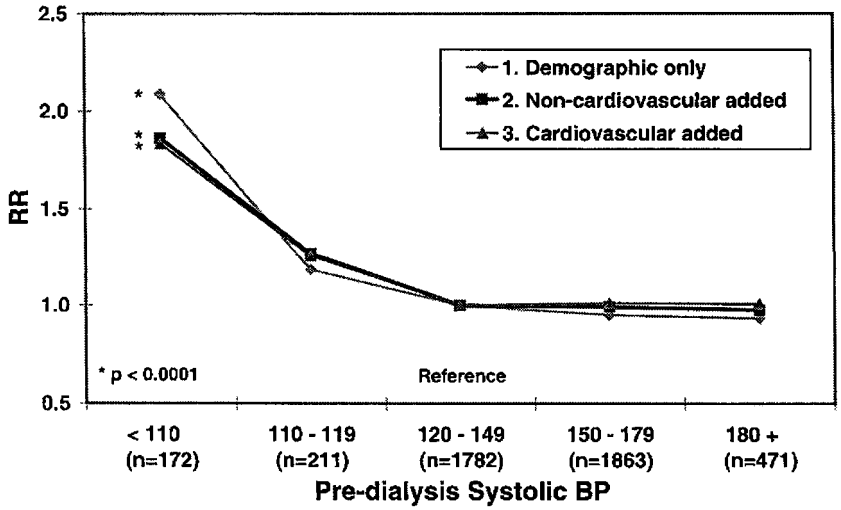

Fig 3. Relative mortality risk (RR) according to predialysis systolic BP compared with the reference group of 120 to 149 mm Hg (RR = 1.00). Three separate models are shown according to the level of statistical adjustment. (◆) Demographic only; (■) noncardiovascular added; (▲) cardiovascular added. Reprinted with permission from Port et al.[43]

Table 1. Reasons for Hypertension in Hemodialysis Patients

Extracellular volume excess/volume overload
Derangements of renin-angiotensin system
Sympathetic overactivity
Impaired endothelium-dependent vasodilatation
Uremic toxins (ADMA, homocysteine)
Genetic factors
Geographic factors/influence of climate
Correction of renal anemia by rHuEPO
Secondary hyperparathyroidism
Sodium intake/dialysate sodium concentration
Hemodialysis regimen

PATHOPHYSIOLOGY OF HYPERTENSION

Potential risk factors responsible for the development of hypertension in hemodialysis patients are summarized in Table 1.

Expanded Extracellular Fluid Volume and Renin-Angiotensin-Aldosteron System

Extracellular fluid expansion is the most consistent finding in hypertensive ESRD patients. Lins et al[53] determined a total body water of 54.7% ± 5.3% in normotensive and of 58.9% ± 4.6% in hypertensive hemodialysis patients. Improved dialysis survival occurs when extracellular fluid volume is controlled by long, slow hemodialysis technique.[9,54,55] Because extracellular fluid expansion in patients suffering from nephrotic syndrome is not necessarily associated with hypertension, pertubations in vascular autoregulation may occur in hypervolemic ESRD patients. Mailloux[56] recently summarized the mechanisms involved as follows: (1) inappropriate increased angiotensin II in relationship to volume and exchangeable sodium, (2) increased vascular sensitivity to endogenous pressors, (3) increased cardiac output in the presence of an inappropriately high peripheral vascular resistance, and (4) failure to fully suppress vasoconstrictor systems.

Hypertension is mainly related to weight gain during the interval between 2 dialysis sessions, and BP may be maintained within the normal range by correcting extracellular volume excess with dialysis.[57] However, the results obtained in different studies in adults and children on chronic hemodialysis therapy are contradictory. For example, some studies found that volume status affects interdialytic BP,[30,44,49,58-60] whereas other studies have failed to show such a relationship.[4,7,29,54,61,62] A possible explanation for this discrepancy can be taken from data by Luik et al.[63] In this study, a 3-L interdialytic fluid load did not result in a BP increase in most hemodialysis patients. Only 3 of 10 patients had a higher systolic but not diastolic BP after fluid load.[63] Interdialytic weight gain, systolic BP, and hematocrit independently influence the left ventricular mass index in chronic hemodialysis patients.[64]

There is a correlation between loss of weight during hemodialysis and lowering of systolic BP.[5] A reduction in postdialysis mean arterial pressure of ≥5%, controlled by ultrafiltration, was found in 68.5% of hypertensive but in 87.5% of normotensive hemodialysis patients.[6] Plasma aldosterone and fluid volume removed by ultrafiltration are significantly correlated.[65] Volume sensitivity is higher in hypertensive as compared with normotensive hemodialysis patients.[66] A correlation between BP and interdialytic weight gain does not exist for normotensive patients,[67] probably because of an adequate vasodilatatory response in these patients that may be less effective or even absent in hypertensive hemodialysis patients. Patients with uncontrolled hypertension are more likely to have hypertension as the cause of their ESRD as compared with normotensive hemodialysis patients.[49]

Role of Sympathetic Nervous System

Increased activity of the sympathetic nervous system may contribute to hypertension in ESRD patients.[68,69] Plasma volume contraction and negative sodium balance during dialysis therapy may induce an increase in plasma catecholamine levels.[70] Grekas et al[65] found no difference between pre- and postdialysis plasma adrenaline, noradrenaline, and renin activity in normotensive and hypertensive hemodialysis patients. These investigators suggested that sympathetic activity is not associated with hemodialysis hypertension. In contrast, Converse et al[71] provided evidence for chronic sympathetic overactivity in hemodialysis patients. Sympathetic-nerve discharge was 2.5 times higher in maintenance hemodialysis patients than in normal subjects. Hemodialysis patients who had undergone bilateral nephrectomy had sympathetic-nerve discharge similar to normal subjects. The rate of sympathetic-nerve discharge was not correlated with either plasma

noradrenaline concentration or plasma renin activity,[71] which may explain the negative findings of Grekas et al[65] reported earlier. Reduced sympathetic-nerve discharge may be 1 important mechanism by which bilateral nephrectomy lowers BP.[71] Fluid overload of greater than 6% of body weight results in activation of the sympathetic nervous system and release of the vasoconstrictor neuropeptide Y,[72] whereas a 3-L interval fluid load does not influence plasma catecholamines.[63] Angiotensin-converting enzyme (ACE) inhibition results in reduction of sympathetic hyperactivity in patients with chronic renal failure.[73]

Impaired Vasodilatation

Endothelium-dependent vasodilatation is impaired in uremia.[74] The vascular endothelium produces and releases vasoactive compounds such as nitric oxide (NO), which may cause vasodilatation and inhibition of vascular smooth muscle cell proliferation.[75] Morris et al[76] showed reduced vasodilatation to carbachol, an endothelium-dependent vasodilatator, in uremic patients, whereas the response to sodium nitroprusside, an endothelium-independent vasodilatator, was preserved. Experimental NO deficiency causes hypertension.[77] NO deficiency occurs in ESRD patients and may contribute to hypertension in this population.[78,79] The production of NO by the vascular endothelium is inhibited by asymmetric dimethylarginine (ADMA), which accumulates in chronic renal failure patients.[80] Plasma ADMA levels are 6- to 10-fold higher in hemodialysis patients than in healthy subjects. These ADMA concentrations may inhibit NO synthases. Plasma ADMA concentration can be reduced during the dialysis procedure by 65%.[79,81] Plasma ADMA levels are also elevated in patients with atherosclerotic diseases and normal kidney function[82] but are particularly enhanced in hemodialysis patients with atherosclerotic complications.[81] Therefore, high plasma ADMA levels may, at least in part, be responsible for impaired endothelium-dependent vasodilatation observed in uremia. No significant correlation, however, was observed between ADMA concentration and BP in dialysis patients.[83] Another factor that may impair endothelial function in ESRD patients is hyperhomocysteinemia.[84]

Hypervolemia enhances the release of adrenomedullin, a potent vasorelaxant. In the study of Mallamaci et al,[85] the average plasma adrenomedullin concentration was 2.6 times higher in uremic patients than in healthy subjects. After fluid subtraction by isolated ultrafiltration, adrenomedullin fell but remained well above the upper limit seen in normal subjects. Systemically administered adrenomedullin has been shown to significantly decrease mean arterial pressure in healthy subjects[86,87] but to a much lesser extent in patients with congestive heart failure.[87]

Influence of Climate and Geographic Factors

Argilés et al[88] accurately evaluated the importance of BP variations associated with seasonal changes in maintenance hemodialysis patients. The variations amounted to 12 mm Hg for mean systolic BP (153 $\pm$ 3 versus 141 $\pm$ 3 mm Hg) and 7 mm Hg for diastolic BP (82 $\pm$ 2 versus 75 $\pm$ 2 mm Hg). The patients were evaluated 3 times weekly for 31 months in the same city. The investigators concluded that high temperature and low humidity facilitate BP control in ESRD patients undergoing regular hemodialysis therapy.[88] Several studies have shown that geographic factors are also determinants of BP in the general population.[89-92]

Erythropoietin and Correction of Renal Anemia

In the study by Mittal et al,[5] the dose of human recombinant erythropoietin (rHuEPO) had no effect on the degree of hypertension. The hemodialysis patients received a mean rHuEPO dose of 5,905 $\pm$ 3,854 U per treatment to maintain a mean hematocrit of 33.3% $\pm$ 3.5%. Similar data were obtained by Coomer et al.[8] In contrast, Raine and Roger,[93] as well as Grekas et al,[6] observed a significant correlation between the weekly dose of rHuEPO and BP. In the study by Grekas et al,[6] the prevalence of hypertension was 62% in rHuEPO-treated hemodialysis patients but only 38% in those not receiving rHuEPO.

In 20% to 30% of kidney failure patients, regular administration of rHuEPO is accompanied by de novo hypertension or aggravation of preexisting hypertension. The increase in arterial BP does not occur immediately but rather within a few weeks to months after initiation of rHuEPO therapy.[93-96] Hypertension associated with rHuEPO therapy is not mediated by the increase in hematocrit. Vaziri et al[97] showed a marked increase in

arterial BP of equal magnitude beginning 1 week after initiation of rHuEPO therapy in both iron-deficient and iron-sufficient rats with chronic renal failure. The investigators could also show that multiple, small, packed red blood cell transfusions failed to increase arterial BP in these animals despite hematocrit values identical to those of iron-sufficient animals achieved by rHuEPO treatment.[97] Kaupke et al[98] observed a marked increase of hematocrit after iron repletion in rHuEPO-treated dialysis patients with preexisting iron-deficiency anemia without further increase in BP.

Alterations of the arterial system in ESRD patients include diffuse dilatation, hypertrophy, and stiffening of the aorta and major arteries.[99-102] Increased aortic stiffness is a strong independent predictor of all-cause and mainly cardiovascular mortality in ESRD patients undergoing hemodialysis. Age and aortic pulse-wave velocity emerged as predictors for the mortality observed, whereas hemoglobin and low diastolic BP interfered to a smaller extent.[103]

Mechanisms of BP increase during rHuEPO therapy in ESRD patients are summarized in Table 2. Increasing the hematocrit from 20% to 30% leads to an increase in peripheral resistance of approximately 25% (from 1,578 to 1,988 dyn $\times$ s $\times$ cm^{-5}).[104] In the study by Lebel et al,[105] systemic vascular resistance increased by 28% but was not adequately counterbalanced by the decrease of only 6% in cardiac output, resulting in an increased predialysis and postdialysis systolic and diastolic BP. Hypoxia causes a reactive peripheral vasodilatation to improve regional blood flow and thus oxygen supply.[104] Roger et al[106] determined forearm vascular resistance and systemic BP in dialysis patients breathing room air and 60% oxygen before and after correction of anemia by rHuEPO. Those patients, who showed an increase in systemic BP during rHuEPO therapy, also had a significant increase in forearm vascular resistance after oxygen breathing in the anemic state. If oxygen breathing, however, did not alter vascular resistance in the anemic state, systemic hemodynamic parameters remained unchanged after correction of anemia.[106]

Table 2. Mechanisms of BP Increase During rHuEPO Therapy in Hemodialysis Patients

Increase in whole-blood viscosity
Activation of various neurohumoral systems
Endothelin release
Vascular endothelial dysfunction
Genetic prediction of hypertension
Preexisting hypertension
Direct vasopressor effect of rHuEPO on renal resistance vessels
Elevation of cytosolic free calcium in vascular smooth muscle cells
Inhibition of NO synthesis
Up-regulation of genes implicated in the regulation of vascular functions
Low baseline hematocrit
(Too) Rapid correction of anemia

An increase in red cell mass during or after correction of anemia leads to an increase in whole-blood viscosity[107] and thereby increases cardiac afterload.[104] Anastassiades et al[108] found a marked expansion of the red cell volume from 912 $\pm$ 127 to 1,471 $\pm$ 222 mL and a concomitant contraction of the plasma volume from 3,923 $\pm$ 250 to 3,178 $\pm$ 326 mL, leaving the blood volume unchanged. In this study, predialysis patients had a similar expansion of the red cell volume but no contraction of the plasma volume, so that the blood volume tended to expand from 4,149 $\pm$ 347 to 4,618 $\pm$ 414 mL. Gradual reduction of plasma volume may be an important strategy for the prevention and control of rHuEPO-induced hypertension.[108] Red cell mass increased significantly in the study by Lebel et al[105] during correction of renal anemia, but plasma volume, extracellular fluid volume, and exchangeable sodium decreased significantly. Therefore, the investigators suggested that volume-independent mechanisms contribute to rHuEPO-induced BP increase. Because an increase in BP may occur even before hematocrit increases, this also argues that other mechanisms contribute to the increase in peripheral resistance associated with rHuEPO therapy.

Other factors in rHuEPO-induced hypertension include activation of various neurohormonal systems,[109,110] endothelin release,[111,112] vascular endothelial dysfunction,[113,114] genetic predisposition of hypertension,[115,116] preexisting hypertension,[117,118] elevation of cytosolic free calcium in vascular smooth muscle cells,[119,120] inhibition of NO synthesis,[121-123] up-regulation of genes implicated in the regulation of vascular

functions,[124] low baseline hematocrit levels,[125] and rapid correction of renal anemia.[126-128]

Chronic administration of rHuEPO increases intracellular calcium by facilitating cellular Ca^{2+} uptake.[97,119,129,130] Elevation of basal intracellular calcium concentration increases vascular smooth muscle tone,[131] and down-regulation of NO production[132] results in hypertension. Normalization of intracellular calcium by calcium channel blockade abrogates rHuEPO-induced hypertension and reverses down-regulation of NO production.[133] Erythropoietin has synergistic effects on angiotensin II– or noradrenaline-induced intracellular calcium mobilization in vascular smooth muscle cells.[120] Erythropoietin enhances vascular responsiveness to norepinephrine, endothelin-1, and constrictor prostanoids.[134,135] Studies on rats with chronic renal failure, however, suggest that rHuEPO-induced hypertension is not mediated by increased plasma endothelin-1 levels but by an increase in blood vessel endothelin-1 production.[136]

Heidenreich et al[137] found a direct vasopressor effect of rHuEPO on renal resistance vessels. On the other hand, longer-term exposure of human endothelial cells in culture with rHuEPO had a vasodilatory effect.[138] Administration of rHuEPO is not associated with an instantaneous increase in BP.[139] A single intravenous infusion of 100 U rHuEPO/kg body weight increases mean arterial pressure. This effect, however, does not occur if the rHuEPO dose is given subcutaneously.[140] Correction of hematocrit to normal with rHuEPO in chronic hemodialysis patients with cardiac disease does not cause increased interdialytic BP or predialysis and postdialysis BPs.[141]

Role of Secondary Hyperparathyroidism

Secondary hyperparathyroidism may also result in hypertension in ESRD patients by encouraging entry of calcium into vessel wall smooth muscle cells.[142] Ifudu et al[143] compared predialysis blood pressure, weight, and dose of antihypertensive medications prescribed in 19 hemodialysis patients before and after total parathyroidectomy. Parathyroidectomy failed to correct hypertension in patients on maintenance hemodialysis.[143] In contrast, treatment of secondary hyperparathyroidism by alfacalcidol resulted in significant decreases in parathyroid hormone, platelet intracellular calcium, and mean BP.[144,145] Furthermore, infusion of physiologic doses of parathyroid hormone increases BP and intracellular calcium in healthy subjects.[146]

Natriuretic Factors in ESRD Patients

Circulating natriuretic peptides, particularly α-human atrial natriuretic peptide (α-ANP), regulate volume homeostasis and control BP and electrolyte balance.[147,148] In dialysis patients, plasma α-ANP levels are elevated because of stimulation of α-ANP secretion, reflecting extracellular volume expansion. The α-ANP values decrease postdialysis but are still significantly higher than those observed in healthy volunteers. Postdialytic α-ANP levels remain elevated in normovolemic patients with altered left atrial hemodynamics. Therefore, α-ANP might only be useful as a parameter for fluid overload when cardiac function is normal. Similar to α-ANP, the concentration of brain natriuretic peptide (BNP) in plasma is higher in hemodialysis patients than in healthy subjects. In contrast to the α-ANP levels, those of BNP were lowered less efficiently by the hemodialysis procedure,[149] probably because of the longer half-life of BNP.

Hypertension is frequently associated with elevated proANP and α-ANP concentrations. Circulating concentrations of proANP(1-30), proANP(31-67), proANP(79-98), and α-ANP increase in patients with high BP in an apparent attempt to overcome the constriction of blood vessels.[150] Winters and Vesely[151] reported a decrease of α-ANP during the hemodialysis session but proANP(1-98) and proANP(31-67) increased. We studied 122 ESRD patients on maintenance hemodialysis.[152,153] ProANP(1-98) levels increased 98-fold, proANP(1-30) levels increased 35-fold, and proANP(31-67) increased 56-fold as compared with healthy subjects. Before hemodialysis, α-ANP was 217-fold elevated as compared with controls. The interdialytic weight gain ranged between 0 and 5.6 kg with a mean value ($\pm$SD) of 2.3 ± 1.0 kg. There was no significant correlation between predialytic plasma levels of α-ANP, proANP(1-30), proANP(31-67), proANP(1-98), and interdialytic weight gain, or between the respective plasma concentrations and volume removal during hemodialysis. The diameter of the vena cava inferior as a possible parameter for volume overload, normovolemia, or underhydration also did not correlate with

proANP(1-30), proANP(31-67), proANP(1-98), or α-ANP.[152] Hemodialysis treatment using cellulose triacetate dialyzer membranes lowered the plasma concentrations of proANP(1-30), proANP(31-67), and proANP(1-98) significantly more than using polysulfone dialyzer membranes, whereas α-ANP was not concentration affected.[153] Hemodialysis patients with moderate or severe hypertension had higher concentrations of proANP fragments and α-ANP than patients with normal BP or patients with only mild hypertension.[152] These data indicate that circulating α-ANP and proANP fragments are influenced by a variety of factors such as ESRD, hemodialysis treatment, dialyzer membrane material, cardiac dysfunction, and hypertension. Therefore, α-ANP and proANP fragments are not useful markers to accurately estimate volume status in hemodialysis patients. Cardiac natriuretic peptides are related to left ventricular mass and function in dialysis patients, and predict overall and cardiovascular mortality.[154]

Sodium Restriction

The most effective way to control hypertension in dialysis patients is with the use of a salt-restricted diet.[155] There is an initial reduction in extracellular volume that corresponds to the volume and weight-loss correction. After a lag period of several weeks to months,[156] BP continues to decrease without a further decrease in extracellular volume.[157] This BP reduction is associated with a decrease in peripheral vascular resistance.[158] Noninvasive assessments of dry weight include radiologic features on chest radiograph such as heart size and intrapulmonary fluid retention, echocardiography, sonography of the inferior caval vein diameter, conductivity measurements such as bioimpedance spectroscopy or multiple-frequency bioelectric impedance, and determination of several biochemical markers such as plasma levels of natriuretic peptides, cyclic guanosine 3′5′-monophosphate, or calcitonine-gene–related peptide. There is, however, no single parameter to define adequate dry body weight of a hemodialysis patient.[159] Therefore, volume expansion may persist in several patients after the clinician has thought the patient reached dry weight.[56] Dialysis patients ingesting a low-sodium (chloride) diet are monitored by following body weight and in those with residual renal function also by the urinary excretion of sodium and chloride.

In Tassin (France), 95% of the patients obtained normal BP without medication in the first weeks of long dialysis therapy because of sodium and volume control.[160] Dietary salt restriction and reduction in dialysate sodium may also control hypertension without lengthening dialysis time.[161,162] Dialysate sodium concentration was gradually lowered from 140 to 135 mmol/L at a rate of 1 mmol/L every 3 to 4 weeks in combination with a NaCl-restricted diet of no more than 6 g/day.[160] In a pilot study, Kooman et al[163] decreased dialysate sodium concentration from 140 to 136 mmol/L during a 6-week time period, but did not find significant changes in predialytic systolic or diastolic BP. These patients, however, were maintained on a sodium-restricted diet, which may explain the failure of a further BP decrease by reduction of dialysate sodium concentration.[163] Sodium overload increases intracellular sodium and calcium concentration and thereby increases the tone of vascular smooth muscle cells. On the other hand, sodium reduction may reverse this mechanism, resulting in BP decrease.[164]

Several studies on dietary salt intake have been performed in dialysis patients. Özkahya et al[162] reemphasized salt restriction, stopped all antihypertensive medication, and intensified ultrafiltration during hemodialysis. Interdialytic weight gain decreased from 2.8 $\pm$ 1.4 kg to 1.6 $\pm$ 0.8 kg. During the total follow-up of 37 $\pm$ 15 months, there was not only a significant reduction in BP but also in wall thickness of the left ventricle. In a further study,[165] these investigators restricted sodium chloride intake to less than 100 mmol/day ($<$6 g/day) in 67 maintenance hemodialysis patients. Average BP decreased from 173 $\pm$ 17/102 $\pm$ 9 to 139 $\pm$ 18/86 $\pm$ 11 mm Hg after 6 months and to 118 $\pm$ 12/73 $\pm$ 6 mm Hg after 36 months despite discontinuation of antihypertensive drugs at the beginning of treatment.

Dialysis sodium concentration influences postdialysis thirst, interdialytic weight gain, and BP, as well as intradialytic morbidity. Hemodiafiltration treatments were compared with high (143 mmol/L) and low (138 mmol/L) dialysate sodium concentration. Low sodium level in dialysate resulted in significantly lower intra- and

interdialytic plasma sodium and potassium concentration as compared with high dialysate sodium. Even moderate hypertonicity at the end of dialysis treatment contributes to the increase of plasma potassium throughout the whole interdialytic period by redistribution of water and potassium from the intracellular to the extracellular compartment.[166] Thus, patients on low dialysate sodium concentration benefit not only from BP reduction but also from lower plasma potassium during the interdialytic period. Flanigan et al[167] compared dialysis by using a dialysate sodium concentration of 140 mEq/L with dialysis by using a programmed exponential decrease of dialysis sodium from 155 mEq/L to 135 mEq/L. Programmed variable sodium dialysis resulted in a reduction in antihypertensive drug use without alterations in predialysis BP, interdialytic weight gain, ultrafiltration tolerance, or the frequency of symptomatic dialysis cramps or hypotension.[167] Linear sodium ramping from 155 mEq/L to 140 mEq/L or stepwise ramping can decrease intradialytic side effects but increases interdialytic symptoms, weight gain, and hypertension.[168] Profiled dialysate sodium and ultrafiltration may lower symptoms in both the intradialytic and the interdialytic periods as compared with constant dialysate sodium and ultrafiltration. Predialysis weight was significantly greater during profiled treatments, but there were no differences in postdialytic weight, BP, or thirst.[169] The use of sodium and conductivity kinetic models guarantees adequate sodium removal in each patient with each treatment.[170]

Effects of Dialysis Regimen

Velasquez et al[171] compared the status of hypertension and adequacy of BP control in ESRD patients treated with different hemodialysis, modalities. The percentage of patients taking antihypertensive medication was less, and control of hypertension was better in patients treated with high-efficiency hemodialysis by using a cuprophane membrane, high-flux hemodialysis, or high-flux hemodiafiltration as compared with patients on conventional hemodialysis.

Low compliance with the dialysis regimen is associated with hypertension. Patients skipping or shortening 1 or more dialysis treatments have higher BPs than compliant patients.[44] Studies from centers that use 8-hour hemodialysis sessions report excellent BP control with dialysis alone.[54,59,172] Good BP control is the principal reason for the low rate of cardiovascular complications in the hemodialysis patient population in Tassin.[9] In the study by Luik et al,[172] 73% of the patients on short dialysis were using antihypertensive medication, but none of the patients on long dialysis were using antihypertensive medication. Adequate BP control of patients on long dialysis is caused by low total peripheral resistance. In another study, only 2 of 24 patients on home hemodialysis (dialyzed for 7.2 ± 1.1 hr 3 times weekly) were taking antihypertensive drugs.[173] The mean 24-hour BP was 129 ± 17 mm Hg (systolic) and 83 ± 14 mm Hg (diastolic). Six patients (25%) had a normal circadian BP rhythm.[173] Normotension can be achieved independently of the duration of hemodialysis if the control of postdialysis extracellular volume is adequate.[174] This is, however, more difficult to obtain with short than with more prolonged hemodialysis procedures. Intradialytic hypotension may occur during short dialysis sessions, particularly in type II diabetic patients. Koch et al[175] found that 2 or 3 hypotensive episodes per week increased the risk for cardiac death by a factor of 3.

Frequent, short hemodialysis sessions can achieve greater urea removal than 3 times per week hemodialysis.[176,177] Pinciaroli[178] reported BP control in 12 hypertensive patients on daily hemodialysis after a few months. By achieving and maintaining true dry body weight, 8 patients were without antihypertensive drugs, and medication was reduced in the other 4 hemodialysis patients. Mean BP decreased from 174/94 mm Hg to 141/82 mm Hg in these patients. The cardiothoracic index declined from 0.52 to 0.46 after 1 year.[178] BP normalized in all patients on daily dialysis in the study conducted by Buoncristiani et al,[179] whether they were initially hypertensive or hypotensive. Woods et al[180] described patient outcomes after increasing hemodialysis frequency from 3 to 6 times per week in a cohort of 72 patients treated at 9 centers during 1972 to 1996. Presystolic and prediastolic BPs fell by 7 and 4 mm Hg, respectively, after starting frequent hemodialysis. BP reductions were greatest among patients being treated with antihypertensive medications, despite reduction in their dosage of medications. In the study by Kooistra et al,[181] ABPM showed a systolic BP of 141.1 ±

17.2 mm Hg before, and 130.9 ± 19.2 mm Hg during daily home hemodialysis. Diastolic BP remained constant but mean arterial pressure decreased from 102.2 ± 9.5 to 94.9 ± 1.4 mm Hg. BP decreased mainly in previously hypertensive hemodialysis patients. The amount of antihypertensive drugs was reduced from 1.88 ± 0.35 to 0.75 ± 0.17. A recent prospective cross-over study confirmed that daily hemodialysis allows optimal BP control, reduction of left ventricular mass, and withdrawal of antihypertensive treatment.[182]

Sleep disorders are common in ESRD patients. Nocturnal hemodialysis enables patients to undergo hemodialysis 7 nights per week at home while sleeping.[183] This procedure corrects sleep apnea associated with chronic kidney failure.[184] Nocturnal hemodialysis improves BP control by decreasing the volume of extracellular fluid.[185] Such a decrease in the airway may have a salutary effect on the pathophysiology of sleep apnea. Sleep-disordered breathing is likely to be a risk factor for hypertension and cardiovascular morbidity.[186]

Long, slow, home hemodialysis or frequent, short hemodialysis sessions or nocturnal hemodialysis result in reduction of BP and left ventricular hypertrophy in ESRD patients.[182,185,187-189]

ANTIHYPERTENSIVE DRUGS

In the study by Agarwal,[190] 85% of the maintenance hemodialysis patients were hypertensive with BPs of 154 ± 23/83 ± 14 mm Hg and 137 ± 23/74 ± 14 mm Hg pre- and postdialysis, respectively. At 3-year follow-up, a BP reduction of 9.4/6.7 mm Hg was obtained by increasing the number of antihypertensive medications from 0.91 ± 0.86 to 1.41 ± 1.16, but keeping body weight and volume status unchanged. Most patients were treated with calcium channel blockers (39%), whereas 27% received β-blockers and 14% received ACE inhibitors.[5] Calcium antagonists were also the most frequently administered antihypertensive drugs (71%) by Zazgornik et al,[191] followed by ACE inhibitors (57%), α-blockers (31%), β-blockers (26%), or centrally acting drugs (16%). Patients with mild or moderate hypertension received on average 1.5 antihypertensive drugs, whereas those with severe hypertension received on average 3.3 antihypertensive drugs. The use of adrenergic blockers increased 2-fold over the duration of the study reported by Agarwal.[192] Atenolol was administered 3 times weekly after dialysis, and effectively controlled hypertension.

Left ventricular hypertrophy can be reversed in dialysis patients.[193,194] Among the antihypertensive agents, ACE inhibitors appear to have the greatest ability to reduce left ventricular mass in renal failure patients with left ventricular hypertrophy.[194,195] Antihypertensive monotherapy with ACE inhibitors in chronic renal failure patients resulted in regression of left ventricular mass index and was associated with a significant improvement in the diastolic function of the left ventricle.[196] In ESRD patients with an increased left ventricular mass index in the face of a normal or reduced left ventricular volume, ACE inhibitors or AT_1-receptor antagonists were recommended, whereas in patients with elevated left ventricular volume, reduction of hypovolemia should be the main therapeutic option.[197] Hemodialysis patients with congestive heart failure, ischemic heart disease, or intradialytic BP increase may benefit from the use of ACE inhibitors and β-blockers.[198,199] Dorhout Mees,[200] however, suggests that hypotensive drugs do not allow adequate BP control for long periods in hemodialysis patients. In contrast, this goal can be achieved by salt restriction and volume control.[201] If dialysis fails to ensure adequate salt and water removal, hypertension will persist despite the use of antihypertensive medication.[202] Antihypertensive medications alone cannot control BP in hemodialysis patients.[203] Malignant or treatment-resistant hypertension with hypertensive crises may be an indication for bilateral nephrectomy with BP normalization in the majority of patients.[204]

CONCLUSIONS

The high mortality rate seen in hemodialysis patients is related to long-standing high BP and the presence of other risk factors for cardiovascular disease.[205,206] High BP is frequent and difficult to control in this patient population. Patients requiring total ultrafiltration volume greater than 2.5 kg may have an elevation in presystolic and prediastolic BPs. Diabetes mellitus, older age, or an increased number of prescribed antihypertensive medications are risk factors for higher pre- and postsystolic BPs.[207] Long-term observations

favor normal BP values not only for the general population but also for the hemodialysis patients. Maintenance of normal BPs has been largely attributed to optimal volume control, but a low-salt diet is an important aspect of this therapy.[208] Left ventricular hypertrophy and sympathetic hyperactivity can be reduced by ACE inhibitor and β-blocker therapy. Monitoring of BP, both home and predialysis, is of particular importance.

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