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Blood Pressure and Hemodialysis

Robert Ekart[1], Sebastjan Bevc[1] and Radovan Hojs[2]
Clinic for Internal Medicine,
[1]Department of Dialysis and
[2]Department of Nephrology,
University Medical Centre Maribor,
Slovenia

1. Introduction

Hypertension is common in patients with advanced stages of chronic kidney disease (CKD) and its prevalence remain very high in patients with end stage renal disease (ESRD) treated with hemodialysis. Using various definitions of hypertension, the prevalence of hypertension in hemodialysis patients is up to 90%. The diagnosis of hypertension in hemodialysis patients is often complicated especially because there are large swings in blood pressure with dialysis and it is difficult to accurately ascertain the blood pressure in the interdialytic period.

The pathogenesis of hypertension in hemodialysis patients is multilayered and at present still not completely elucidated. One or more of the factors play a role in a individual patient – hypervolemia, increased sympathetic activity, erythropoietin, altered endotelial cell function and many others.

Poorly controlled hypertension is a risk factor for cardiovascular disease, congestive heart failure, and cerebrovascular disease in the general population. The influence of hypertension on cardiovascular outcomes in hemodialysis patients is less clear, and complicated because of the high prevalence of comorbid conditions in these patients. The management of hypertension is difficult in hemodialysis patients, because there is a significant difference in blood pressure between the pre-, post- and interdialytic period. The best timing and method of blood pressure measurement in hemodialysis patients is still uncertain. The blood pressure variability and extreme changes of the volemic state make it difficult to obtain a truly representative value of blood pressure in hemodialysis patients if based only on an isolated blood pressure measurements in dialysis center. There are many differences related to technique of blood pressure measurement, timing of measurement in relation to hemodialysis session, and reliance on the use of home blood pressure measurements or ambulatory blood pressure monitoring (ABPM). Casual conventional sphygmomanometry blood pressure measurements at home and in dialysis center are far from being ideal to reflect blood pressure levels precisely in hemodialysis patients and adjusting antihypertensive treatment according to casual blood pressure measurements may cause an inadequate blood pressure control.

ABPM is the most reproducible method of blood pressure measurement in hemodialysis patients, and most would argue that it should be used as the gold standard for the definition

of hypertension in ESRD. ABPM has also been used to better define the relationship between blood pressure, target organ damage, and outcomes in patients with CKD and ESRD. ABPM has been shown to predict cardiovascular events better than conventional blood pressure measurement in patients with essential hypertension. Although many patients received antihypertensive drugs, only small percent have adequately controlled blood pressure. There are many reasons for this problem.

The purpose of this chapter is to discuss about the pathogenesis of hypertension, definition of hypertension, optimal time and target blood pressure, different methods of blood pressure measurements, discuss the relationship between blood pressure and cardiovascular outcomes and – finally outline the therapies to control blood pressure in hemodialysis population.

2. Pathogenesis of hypertension in end stage renal disease

Several of the generally accepted pathogenetic factors that may be involved in the development of hypertension in ESRD and CKD are listed in Table 1. These will be discussed separately.

2.1 Sodium and volume excess

The normal physiologic response to intravascular volume expansion in the healthy person is to increase glomerular filtration via a rise in cardiac output, enhance urinary sodium excretion by supression of the renin-angiotensin-aldosterone system, and increase natriuresis as a result of the effects of atrial natriuretic peptide and an endogenous digitalis-like factor. The result of these physiologic adaptations is natriuresis and diuresis, and restoration of normal plasma volume. In contrast, excess extracellular fluid volume and increases in total body exchangeable sodium are common in patients with ESRD, because of diminished sodium and fluid excretory capacity. It has been shown that normotensive patients have significantly less total body water than hypertensive hemodialysis patients, demonstrating the importance of intravascular volume in the pathogenesis of hypertension in patients with ESRD (Lins et al, 1997).

Sodium and volume excess
Increased sympathetic activity
Activation of the renin – angiotensin - aldosterone system due to primary vascular disease or regional ischemia induced by scarring
Erythropoietin administration
An increase in endothelium-derived vasoconstrictors (endothelin) or a reduction of endothelium-derived vasodilators (nitric oxide)
Parathyroid hormone excess secretion
Renal vascular disease
Worsening of preexisting essential hypertension
Reduced production of prostaglandins/bradykinins

Table 1. Putative Pathogenetic Mechanisms of Hypertension in ESRD patients.

Overhydration and sodium retention plays a role not only by volume overload, but also by nonhemodynamic direct effects on the left ventricle and vascular system. The patients at greatest risk in a vicious cycle (fluid overload → problems in removing fluid → further fluid overload) are those who begin dialysis with low predialysis blood pressures as the result of severe cardiac failure. The prognosis of these patients is very poor because fluid can be removed only very slowly in such patients. To further aggravate this situation, dialysis patients often have diastolic dysfunction. In these patients, even a small decrease in filling pressure following dialysis ultrafiltration may result in decreased cardiac output and hypotension. As a result, fluid accumulation progresses inexorably. In addition, autonomic neuropathy complicating uremia and diabetes with inadequate peripheral arteriolar tone reactivity further increases the risk that hypotension occurs when the patient is still fluid overloaded. While the importance of salt regulating fluid balance by dietetic means and avoidance of sodium loading during dialysis has received major emphasis, sodium has also been proposed as a uremic toxin with specific effects stimulating oxidative stress. Possibly related to this is the finding that excess sodium may be stored nonosmotically at concentrations of 180 to 190 mEq/L in skin, connective tissue, cartilage, and bone, possibly bound to glucosoaminoglycans. Under various circumstances, this sodium could be intermittently released into the circulation causing hypervolemia and oxidative stress. Control of volume status can either normalize the blood pressure or make the hypertension easier to control in the great majority of dialysis patients. Volume status of ESRD patients influences both pre- and postdialysis blood pressure. Volume status is perhaps the most important factor in the development and maintenance of hypertension in dialysis patients (Mailloux & Haley, 1998). Volume expansion leads to an elevation in blood pressure through the combination of an increase in cardiac output and an inappropriately high systemic vascular resistance. Numerous authors described a correlation between hypertension and hypervolemia in dialysis patients, since hypervolemia is the cause of hypertension in up to 90% of dialysis patients (De Leeuw, 1994, Katzarski et al, 1997, Kirchner, 1997, Luik et al, 1998, Özkahya et al, 1999, Remuzzi, 1999, Agarwal et al, 2011). Also our study with 86 included hemodialysis patients confirmed this as well (Ekart & Hojs, 2006). Estimation of excess of volume is dependent upon estimation of dry weight. In a dialysis patient, dry weight is that body weight at the end of dialysis at which the patient can remain normotensive until the next dialysis despite the retention of salt water (saline). Dry weight varies over time as lean body mass and body fat change. At dry weight, the extracellular volume is at or near normal but not less than normal (Charra et al, 1996). An incorrect estimation of dry weight will lead either to chronic fluid overload or chronic underhydration. The blood pressure should remain in the normal range during the whole interdialytic period. If the patient remains hypertensive after a dialysis or becomes hypertensive before the next dialysis, he is, by definition, above his dry weight (Charra et al, 1996). The postdialysis body weight should ideally reflect a state of normohydration. The assessment of dry weight is usually based on clinical observations, such as weight gain, blood pressure, jugular venous pressure, presence of edema, congestion, and chest X-ray parameters (Cheriex et al, 1989, Katzarski et al, 1997). These methods are not very reliable, and a more accurate, objective, non-invasive assessment of optimal dry weight is therefore mandatory. The diameter of the inferior vena cava may be used to evaluate the volume state and serve as a guideline for assessing dry weight. Inferior vena cava diameter measured in expiration just below the diaphragm in the hepatic segment in patients lying in a supine

position, correlated well with central venous pressure (Figure 1). Inferior vena cava diameter, corrected for body surface area between 8.0 and 11.5 mm/m², was considered to represent normovolemia (Cheriex et al, 1989). The collapse index was defined as ({maximal diameter on expiration minus minimal diameter on deep inspiration}divided by maximal diameter on expiration) times 100 (Figure 2 & 3). Hypervolemia (mean right atrial pressure > 7 mmHg) was defined as a collapse index of less than 40% and/or inferior vena cava diameter of above 11.5 mm/m². Hypovolemia (mean right atrial pressure < 3 mmHg) was defined as a inferior vena cava diameter of less than 8 mm/m² and/or collapse index of more than 75% (Cheriex et al, 1989). In patients with severe valvular and pulmonary disease, and patients in whom there is an increased inthrathoracic or intrabdominal pressure, these measurements are unreliable. Unfortunately, one problem with a reliance upon a clinical assessment of volume status is that volume expansion may persist even among those thought to have attained dry weight. The timing of the postdialysis inferior vena cava diameter measurement is critical. During hemodialysis, ultrafiltrated fluid is primarily removed from the circulating blood volume, which is refilled by fluid from the interstitial space. Since this process does not occur instantaneously, a state of disequilibrium follows hemodialysis, during which refilling continues and blood volume increases until equilibrium is attained; this must be taken into account when using inferior vena cava diameter to assess dry weight. The lowest values of inferior vena cava diameter were found immediately at the end of hemodialysis, followed by an increase during the following 2 hours due to refilling of the plasma volume from the interstitial space (Katzarski et al, 1997). Thus, it seems doubtful that measurements of inferior vena cava diameter within 2 hours after hemodialysis reliably reflect the state of hydration.
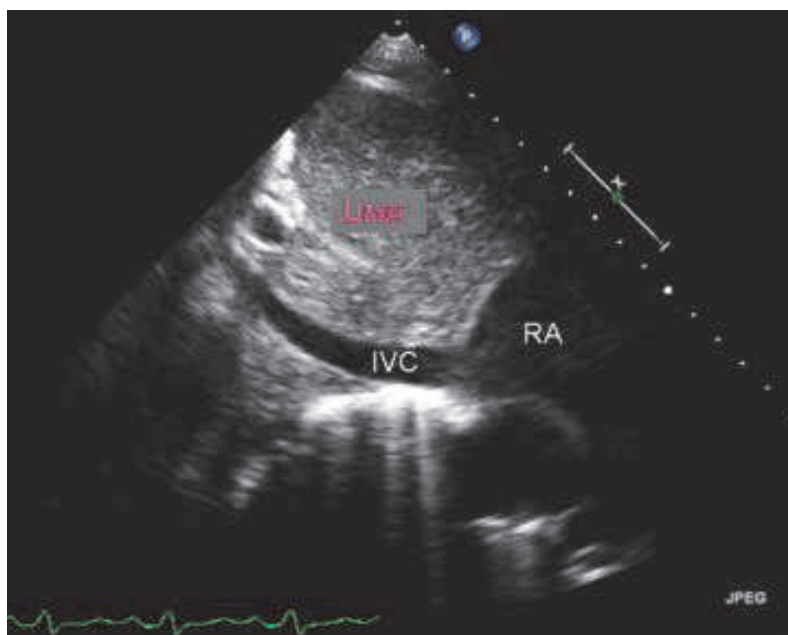

Fig. 1. Ultrasound determination of inferior vena cava (IVC) diameter; RA=right atrium.
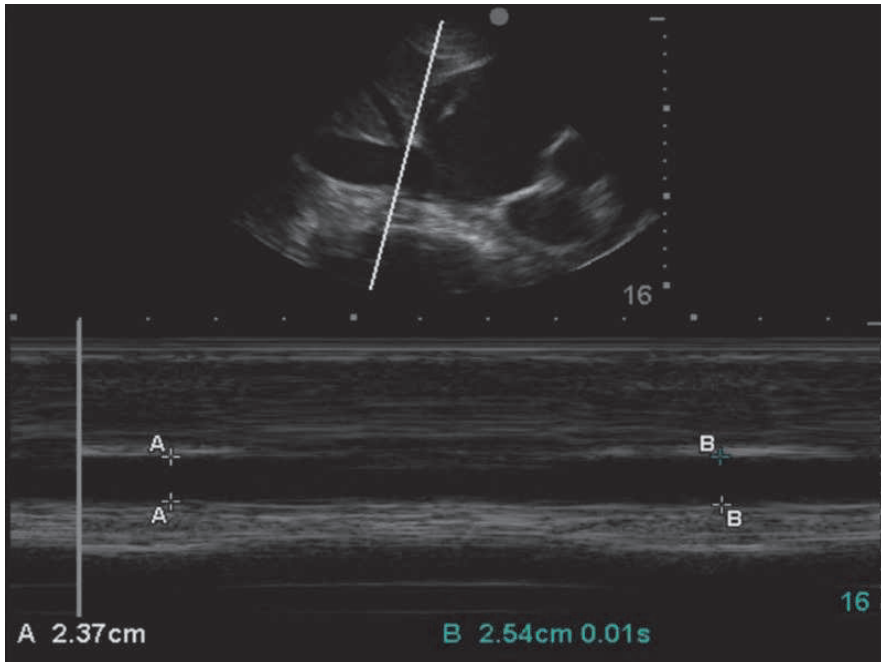
Fig. 2. Inferior vena cava diameter through the respiratory cycle using M mode.
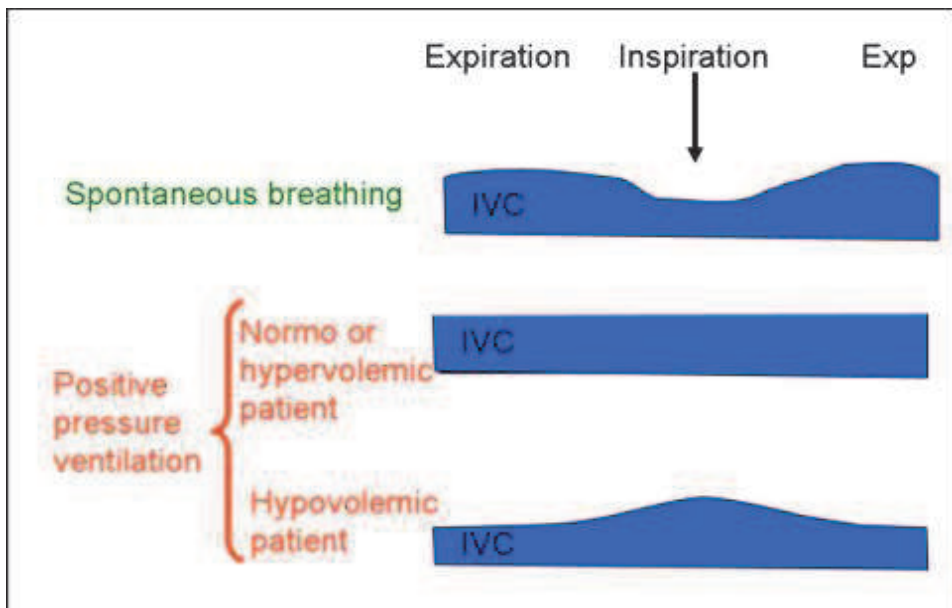

Fig. 3. Inferior vena cava diameter variations with the respiratory cycle.

This is especially true if the duration of hemodialysis is short and the ultrafiltration rate is rapid. It appears that inferior vena cava diameter before hemodialysis may be useful as an indicator of extracellular fluid overload. Inferior vena cava diameter measured at the end or shortly after hemodialysis may be misleading in assessing dry weight (Katzarski et al, 1997). Among hemodialysis patients a period of time must ensue between the attainment of dry weight and adequate control of blood pressure, a property termed the lag phenomen (Charra et al, 1998). In clinical practice, the dry weight is usually established by a progressive decrease in the post-dialysis body weight, usually over a 4-8 week period after the initiation of maintenance hemodialysis (Chazot et al, 1999). Acquired cystic kidney disease (ACKD) and hypertension are frequent complications of CKD. ACKD is a result of CKD, its prevalence and grade depending on the duration of CKD and dialysis treatment. We know that renal cysts are present prior to hemodialysis treatment in approximately one third of all patients. The prevalence of ACKD described in hemodialysis patients lies between 35 and 79% (Ishikawa, 1991). So far the literature offers only few data to clarify whether hypertension is also a possible complication of ACKD. Described are individual clinical cases of hypertension in patients with simple renal cysts. Some studies established a connection between simple renal cysts and hypertension in a large number of patients with normal renal function (Pedersen et al, 1993, 1997, Ekart et al, 2001). The question of whether perhaps ACKD is also involved in the pathogenesis of hypertension in hemodialysis patients and whether hypertension is also a complication of ACKD remains open. Hardly any studies dealing with this specific topic are to be found while the results of available studies do not clarify the likely involvement of ACKD in the development of hypertension in hemodialysis patients. The aim of our published study was to establish the prevalence and the grade of ACKD in patients on renal replacement therapy with hemodialysis, the frequency of hypertension in these patients as well as the possible connection between the presence of ACKD and hypertension in hemodialysis patients (Ekart & Hojs, 2006). In the study 86 hemodialysis patients (46 males and 40 females; mean age 51.3 years; mean duration of hemodialysis treatment 55.3 months) were included. Their native kidneys were examined with an ATL-HDI 3000 ultrasound device (2-4 MHz convex probe). Depending on the number of cysts in the kidney, the manifestations were divided into three grades: grade 0: no cysts; grade 1: less than ten cysts in both kidneys; grade 2: more than ten cysts in both kidneys. Blood pressure was measured 30 minutes before and after hemodialysis. Mean one-month values were analyzed. Hypertension was defined as systolic blood pressure of ≥ 150 mmHg, diastolic blood pressure of ≥ 90 mmHg and/or antihypertensive treatment. The diameter of the inferior vena cava (indicator of dry weight) was measured with the same ultrasound device as the kidneys 3 hours after hemodialysis. ACKD was present in 48 (55.8%) patients, there was no statistically significant difference regarding sex. 24 (50%) patients had grade 1 ACKD and 24 (50%) grade 2 ACKD. 68 (79.1%) patients suffered from hypertension, which was statistically significantly more common in male patients (p=0.048). In 68 (79.1%) patients hypertension was detected before hemodialysis and in 54 (62.8%) patients also after hemodialysis. 39 (45.3%) patients suffered simultaneously from ACKD and hypertension; 22 (56.4%) of them were males and 17 (43.6%) females. No statistically significant correlation between hypertension and ACKD was established. The prevalence and grade of ACKD were statistically significantly associated with the duration of dialysis treatment (p<0.01). Multiple regression analysis detected a significant correlation only between hypertension and the diameter of the inferior vena cava (p<0.05). Prevalence and

grade of ACKD increase with the duration of dialysis treatment. ACKD was not associated with hypertension. There was a correlation between the diameter of the inferior vena cava as a factor of circulating fluid volume and hypertension in hemodialysis patients (Ekart & Hojs, 2006).

2.2 Increased sympathetic activity

Sympathetic activity is a common finding in ESRD, correlating with the increase in both vascular resistance and systemic blood pressure (Converse et al, 1992). Investigators have demonstrated that sympathetic activity is increased in those patients on chronic hemodialysis who still have their native kidneys. Sympathetic nerve activity was found to be normal in hemodialysis patients with bilateral nephrectomy, leading to the hypothesis that sympathetic overactivity in uremia is caused by a neurogenic signal (carried by renal afferents) arising in the failing kidney (Augustyniak et al, 2002). This hypothesis is supported by rat studies showing that renal deafferentation abrogates hypertension in the 5/6 nephrectomy model of chronic renal insufficiency. In addition, in patients with chronic renal insufficiency and renin-dependent hypertension, sympathetic overactivity was normalized by chronic angiotensin converting enzyme inhibition but not by calcium channel blockade, implicating a major central neural action of angiotensin II. Factors such as renal ischemia, chronic inflammation, oxidative stress, obesity, nocturnal hypoxia, and elevated plasma levels of asymmetric di-methyl-arginine (ADMA) may contribute to increased sympathetic activity (Levin et al, 2010).

2.3 Activation of the renin – angiotensin - aldosterone system

Although many patients may have plasma renin activity in the normal range, inappropriately increased plasma renin activity in relation to exchangeable sodium has long been recognized in uremic patients with hypertension (Kornerup et al, 1984). That the renin-angiotensin system is activated even in hemodialysis patients is illustrated by the fact that renin is increased with ultrafiltration dialysis (Henrich et al, 1977) and infusion of angiotensin II antagonist, improves blood pressure. Furthermore, patients treated with the angiotensin-converting enzyme inhibitor lisinopril have a dose-dependent increase in plasma renin activity and an improvement in blood pressure (Agarwal et al, 2001). Patients whose blood pressure is not controlled by maintenance of dry weight have increased plasma renin activity and demonstrate a dramatic improvement in hypertension control after interruption of the renin-angiotensin axis by bilateral nephrectomy (Bellinghieri et al, 1999).

2.4 Erythropoietin

Hypertension is a common adverse effect of erythropoietin therapy. It occurs more commonly in those people with preexisting hypertension, a positive family history of hypertension, rapid correction of anemia, or with severe anemia (Ishimitsu et al, 1993, Lebel et al, 1994, Bellinghieri et al, 1999). Nearly one third of renal failure patients treated with erythropoietin develop an increase in blood pressure of 10 mmHg or more (Eschbach et al, 1989). Although the exact mechanism by which erythropoietin increases blood pressure is not known, it may involve reduced nitric oxide activity due to scavenging by hemoglobin, increase in whole blood viscosity (Koppensteiner et al, 1990), and increased vascular reactivity to norepinephrine (Hand et al, 1995) or other mechanisms (Bode-Boger et al, 1996). There also may be more hypertension associated with the intravenous route of administration and larger dose ranges.

2.5 Endothelium – derived factors

The endothelium plays an important role in the regulation of vasomotor tone. Endothelin-1, an endothelium-derived peptide with vasoconstrictive and mitogenic effects on smooth muscles, is involved in vascular tone regulation and in the pathogenesis of atherosclerosis (Stefanidis et al, 2004). Elevated plasma levels of endothelin-1 have been found in uremic patients. The concentrations of other endothelin isoforms also may be increased, but only endothelin-1 has been linked to the high blood pressure. Endothelium-derived nitric oxyde plays a critical role in the maintenance and regulation of vascular tone and modulates key processes mediating vascular disease, including leukocyte adhesion, platelet aggregation, and vascular smooth muscle proliferation (Furchgott, 1996). The endothelium also produces potent vasodilators, such a prostacycline and nitric oxide. Endothelial nitric oxide synthase enzymatically produces nitric oxide from the substrate L-arginine. L-arginine supplementation can partially reverse renal failure – associated endothelial dysfunction. A circulating inhibitor of nitric oxide synthase, ADMA, competes with L-arginine for nitric oxide synthase. In humans with salt-sensitive hypertension, administration of a high-salt diet increases plasma ADMA and blood pressure (Fujiwara et al, 2000). Circulating ADMA is increased in subjects with CKD (Vallance et al, 1992) and ESRD (Mallamaci et al, 2004) and may contribute to endothelial dysfunction and increased blood pressure. In ESRD patients, ADMA is a death predictor (Aucella et al, 2009) and is correlated with increased left ventricular thickness and reduced ejection fraction, consistent with its ability to increase systemic vascular resistence (Zoccali et al, 2002). Oxidative stress leads to the accumulation of ADMA and promotes endothelial dysfunction. Inflammation, increased homocysteine levels, reduced antioxidant defenses, and increased free radicals in ESRD may therefore provide an explanation for the relationship between oxidative stress, endothelial dysfunction, and the generation of hypertension.

2.6 Parathyroid hormone excess secretion

There may be a correlation between an increase in intracellular calcium levels induced by parathyroid hormone excess and hypertension. Calcium entry into smooth muscle cells of the blood vessels can lead to vasoconstrition and hypertension. Some observations linking the correction of hyperparathyroidism by either vitamin D administration or parathyroidectomy in chronic dialysis patients, resulting in a lower blood pressure, have supported this hypothesis. In one small series, administration of alfacalcidiol, a vitamin D analogue, to treat hyperparathyrodism resulted in significant decreases in levels of parathyroid hormone, platelet intracellular calcium, and mean blood pressure (Raine et al, 1993).

2.7 Renal vascular disease

Ischemic renal disease is defined as a clinically important reduction in glomerular filtration rate (GFR) or loss of renal parenchyma caused by hemodynamically significant renal artery stenosis. Many patients with a presumed diagnosis of hypertensive nephrosclerosis actually have undiagnosed ischemic nephropathy as the etiology of their ESRD. It is important for the clinician to identify ischemic renal disease, because ischemic renal disease is a potentially reversible cause of chronic renal failure in a hypertensive patient. Atherosclerotic renal artery disease is common among patients with coronary artery disease and aortic and peripheral vascular disease. Atherosclerotic renal artery disease is a progressive disorder,

and its progression is associated with loss of renal mass and functioning (Preston & Epstein, 1997). In a review of hypertension in ESRD patient, the diagnosis of ischemic nephropathy and renal vascular disease should not be overlooked.

2.8 Reduced production of prostaglandins/bradykinins

The kidneys produces several vasodilating substances such as kinins, prostaglandins, or antihypertensive neural renomedullary lipids, and decreased production and activity of these substances could play a role in the pathogenesis of hypertension. Indeed, decreased blood levels of vasodilating prostaglandin PgE_2 have been observed in hypertensive ESRD patients, and a negative correlation between the prostacyclin metabolite 6-keto-PgF1α and blood pressue has been observed in uremic patients.

3. Time of measurement of blood pressure, definition, and meaning of hypertension in hemodialysis patients

3.1 When should blood pressure be measured?

The prevalence of hypertension in hemodialysis patients is very high: in the time of progression from different stages of CKD to ESRD is between 40 and 90% (Salem, 1995, Agarwal & Lewis, 2001, Agarwal, 2002). Despite this high prevalence, there is limited knowledge about how to manage it in hemodialysis patients. Blood pressure variability is present in all people but is particularly prevalent in hemodialysis patients. This greater variability is related to the following: changes in volume status, change of sympathetic activity, hypotensive episodes during hemodialysis, antihypertensive drugs concentration and their dialyzability, erythropoietin, renin-angiotensin-aldosterone system activation, secondary hyperparathyroidism and other factors. Unlike the general population, for which there is a clear consensus of how to measure blood pressure and the blood pressure goal that is needed to reduce risk, this is not the case for people who receive renal replacement therapy. Moreover, in the patient with ESRD, a consensus for how to measure blood pressure has not been reached. In hemodialysis patients we can see blood pressure changes during hemodialysis in the dialysis center and in the interdialytic period. Which blood pressure should be taken to signify hypertension is more pertinent in dialysed individual than in the general population because of their fluctuating fluid status and other factors associated with the hemodialysis session. In the general hypertensive population it is known that the use of single measurements as a reliable indicator of the overall blood pressure control is fraught with difficulty because of transient and persistent elevations of pressure in clinical settings (Mezzeti et al, 1997). The variability of casual measurements in relation to the dialysis cycle confound management decisions and pose a dilemma with regard to the optimum timing and method of blood pressure measurement in this setting. Treatment decisions are mostly based on pre-dialysis blood pressure measurements. However the relevance of these measurements has been questioned. Several options exist for blood pressure measurement in hemodialysis patients, such as pre- or post-dialysis blood pressure, ABPM, and interdialytic home blood pressure. There is a marked difference in blood pressure between the pre-, post- and interdialytic period. It is unclear as to which time of blood pressure measurement best reflects the burden of hypertension and correlates best with cardiovascular outcomes (Rahman, 2005). Pre-dialysis blood pressure often overestimated basal blood pressure while post-dialysis blood pressure underestimated it,

although the latter is closer to the basal blood pressure value. Blood pressure variability pre-dialysis, post-dialysis and in interdialytic period is the reason for different conclusions in the studies – studies concluded, that the most important and representative are pre-dialysis (Conion et al, 1996, Agarwal, 1999), post-dialysis blood pressure measurements (Kooman et al, 1992, Mitra et al, 1999), in other study there were most representative the combination of pre- and post-dialysis blood pressure values (Coomer et al, 1997).

It is well known »white-coat effect«, which is defined as transient rise in blood pressure that occurs in the clinical settings (Myers et al, 1997). ABPM is required for the diagnosis of the white-coat effect. Mitra et al compared interdialytic ABPM with blood pressure obtained in hemodialysis patients at arrival to the dialysis center, after 10 minutes of rest in a quiet room, and at other time points (Mitra et al, 1999). White-coat effect was defined as the rise in blood pressure of > 20/10 mmHg in the reading on attendance to the dialysis center above the daytime ambulatory blood pressure during the 6 hours prior to attending the dialysis center (Mitra et al, 1999). White-coat effect was observed in 41% patients at arrival to dialysis center and this effect did not persist throughout the dialysis session (Mitra et al, 1999). The timing of the dialysis session did not influence the presence of white-coat effect, which persists even in patients on antihypertensive therapy (Mitra et al, 1999). The white-coat effect may be more common in renal patients than in the general hypertensive population perhaps due to an exaggerated sympathetic response conditioned by uremia (Rosansky et al, 1995). The timing of casual pre-dialysis and post-dialysis blood pressure measurement is crucial. Both can be biased by the dialysis procedure itself. The traditional diagnosis of hypertension based solely on pre-dialysis clinic measurements can lead to gross overestimation attributable to a white-coat effect. The best single approximation of interdialytic blood pressure is the 20-min post-dialytic measurement (Mitra et al, 1999). Canella and associates have pointed out that »false normotensive classification to subjects who are actually hypertensive, may possibly cause the link between arterial hypertension and left ventricular hypertrophy to be missed« (Canella et al, 2000). Those patients who have normal blood pressure in the dialysis center, but increased blood pressure outside the dialysis center as assessed by ABPM have »masked hypertension«. In an elderly population of patients with essential hypertension but without kidney disease, 9% were found to have masked hypertension (Bobrie et al, 2004). The cardiovascular prognosis of such patients is similar to that of poorly controlled hypertensives. The causes of masked hypertension in the dialysis population are not known. However, sleep apnea, which commonly occurs in hemodialysis patients, may be an important cause of masked hypertension. Sleep apnea causes a nocturnal increase in blood pressure, the magnitude of which increases with the severity of sleep apnea (Zoccali et al, 1998). The daytime blood pressure in these patients may not be elevated or may not accurately reflect the cardiovascular burden of hypertension; ABPM may be of particular value in assessing cardiovascular risk in such individuals. Hemodialysis blood pressure measurement and ABPM correlation is poor. A recent meta-analysis showed that pre- and post-dialysis blood pressure measurements are imprecise estimates of interdialytic ambulatory blood pressure (Agarwal et al, 2006a). In this meta-analysis median pre-dialysis systolic blood pressure and diastolic blood pressure were 8.6 and 2.6 mmHg higher than ABPM, respectively. In a single-center cross-sectional study, 1-week-averaged home systolic blood pressure was similar to interdialytic ABPM and superior to pre- and post-dialysis blood pressure in predicting left ventricular hypertrophy; diastolic blood pressure was not associated with left ventricular hypertrophy (Agarwal et al,

2009a). In an earlier study, ABPM added minimal information to the prediction of left ventricular hypertrophy, compared with the average of 12 routine pre-dialysis blood pressure measurements (Zocalli et al, 1999). Although a worthy goal, neither measurement of ABPM nor self-measured home blood pressure may be feasible for most patients throughout the world, leaving pre-dialysis and post-dialysis blood pressure measurements to be used, but with caution and with the knowledge that these are inferior (Levin et al, 2010).

3.2 Target blood pressure and what blood pressure level defines hypertension in chronic hemodialysis patients

There is still no consensus about whether to lower increased blood pressure in hemodialysis patients or the level to which blood pressure should be targeted (Agarwal, 2005, Foley & Agarwal, 2007). Hypertension is common and difficult to control and define in ESRD patients undergoing hemodialysis. ESRD patients are most frequently characterized by an increased systolic blood pressure with diastolic blood pressure within the normal range (<90 mm Hg) or even lower, resulting in increased pulse pressure. The increased systolic blood pressure is already found in young hemodialysis population. Diastolic blood pressure is usually higher in younger hemodialysis patients and declined with advancing age. All these changes result in a blood pressure pattern close to that observed in older subjects in general populations, i.e., isolated (or predominant) systolic hypertension, and attributable to »accelerated ageing« in ESRD. The definition of blood pressure targets and normotension in ESRD is not defined and in the absence of prospective controlled interventional studies, values accepted for general populations (<140/90 mm Hg) cannot be extrapolated to uremic patients.

In ESRD patients consensus to which level blood pressure should be reduced has not been reached. For definition and treatment of hypertension in hemodialysis patients, we need to know exactly blood pressure measurements. To evaluate blood pressure fluctuations better over the 2-days period (on the hemodialysis and on interdialytic day), ABPM is the gold standard to define a hemodialysis patient`s blood pressure. ABPM can provide information during sleep and early morning awakening, when blood pressure and cardiovascular risk are highest (Hopkins & Bakris, 2009a). In the general population, ABPM provided a more accurate prediction of cardiovascular outcomes than office blood pressure (Levin et al, 2010). Blood pressure levels defining the presence or absence of hypertension differ with the use of pre-dialysis, post-dialysis, self-measured home blood pressure, and ABPM. The recent National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines suggest that pre-dialysis and post-dialysis blood pressure should be <140/90 and <130/80 mmHg, respectively (K/DOQI Workgroup, 2005). These targets were largely based on the expert judgment of the workgroup, applying weak evidence. Future research will decide whether the definition of hypertension on the basis of home blood pressure should be the same as that for the general population, as outlined in the Seventh Report of the Joint Natonal Committee (JNC 7) (Chobanian et al, 2003), with systolic blood pressure > 139 mmHg or diastolic blood pressure > 89 mmHg. In summary, the target goals should be realized upon individual patient. In some younger patients, the target blood pressure may even be set as low as 120/80 mmHg.

4. Blood pressure measurement in hemodialysis patients

In patients with ESRD, routine clinic and dialysis center blood pressure measurements may be poor indicators of blood pressure control. Patients on hemodialysis typically do not have their blood pressure measured under standardized conditions, a source of error in the assessment of their blood pressure. There are some unique sources of error involving interdialytic weight gain, occurence of sleep apnea and consequent nocturnal hypertension, inability to take blood pressure in both arms in patients who have hemodialysis angioaccess in the arm, and the white coat effect in these patients as well (Agarwal, 2002). Although blood pressure is measured frequently in the dialysis treatment enviroment, the technical aspects are often unsatisfactory. The recommendation for measuring blood pressure in the general population includes the patient´s sitting quietly upright in a chair for approximately 5 min with the arm supported at heart level. In addition, an appropriately fitting sphygmomanometer cuff is recognized as vital to accurate readings (Chobanian et al, 2003). Conversely, there remains disagreement concerning the utility and reproducibility of such method in hemodialysis patients. In most studies of ESRD patients, dialysis center measurements were used to explore the relationship between hypertension and cardiovascular events. However, dialysis center measurements fail to accurately characterize blood pressure in ESRD patients on hemodialysis, making it difficult to define the prognostic significance of hypertension in this population (Thompson & Pickering, 2006). ABPM has a better reproducibility than isolated or aggregated pre-dialysis and post-dialysis blood pressure values (Peixoto et al, 2000). Out-of-office blood pressure measurements (home blood pressure or ABPM) are better predictors of target organ damage and mortality in patients with essential hypertension and in patients with kidney disease (Agarwal et al, 2009a). The reproducibility of blood pressure measurements followed the following order: home blood pressure monitoring > ABPM >> pre-dialysis blood pressure > post-dialysis blood pressure (Agarwal et al, 2009b). A substantial number of prospective studies has shown that ABPM predicts cardiovascular events better than clinic-based readings, and also correlates more closely with target organ damage. In many studies a poor correlation was found between dialysis center measurements and ABPM readings obtained in the interdialytic period (Thompson & Pickering, 2006). In a study performed with ABPM in a group of dialysis patients, 44-hour interdialytic ABPM was compared with dialysis center measurements taken by a nurse. In that study, 43% of patients classified as hypertensive by pre-dialysis systolic blood pressure were normotensive on ABPM, whereas 25% of patients classified as normotensive by pre-dialysis systolic blood pressure were hypertensive (Santos et al, 2003). However, other studies found good agreement between average pre-dialysis blood pressure and interdialytic ABPM (Agarwal & Lewis, 2001). Changes that occur in ABPM during the interdialytic period likely account for the discrepancies with dialysis center measurements found in some studies. Conlon et al averaged dialysis center measurements from multiple visits and showed that pre-dialysis blood pressures averaged over 12 treatment sessions showed a strong correlation with ABPM (Conlon et al, 1996). Based on the results of 48-h ABPM in 36 hemodialysis patients, Coomer et al developed a model to predict mean blood pressure based on age, sex, race, and pre- and post-dialysis blood pressure (Coomer et al, 1997). Agarwal and Lewis compared ABPM with a 2-week average of dialysis center measurements in 70 dialysis patients and found that a 2-week average cutoff pre-dialysis blood pressure of 150/80 mmHg or higher had 80% sensitivity and 67% specificity to detect interdialytic hypertension as defined by an average ambulatory blood pressure of 135/85 mmHg or higher (Agarwal & Lewis, 2001).

Although these methods can be used to obtain a better estimate of interdialytic control, they cannot reliably determine blood pressure in any individual patient. Home blood pressure monitoring and standardized predialysis blood pressure measurements can aide in the assessment of blood pressure control. In a prospective cross-sectional study, home blood pressures averaged over one week were shown to be superior to routine dialysis center measurements averaged over 2 weeks in predicting hypertension on 44-h ABPM. Standardized pre-dialysis blood pressure averaged over 2 weeks had similar predictive ability as home measurements (Agarwal et al, 2006b). ABPM is superior to dialysis center blood pressure measurements in predicting target organ damage in patients with ESRD (Thompson & Pickering, 2006). In one of the largest study to date 44-h ABPM and home blood pressure monitoring, although weak determinants of left ventricular hypertrophy, were superior to a 2-week average of standardizes and routine dialysis center measurements in 140 chronic hemodialysis patients (Agarwal et al, 2006c). The correlation between left ventricular hypertrophy and blood pressure was similar using ABPM and an average of 12 standardized pre-dialysis measurements in a study of 35 stable hemodialysis patients (Conlon et al, 1996). In last decade, a few studies have assessed the prognostic power of ABPM and outcomes in hemodialysis patients (Amar et al, 2000, Liu et al, 2003, Tripepi et al, 2005, Agarwal et al, 2007, Moriya et al, 2008, Agarwal, 2010). In all these four studies ABPM contain greater prognostic information compared to blood pressure measurements in the dialysis center. The use of out-of-office blood pressure measurement techniques including self-measured blood pressure and ABPM in the management of hemodialysis patients is increasing. In the general population, blood pressure falls on average by 10-20% during sleep, a phenomen reffered to as »dipping«. In about 25% of healthy subjects, and in certain disease states, however, a loss in diurnal variation in blood pressure has been reported (non-dipping) (Thompson & Pickering, 2006). Non-dipping is particularly common in both children and adults with CKD, and an inverse relationship between GFR and the prevalence of non-dipping has been described (Farmer et al, 1997). Although the reported prevalence of non-dipping in adults with CKD varies, rates of 50% or higher have been observed at the earliest stages of disease, whereas rates of more than 80% have been observed in patients on dialysis (Farmer et al, 1997). A loss of diurnal variation in blood pressure has been associated with a poor renal prognosis and linked to left ventricular hypertrophy, adverse cardiovascular outcomes, and all-cause mortality in patients with ESRD. In a study of 59 hemodialysis patients, a correlation was found between the day/night ratio and left ventricular mass index (Rahman et al, 2005). In a cohort of 80 dialysis patients without a history of congestive heart failure or significant cardiovascular disease, non-dipping status was associated with an increased adjusted hazard ratio for cardiovascular morbidity and mortality (Liu et al, 2003). A study of 57 hypertensive ESRD patients without a history of systolic cardiac disfunction or valvular disease found that after controlling for age, sex, and cardiovascular history, an elevated nocturnal blood systolic blood pressure was associated with increased cardiovascular mortality (Amar et al, 2000). In a study by Tripepi et al, 168 dialysis patients without a history of diabetes, cardiovascular disease, or clinical evidence of heart failure were followed for 38 months. In a multi-regression analysis model not including left ventricular hypertrophy, an association between the highest night/day blood pressure tertile and increased cardiovascular and all-cause mortality was found. In contrast, the predialysis blood pressure averaged over one month did not predict events (Tripepi et al, 2005). Why this loss of nocturnal variation carries such a poor prognosis is unknown. It is possible that the absence of a nocturnal decline in blood pressure is not itself a cause of

adverse outcomes, but is instead just a marker of sicker patients. In the meantime, ambulatory or some form of home blood pressure monitoring should be used to obtain a more accurate picture of blood pressure control in patients with ESRD. Clinic blood pressures frequently under- or overestimate the true blood pressure in CKD patients and dialysis center blood pressure measurements, although widely used to guide therapy, are poor indicators of interdialytic blood pressures.

5. Cardiovascular changes in hemodialysis hypertension

The association between uraemia and an increased risk of cardiovascular disease was first documented by Lindner (Lindner et al, 1974). Cardiovascular disease is the leading cause of morbidity and mortality in patients with ESRD (Guerin et al, 2006). Compared to the general population the annual cardiovascular death rate in dialysis patients is higher for all age groups, though particularly for the young whose mortality is up to 100 times greater than the general population. The average life expectancy of patients with ESRD is approximately 5 years, regardless of the modality of dialysis. Most patients with ESRD have a higher prevalence of traditional and also nontraditional cardiovascular disease risk factors when compared to the general population. The associations between traditional cardiovascular disease risk factors and atherosclerosis such as age, diabetes mellitus, hypertension, smoking, obesity, and dyslipidemia have been well described in dialysis patients. Cardiac deaths account for the majority of cardiovascular deaths in dialysis patients. The exact etiologies of these cardiac deaths are often unknown and likely include primary and secondary arrhythmias, cardiomyopathy, and coronary artery disease, and involve complex pathogenes. Although fluid overload, increased afterload from hypertension and vascular calcification, calcified valvular disease, and ischemia are probably important contributory factors, uremia per se seems to be an additional factor. To what extend hyperkalemia and hypokalemia, frequently present in this patients, contribute to the high incidence of sudden death in dialysis patients is not certain, but recent papers suggested the greater danger of hypokalemia (Karnik et al, 2001, Herzog et al, 2008,). Hypertension is a frequent finding in all stages of CKD. Because the pathogenesis of atherosclerosis in patients with CKD is multifactorial, it has been difficult to ascertain the precise role of hypertension in its development. Hypertension increases nearly linearly as renal function falls, and the vast majority of patients with significant renal failure present with high blood pressure. Blood pressure control is of paramount importance in slowing the progression of CKD toward ESRD, and also decreasing cardiovascular risk in these patients. Adequate blood pressure control should be a major objective in the management of patients with CKD in both the earlier and late stages. Uncontrolled hypertension in pre-ESRD patients is an important predictor for cardiovascular mortality during ESRD. More than 80% of patients have a history of hypertension, and more than two-thirds of these are uncontrolled (Agarwal et al, 2003). Foley et al found in a study with 432 hemodialysis patients that high blood pressure during dialysis therapy was associated with several adverse outcomes, including concentric left ventricular hypertrophy, left ventricular dilatation, ischemic heart disease and cardiac failure (Foley et al, 1996). They found an inverse association between average blood pressure level while on dialysis and mortality. Low blood pressure was associated with earlier death independently of age, diabetes, ischemic heart disease, anemia and hypoalbuminemia. There was an inverse relationship between average blood pressure and mortality (Foley et al, 1996). Port et al in a study of 4499 hemodialysis patients found the

association of a low pre-dialysis systolic blood pressure with an elevated adjusted mortality risk (relative mortality risk = 1.86 for systolic blood pressure < 110 mmHg, P < 0.0001) (Port et al, 1999). A »U-shaped« curve (Figure 4) exists between blood pressure level and mortality in hemodialysis patients, with higher mortality noted at lower levels of blood pressure <120 mmHg and levels >180 mmHg measured before hemodialysis (Zager et al, 1998, Port et al, 1999, Kalantar-Zadeh et al, 2005, Luther & Golper, 2008, Hopkins & Bakris, 2009b). An analysis based on the CREED study cohort adjusted for Framingham risk factors, background cardiovascular complication, and left ventricular mass and ejection fraction shows that the risk of death is lowest in dialysis patients with a pre-dialysis systolic blood pressure between 100 and 125 mmHg (Zager et al, 1998), whereas systolic blood pressure > 150 mmHg was associated with increased mortality (Zoccali, 2003). Both post-dialysis systolic blood pressure ≥ 180 mmHg and diastolic blood pressure ≥ 90 mmHg were associated with a substantial increase in cardiovascular mortality (Zager et al, 1998). Severe cardiomyopathy modifies the relationship between blood pressure and mortality, and survival is very low in ESRD patients with systolic blood pressure < 115 mmHg (Klassen et al, 2002, Li et al, 2006).
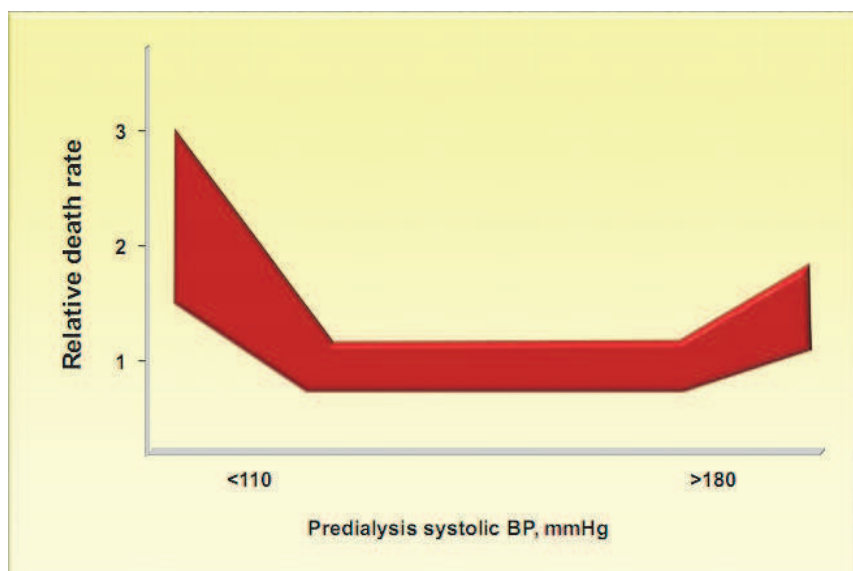

Fig. 4. Basic relationship of blood pressure to mortality in dialysis patients, as obtained from observational studies (Luther & Golper, 2008).

In an observational study in incident hemodialysis patients pre-dialysis systolic blood pressure ≥ 200 mmHg was associated with increased mortality or cardiovascular events (Li et al, 2006). Therefore, pre-dialysis blood pressure above this level should be treated aggressively. It is assumed, that carotid intima media thickness (IMT) is mirror for general atherosclerosis. IMT and plaque occurrence in the carotid arteries are strong predictors for cardiovascular events in the general population (Burke et al, 1995). B-mode ultrasound imaging is a useful and noninvasive tool to directly quantitate the atherosclerotic burden (Kato et al, 2003). Hemodialysis patients are known to have an advanced carotid IMT

compared with age- and gender-matched normal controls (Kato et al, 2003). We performed the study in which determined that carotid IMT, measured with high resolution B-mode ultrasound, may be usefully applied for cardiovascular mortality risk stratification in non-diabetic HD patients (Ekart et al, 2005). Ninety-nine non-diabetic hemodialysis patients were included in the study. During a follow-up of 42.4 ± 19.5 months (from 12 to 76 months) 33 patients died, 19 (57.6 %) of them of cardiovascular causes (myocardial infarction, sudden cardiac death, heart failure, cerebrovascular insult). In these patients IMT values of the common carotid arteries was significantly higher (0.89 vs 0.69 mm; P < 0.0001) than in those who survived. Correlation between cardiovascular mortality and IMT was also found (r = 0.433; P < 0.001). Hemodialysis patients were divided in relationship to the tertiles of IMT and the survival rates were analyzed using Kaplan-Meier curves (Figure 5).The risk for cardiovascular death was progressively higher from the first tertile of IMT onward (log rank test; P < 0.0006). In a Cox regression model that included calcium, phosphate, intact parathyroid hormone (iPTH), duration of dialysis treatment, smoking, presence of hypertension, cholesterol (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol), triglycerides and lipoprotein (a), IMT turned out to be an independent predictor of cardiovascular death (P < 0.025). Our results suggest that measurement of IMT thickness in patients with ESRD could be a good predictor for the risk of cardiovascular event and also for cardiovascular death (Ekart et al, 2005).
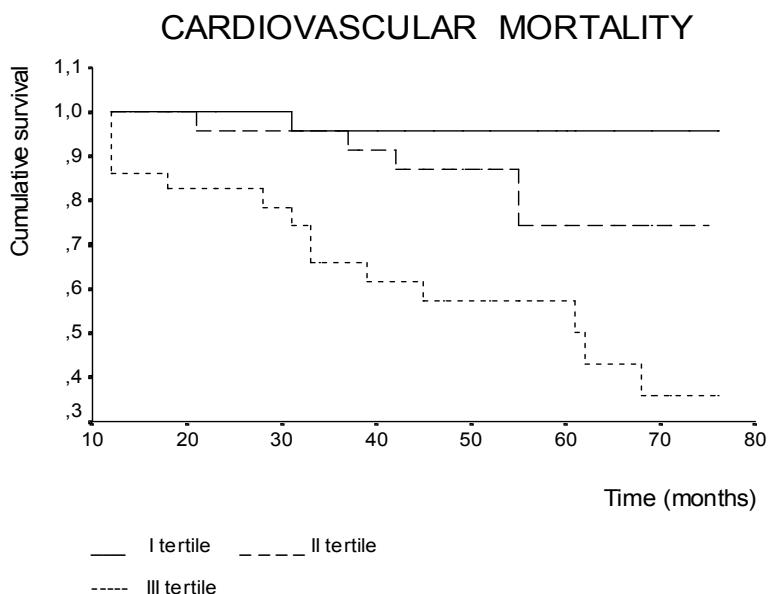

Fig. 5. Hemodialysis patients (N=99) were divided in relationship to the tertiles of IMT: I tertile, <0.65 mm; II tertile, ≥ 0.65 and < 0.8 mm; III tertile, ≥ 0.8 mm. Survival rates were analyzed using Kaplan-Meier curves. (Ekart et al, 2005).

We also performed a cross-sectional study in which we assess the relationship between carotid IMT as a marker of asymptomatic atherosclerosis and blood pressure measurements

obtained with a standard mercury sphygmomanometer before and after the hemodialysis session, the average one-monthly values of the routine blood pressure measurements and 24- and 48-hour ABPM (Ekart et al, 2009). Hypertension was defined as systolic blood pressure of 140 mmHg (ABPM ≥ 135 mmHg), diastolic blood pressure of ≥ 90 mmHg (ABPM ≥ 85 mmHg) and/or also lower levels if the patient was taking antihypertensive drugs. In 85 hemodialysis patients we found statistically significant correlation between carotid IMT and average one-monthly pre-hemodialysis diastolic blood pressure (P<0.05), diastolic blood pressure on the hemodialysis day ABPM, interdialytic day ABPM and 48-hour ABPM (P<0.05). We also found a high prevalence of uncontrolled blood pressure despite treatment with antihypertensive drugs (Figure 6). The possible reason for uncontrolled hypertension in hemodialysis patients is probably bad compliance and withholding antihypertensive drugs on the hemodialysis day. Using multiple regression analysis we found statistically significant correlation only between carotid IMT and diastolic blood pressure on the hemodialysis day ABPM, interdialytic day ABPM and 48-hour ABPM (P<0.05). It is important that carotid IMT correlated only with long-term blood pressure measurements (one-monthly, 24- and 48-hour ABPM). Isolated systolic hypertension was more prevalent compared with isolated diastolic hypertension. It was interesting finding about casual connection between carotid IMT and values of diastolic blood pressure on the hemodialysis day ABPM, interdialytic day ABPM and 48-hour diastolic blood pressure values (Ekart et al, 2009).
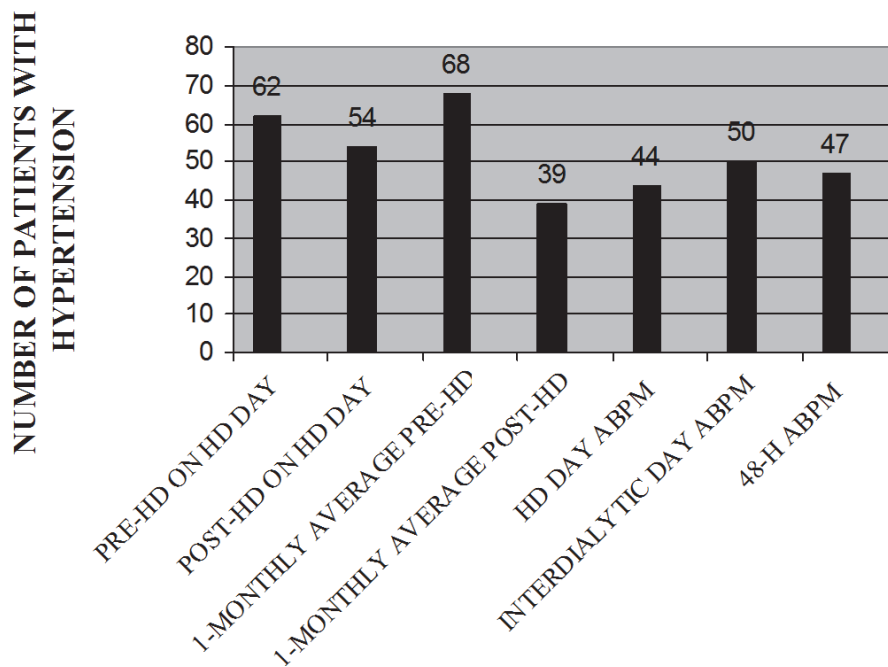

Fig. 6. Prevalence of uncontrolled hypertension in hemodialysis patients (N=85): different blood pressure measurements and not regarding treatment with antihypertensive drugs; HD=hemodialysis; (Ekart et al, 2009).

6. Treatment

The complex pathogenesis of hypertension in hemodialysis patient explains the difficulty of its treatment. Management of blood pressure in hemodialysis population requires both generally applicable plans and individualization in order to determine the blood pressure target and the treatment regimen. For patients with essential hypertension, CKD not yet on dialysis, and those with diabetes mellitus, clear guidelines on blood pressure targets exist. There are no such guidelines for ESRD patients on hemodialysis. The reason is because no randomized controlled trials have been performed in this patients to demonstrate the advantages of a given blood pressure target. Very low blood pressure in these individuals may make them intolerant to the hemodynamic stress of hemodialysis. An ideal blood pressure for a dialysis patient is the lowest that ensures hemodynamic stability during dialysis as well as orthostatic tolerance immediately postdialysis and is associated with good health-related quality of life. Such a blood pressure should also be associated with the lowest cardiovascular morbidity and mortality. A single blood pressure target may not be appropriate for all hemodialysis patients. Those patients who are older, who have vascular disease, and those with underlying diabetes may have different blood pressure goals than those with more pliable circulations and little or no left ventricular hypertrophy. Even though blood pressure targets are not defined for hemodialysis patients, most clinicians agree that treatment of high blood pressure is warranted. It seems that reaching a pre-dialysis blood pressure in the range of 130-160 mmHg/80-100 mmHg is safe and advisable (Peixoto & Santos, 2010).

6.1 Control of volume status

Whatever the target chosen, the strategies should focus first on management of salt and water balance, as control of extracellular fluid volume is associated with better blood pressure control (Katzarski et al, 1999). This includes dietary sodium restriction (Kayikcioglu et al, 2009), increased ultrafiltration and closer attention to the dialysate sodium prescription. The control of overhydration in ESRD patients is also of primary importance. The absolute content of total body water and sodium must be at level that does not cause signs and symptoms of volume overload, including hypertension and signs and symptoms of sodium and water depletion, such as dizziness and hypotension. The primary goal in the treatment of hypertension should be to attain a dry-weight. In the Tassin experience, the »dry weight method«, must be applied and is efficient to correct hypertension in these patients. Avoidance of large weight gains in the interdialytic period is desirable. To achieve this goal, patients should adhere to a restricted salt diet (750-1000 mg os sodium per day), which also helps decrease thirst (Mailloux, 2000, Locatelli et al, 2004). The clinician must define the dry weight and goal blood pressure for each dialysis patients based upon his or her best judgment. In attempting to achieve dry weight, particularly in incident patients starting dialysis, clinicians should me mindful also of the lag in time (from several weeks to months) between correction of extracellular volume and hypertension (Charra et al, 1998). The lag phenomenon reflects the time required to convert the patient from a catabolic to an anabolic state, a period in which extracellular fluid space slowly stabilizes (Charra et al, 1998). Two other factors may limit the degree of fluid removal by predisposing to episodes of hypotension during the hemodialysis procedure: antihypertensive drugs; and rapid fluid removal required by shorter dialysis times. Thus, tapering drug therapy and gradual fluid removal may be beneficial in patients in whom

hypotension during dialysis prevents the attainment of dry weight and a normal blood pressure.

6.2 Prolonged and or more frequent hemodialysis

Longer and/or more frequent dialysis results in better blood pressure control both in observational studies and in clinical trials (Walsh et al, 2005, Chan, 2009). In most programs of long daily hemodialysis, 80-95% of patients are normotensive without medications. Patients in a dialysis center in Tassin, France and some home hemodialysis patients undergo long, slow hemodialysis in which the standard regimen is eight hours, three times per week. This regimen is associated with the maintenance of normotension without medications in allmost all patients (Charra et al, 1992, Covic et al, 1999, McGregor et al, 1999). Although these results have been largely attributed to optimal volume control, other factors may also contribute, such as more complete control of uremia (Chazot et al, 1995), which may decrease afferent renal nerve activity and efferent sympathetic activation (Converse et al, 1992). A subset of these patients are normotensive despite the presence of increased extracellular fluid volume while having achieved clinical dry weight (Katzarski et al, 1999). Nocturnal hemodialysis, procedure in which dialysis is performed six or seven nights a week during sleep for a variable amount of time based upon the length of sleep desired (usually 6 to 12 hours in total), is also associated with excellent blood pressure control (Agarwal, 2003). Allmost all patients become normotensive without medications. To achieve this, the »target weight« is progressively decreased until all antihypertensive agents are discontinued (Henrich & Mailloux, 2010). Some studies also suggest that more frequent hemodialysis treatments, via short daily hemodialysis, may also be associated with normotension without medications and with regression of left ventricular hypertrophy (Henrich & Mailloux, 2010). The 2007 European Best Practice Guidelines recommend that the treatment time and/or frequency of dialysis should be increased in patients with hypertension despite optimal volume removal (Tattersall et al, 2007). The prescription of longer and/or more frequent hemodialysis sessions allows the decrease in ultrafiltration rate and reduces the risk of intradialytic complications (Brunet et al, 1996, Laurent & Charra, 1998, Okada et al, 2005).

6.3 Dialysate sodium management

Achievement of adequate extracellular fluid volume requires not only assessment of dry weight and ultrafiltration, but also minimization of exposure to sodium. This occurs by dietary salt restriction and optimization of the dialysate sodium prescription. Most hemodialysis patients have serum sodium levels that are lower than normal and have a relatively fixed set points at these lower levels (Peixoto et al, 2010). Because of these lower serum sodium levels, approximately two-thirds of patients will have a high dialysate-to-plasma sodium gradient if dialyzed against a typical dialysate sodium concentration of 140 mmol/l (Santos & Peixoto, 2008). This unfavorable gradient leads to decreased sodium dialysance, which contributes to sodium overload (Peixoto & Santos, 2010). Use of lower dialysate sodium levels (134-136 mmol/l) results in increased sodium removal (Manlucu et al, 2010) and, in most but not in all studies, better blood pressure control (Thein et al, 2007, Santos & Peixoto, 2010, Manlucu et al, 2010). This effect is the result of a modest (~10%) decrease in the extracellular to intracellular water volume ratio (Manlucu et al, 2010) and a 33% fall in peripheral vascular resistence (Farmer et al, 2000). However, indiscriminate

decreases in dialysate sodium may lead to hemodynamic instability and cramping in those patients whose baseline serum sodium is 140 mmol/l or higher. Therefore, individualizing the dialysate prescription to the patient`s own serum sodium is a preferable approach that results in decreased thirst, interdialytic weight gain and blood pressure without causing any increase in dialysis-related symptoms (De Paula et al, 2004). Attention to the prescribed dialysate sodium level is an essential part of achieving volume control in hemodialysis patients. Lowering the dialysate sodium level to match the patient`s own serum sodium is an effective means of accomplishing this goal.

6.4 Antihypertensive drugs

The majority of patients with ESRD on chronic dialysis undergoing standard thrice weekly treatment need antihypertensive drug therapy (Agarwal et al, 2003). Several observational studies have suggested that the use of antihypertensive drugs is associated with improved survival (Salem & Bower, 1996, Zager et al, 1998). Furthermore, among antihypertensive drugs, beta blockers have been reported to be associated with improved outcomes in observational studies (Foley et al, 2002). Therefore it appears that the use of antihypertensive drugs at least does not increase mortality among hemodialysis patients. Drug therapy for hypertension in hemodialysis patients includes all classes of antihypertensive drugs, but only selected patients may benefit from loop diuretic therapy (Hörl & Hörl, 2004). In addition to their antihypertensive effects, some drugs are variably cardioprotective, which may be independent of their blood pressure-lowering effects. The meta-analysis by Agarwal and Sinha showed a cardiovascular benefit for hypertensive hemodialysis patients from blood pressure lowering unlike what is suggested by observational studies (Agarwal & Sinha, 2009). However, the possibility that the benefits of antihypertensive drugs used in hemodialysis patients were because of non-hemodynamic actions is not ruled out. Pharmacokinetics of antihypertensive and putative cardioprotective drugs are altered by both impaired kidney excretion of the drugs and by their dializability. The multitude of drugs that these patients usually take reduces compliance, because of tolerability, interactions with other drugs, side effects, and financial costs (Schmid et al, 2009). Pharmacotherapy to lower blood pressure may cause additional problems that are unique to dialysis patients, such as intradialytic hypotension and vascular access thrombosis. The selection of antihypertensive drugs should be guided by considering their comorbidities, pharmacokinetics, and hemodynamic effects. For example, in patients with left ventricular hypertrophy, angiotensin converting enzyme (ACE) inhibitors may be effecting in causing regression (Paoletti et al, 2002). Hemodialysis patients may be more prone to side effects of certain drugs than patients with earlier stages of CKD. The presence of and propensity to these side effects may be easily overlooked. For example, minoxidil may potentiate or be confused with uremic pericardial effusion (Levin et al, 2010). A 2009 systematic review and meta-analysis of eight randomised controlled trials (three with and five without hypertensive patients) that enrolled 1679 dialysis patients found that lowering blood pressure with antihypertensive therapy was associated with decreased risks of cardiovascular events (RR of 0.71, 95% CI 0.55-0.99), all cause mortality (RR 0.80, 0.66-0.96) and cardiovascular mortality (0.71, 0.50-0.99) (Heerspink et al, 2009). Although there was significant variation in attained blood pressure, the overall mean decrease in systolic and diastolic blood pressure with active therapy was 4 to 5 mmHg and 2 to 3 mmHg, respectively. There were no studies that compared the efficacy of different antihypertensive agents. Additional limitations included the low number of patients, lack of information

concerning volume control, and marked variations in blood pressure reduction (Tomson, 2009). Despite these limitations, it generally appears that renin-angiotensin-system blockers, beta blockers, and calcium-chanell blockers provide similar efficacy in dialysis patients. Recommendations on antihypertensive drugs are usually based on their efficacy in blood pressure reduction, interdialytic and intradialytic pharmacokinetics, side-effect profile, independent cardioprotective effects and non-cardiovascular effects of the specific class, as well as on the comorbidities of the patient. Calcium-chanell blockers are both effective and well tolerated in dialysis patients, even in those who are volume expanded (London et al, 1990). The only randomized prospective study found, that amlodipine, compared with placebo, improved overall mortality among hypertensive dialysis patients (Tepel et al, 2008). Calcium-channel blockers are particularly useful in patients with left ventricular hypertrophy and diastolic dysfunction. Calcium-channel blockers do not require supplementary postdialysis dosing. ACE inhibitors are well tolerated and are particularly effective in patients with heart failure due to systolic dysfunction and in many patients after myocardial infarction. The 2006 K/DOQI guidelines also suggest that ACE inhibitors and/or angiotensin II receptor blockers (ARB) are preferred in dialysis patients with significant residual renal function (K/DOQI, 2006). These agents may help preserve native kidney function. ACE inhibitors and ARB are associated with a decrease in left ventricular mass among hemodialysis patients (Canella et al, 1997, Tai et al, 2010). ARB and ACE inhibitors have similar issues in terms of adverse effects, including hyperkalemia and possible dampened erythropoiesis (Hörl & Hörl, 2004). Beta blockers are particularly indicated in patients who have had a recent myocardial infarction. As in nonuremic subjects, ESRD patients who have heart failure due to systolic dysfunction may also benefit from therapy with a beta blockers. Such therapy should be initiated at very low doses to minimize the risk of hemodynamic deterioration. In addition, beta blockers should be used cautiously in patients also taking a calcium-channel blocker, since there are often additive negative chronotropic and inotropic actions.

7. Summary

Hypertension is common in hemodialysis patients with major implications for survival. Accurate measure of blood pressure is an essential precursor for management. Pre- and post-dialysis blood pressure measurement may not reflect the average blood pressure experienced by the patient. Most management decisions for the diagnosis and treatment of hypertension are made using blood pressure measurements made in the dialysis center. However, ABPM and home blood pressure recordings may be of superior prognostic value. They are generally superior to the dialysis center blood pressure measurements in predicting long-term prognosis. In addition, ABPM and home blood pressure recordings significantly and strongly predict cardiovascular events. The reference standard for diagnosing hypertension among hemodialysis patients is 44-48 hour interdialytic ABPM. Hypervolemia that is not clinically obvious is the most common treatable cause of hypertension among patients with ESRD; thus, volume control should be the initial therapy to treat hypertension in most hemodialysis patients. Reducing dietary and dialysate sodium is an often overlooked strategy to improve blood pressure control. The treatment should be guided by blood pressure obtained outside the dialysis center. In general, all antihypertensive drugs can be used in the hemodialysis population with doses determined by dialyzability and hemodynamic instability. 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.

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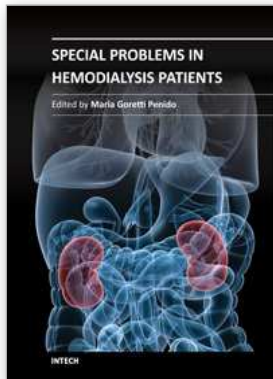
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Edited by Prof. Maria Goretti Penido

This book provides an overview of special cases in hemodialysis patients. Authors have contributed their most interesting findings in dealing with patients suffering of other diseases simultaneously, such as diabetes, cardiovascular disease and other health problems. Each chapter has been thoroughly revised and updated so the readers are acquainted with the latest data and observations in these complex cases, where several aspects are to be considered. The book is comprehensive and not limited to a partial discussion of hemodialysis. To accomplish this we are pleased to have been able to summarize state of the art knowledge in each chapter of the book.

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