

Hypertension in end-stage renal disease: different measures and their prognostic significance

Walter H. Hörl

Division of Nephrology and Dialysis, Department of Medicine III, University of Vienna, Vienna, Austria

Correspondence and offprint requests to: Walter H. Hörl; E-mail: Walter.hoerl@meduniwien.ac.at

Abstract

Hypertension is a risk factor for cardiovascular morbidity and mortality. Hypertension affects the majority of haemodialysis (HD) patients. However, in the absence of prospective data, accurate assessment of blood pressure (BP) and the level to which BP should be targeted remain still to be defined. A direct relationship between volume status and BP as well as between hypervolaemia and morbidity and mortality in HD patients indicates that normovolaemia is the key therapeutic target. Dry-weight reduction by additional ultrafiltration (even in the absence of clinical signs of volume overload) combined with daily dietary salt restriction or individually lowered dialysate sodium is recommended. Strict volume control allows marked reduction of antihypertensive drug treatment or makes it even unnecessary. Long, slow, home HD or frequent, short HD sessions or nocturnal HD also result in reduction of BP and left ventricular hypertrophy in end-stage renal disease patients. It will be interesting to see which recommendations will come from a conference sponsored by the Kidney Disease: Improving Global Outcomes on optimal BP treatment target in relation to end-organ damage and outcomes in HD patients, on antihypertensive drugs and on non-pharmacological therapies are to be considered in achieving BP targets in this population based on a paucity of prospective data.

Keywords: euvolaemia; haemodialysis; hypertension; salt restriction

The majority of patients starting dialysis are hypertensive [1], suggesting that blood pressure (BP) control might be an important target for intervention to reduce cardiovascular mortality. There is, however, still no consensus about whether to lower increased BP in haemodialysis (HD) patients or the level to which BP should be targeted [2,3]. An explanation may be difficulties associated with accurate assessment of BP in this patient population.

Blood pressure recording and target levels

Routine peri-dialytic BP recordings performed by a dialysis unit staff shortly before and after the HD session are highly

variable and poorly reproducible [4,5] and do not correlate well with end-organ damage [6,7]. In addition, achieving the National Kidney Foundation Disease Outcomes Quality Initiative (NKF-KDOQI)-recommended peri-dialytic BP targets of <140/90 mmHg pre-dialytic and <130/80 mmHg post-dialytic [8] is associated with increased frequency of intra-dialytic hypotension [9]. The 12th annual report of the UK Renal Registry (UKRR) indicates that in 2008, 43.1% of HD patients achieved a pre-dialytic BP of <140/90 mmHg and 46.8% a post-dialytic BP of <130/80 mmHg [10]. However, BP control varied significantly between centres. For example, the median pre-dialysis systolic BP for all HD patients was 143 mmHg, ranging from 130.5 to 160.0 mmHg, while the median post-dialysis systolic BP for all HD patients was 129 mmHg, ranging from 119 to 143 mmHg between centres [10]. Meanwhile, the revised KDOQI Clinical Practice Guidelines, issued in 2006, removed a specific BP target for HD patients [11].

Observational studies in HD patients have shown an increase in mortality with low or even normal pre-dialytic BP levels [12,13]. Significant decreases in myocardial perfusion in adults [14] and children [15] during HD, even in the absence of intra-dialytic hypotension, may explain concerns with lowering BP in HD patients. Intra-dialytic hypotension may damage the heart [16] and is associated with increased mortality [17]. However, lower BPs have been associated with decreased mortality in HD patients who survived for >3 years [18]. Unfortunately, there is a paucity of prospective data to support the safety and efficacy of treating hypertensive HD patients [19]. Antihypertensive drugs may increase the risk of symptomatic intra-dialytic hypotension by interfering with the compensatory vasoconstriction that maintains BP in the face of rapid changes in intravascular volume during conventional HD [20]. Nevertheless, peri-dialytic BP measurements are used for management of hypertension in the majority of HD patients today [21].

Since observational studies reveal that the association between BP and death risk in end-stage renal disease (ESRD) patients is not the same as in the general population, recommendations for substantially increased systolic BP thresholds in HD patients were proposed: based on

available observational data, a pre-dialysis systolic BP between 140 and 160 mmHg and a pre-dialysis diastolic BP between 70 and 90 mmHg were recommended. For post-dialysis BP, optimal mortal risk was considered for systolic BP at 135–154 mmHg, and diastolic BP was still at 70–90 mmHg [22]. Data from the HEMO Study support these recommendations: Chang *et al.* [23] conducted a secondary analysis of data from the HEMO Study, a randomized trial in prevalent HD patients. In this study, a pre-dialysis systolic BP <120 mmHg was associated with a higher risk of mortality compared with the reference group with a pre-dialysis systolic BP between 140 and 159 mmHg. Interestingly, even higher pre-dialysis systolic BP was not associated with higher risk of mortality. Thus, in agreement with previous epidemiological studies, a robust association between lower pre-dialysis systolic BP and higher risk of all-cause and cardiovascular mortality was demonstrated in a well-characterized cohort of prevalent HD patients [23]. No study has definitively shown whether BP reduction is causally associated with improved outcome in HD patients [24].

The patterns of systolic BP, diastolic BP, mean arterial pressure (MAP) and pulse pressure (PP) in the general population differ markedly from the pattern observed in HD patients. For example, systolic BP, diastolic BP, MAP and PP were elevated among young HD patients. This pattern may reflect an acceleration of cardiovascular disease in young HD patients [5], suggesting a benefit of BP-lowering therapy of this subgroup of HD patients. Inter-dialytic ambulatory blood pressure monitoring (ABPM) has a better reproducibility than isolated or aggregated pre-dialysis and post-dialysis BP values [25]. Kaplan–Meier survival curves for ambulatory or home systolic BP among 326 patients on long-term HD showed a significant relationship between all-cause mortality and quartiles of BP. Mortality of this patient population with a mean age of 54.9 ± 12.9 years was lowest when home systolic BP was between 120 and 130 mmHg and ambulatory systolic BP was between 110 and 120 mmHg. Again, BP recorded before and after HD was not statistically significant in predicting mortality [26]. However, the reproducibility of the decrease in BP during sleep is poor, with up to 43% of the patients changing the dipping category within or between inter-dialytic periods. Thus, one of the important and unique features of ABPM is flawed by an excessive variability in this population [25]. ABPM can be cumbersome to perform. Data from the Dry-Weight Reduction in Hypertensive Hemodialysis (DRIP) trial provide support for the use of home BP measurement, recorded by each subject three times daily in the morning, afternoon and before going to bed, for the management of hypertension in HD patients. The reproducibility of BP measurements followed the following order: home BP monitoring > ABPM >> pre-dialysis BP > post-dialysis BP [27]. BP increases in the inter-dialytic period [0.07 mmHg/h with each 1-kg increase in inter-dialytic weight gain (IDWG)] and reaches a plateau after ~48 h. The increase in diastolic BP does not match the increase in systolic BP, resulting in detrimental amplification of PP [28]. This phenomenon is also seen with ABPM [29]. When home BP recordings are subdivided into thirds in relationship to the end of the dialysis

treatment, the greatest agreement in home BP with ABPM for systolic BP was found in the middle third and for diastolic BP in the last third of the inter-dialytic interval. Timing the home BP measurements between 18 and 30 h after completion of the dialysis treatment was recommended; if limited, home BP measurement can be performed. Nevertheless, measurement of BP during each third of the inter-dialytic interval gives the best precision in predicting ambulatory BP. Thus, the time elapsed after a dialysis treatment must be considered in interpreting home BP recording in HD patients [28]. Intra-dialytic BP recording is not a substitute for ABPM or home BP measurements [24]. Intra-dialytic BP recordings may improve the diagnosis and management of hypertension among HD patients, if home BP monitoring is not available or not possible. Even multiple measurements of pre-dialysis or post-dialysis BP were not superior to median BP obtained over just one dialysis treatment [30]. Increasing peri-dialytic systolic BP in incident HD patients with normal pre-dialysis systolic BP was recently associated with mortality at 2 years [31]. Since these patients, however, also had clinical signs of wasting, an increase in mortality by advanced chronic illness is not excluded [21].

Antihypertensive drugs

Most patients undergoing conventional HD require a number of antihypertensive medications to achieve an appropriate BP [32,33]. Drug therapy for hypertension in HD patients includes all classes of antihypertensive drugs, but only selected HD patients may benefit from loop diuretic therapy [34]. The meta-analysis by Agarwal and Sinha showed a cardiovascular benefit for hypertensive HD patients from BP lowering unlike what is suggested by observational studies. However, the possibility that the benefits of antihypertensive drugs used in HD patients were because of non-haemodynamic actions is not ruled out [35].

A systematic review and meta-analysis of eight relevant trials, which provided data for 1679 patients and 495 cardiovascular events, were performed in order to evaluate the effect of lowering BP on cardiovascular events and mortality in patients on dialysis. In actively treated patients, reduction of blood pressure was associated with lower risks of cardiovascular events (RR 0.71; CI 0.55–0.92; $P = 0.009$), all-cause mortality (RR 0.80; CI 0.66–0.96; $P = 0.014$) and cardiovascular mortality (RR 0.71; CI 0.55–0.99; $P = 0.04$) than control regimens. It was concluded that treatment with agents that lower BP should routinely be considered for individuals undergoing dialysis to reduce the very high cardiovascular morbidity and mortality in this population [36]. This recommendation has been criticized as a sweeping statement to be applied to over 1 500 000 patients on dialysis worldwide, based on eight studies of 1679 subjects [37]. In addition, the clinical disparity between the trials included into the meta-analysis is striking, and the inclusion criteria for trial entry and the cardiovascular end points vary substantially. Thus, such recommendation is premature and could potentially be fatally flawed [38]. In three of these studies, intervention and control groups did not differ for BP [39–41], and the use of angiotensin II receptor blockers resulted in a reduction in

deaths from congestive heart failure [40]. A prospective, randomized study in HD patients with symptomatic congestive heart failure showed an impressive and significant decreased death and hospitalization rates attributable to cardiovascular causes in patients on carvedilol as compared with placebo [42]. Sympathetic overactivity is an important contributor in increasing the risk of cardiovascular events in ESRD patients [43]. Concerns of possible adverse effects, such as hypotension and hyperkalaemia, and adverse metabolic effects may explain the (too) low rate of beta-blocker use in this high-risk population. Risks of dangerous side effects among chronic HD patients appear to be low and manageable [44]. A study of amlodipine in 251 hypertensive HD patients found no reduction in all-cause mortality but showed a significant reduction in the composite secondary end point of all-cause mortality or cardiovascular event [45].

A meta-analysis on the cardiovascular effects of angiotensin-converting enzyme inhibition (ACEI) or angiotensin II receptor blockade (ARB) in HD patients showed that treatment with ACEI or ARB reduced left ventricular mass. Their use, however, was not associated with a statistically significant reduction in the risk of fatal and non-fatal cardiovascular events [46]. In contrast, for subjects without kidney disease and with or without significant cardiovascular disease burdens, any form of BP-reducing therapy profoundly reduced cardiovascular burdens [47]. In HD patients, low BP achieved by intervention, which may be of benefit, differs from low BP achieved because of, for example, a serious underlying cardiomyopathy, or as a result of some haemodynamic insult which arises on HD [38]. The high short-term mortality being seen in HD patients with low BP is frequently the result of heart failure. Longer-term studies and those in HD patients without major comorbidity show the expected relation between hypertension and reduced survival [48,49].

Normovolaemia as a therapeutic target

In patients with ESRD treated with dialysis, a direct relationship between volume status and BP has long been recognized. An increase in pre-dialytic systolic BP may reflect hypervolaemia. Data from the CRIT-Line Intradialytic Monitor Benefit (CLIMB) Study obtained during 32 295 sessions of 442 subjects followed up for 6 months confirmed that an increasing percentage of IDWG is associated with a greater pre-dialysis BP and a greater decrease in BP associated with HD. The magnitude of the relationship between BP and IDWG, however, was found to be modest and modified by other clinical factors such as (mal)nutrition or inflammation [50]. Nevertheless, HD patients with a 15% or greater extracellular volume increase over the normal display an increased risk of mortality [51].

Of 47 hypertensive peritoneal dialysis (PD) patients, 20 were excellent salt responders. Four weeks after initiation of dietary salt restriction to 4 g/day, body weight, systolic BP and diastolic BP decreased significantly. In this study, 17 hypertensive PD patients were excellent responders of a combined therapy of dietary salt restriction plus additional ultrafiltration by the addition of hypertonic dextrose solu-

tions [52]. In the DRIP Study, 100 hypertensive HD patients were randomly assigned to receive ultrafiltration, while 50 hypertensive HD patients acted as control group. Patients in the ultrafiltration group did not have clinical signs of volume overload but received an additional weight loss of 0.1 kg/10 kg body weight per dialysis. If ultrafiltration was not tolerated, the additional prescribed weight loss was reduced by 50%. If ultrafiltration was still not tolerated, the additional weight loss was further reduced by 50% until the patient did not tolerate even a 0.2-kg incremental weight loss per HD session. The patient was at this point considered to have reached his or her dry body weight. An average reduction of post-dialysis weight of 0.9 kg was achieved at 4 weeks, which resulted in a -6.9 -mmHg ($P = 0.016$) change in systolic BP and a -3.1 -mmHg ($P = 0.037$) change in diastolic BP from baseline. Interestingly, more than half of the patients in the intervention group had a reduction in systolic BP of 10 mmHg or more, suggesting that such a procedure results in improved systolic BP equivalent to or greater than administration of a single antihypertensive drug [53]. Salt and water overload is a key promoter of raised BP in dialysis patients. Therefore, controlling the body sodium content and the extracellular volume is the first condition to achieve BP normalization and reduce the cardiovascular mortality in this patient population [54]. Dry-weight reduction by additional ultrafiltration combined with obsessive daily dietary salt restriction should be recommended to hypertensive HD patients even in the absence of clinical signs of volume overload [55]. This recommendation is limited by the fact that dietary salt restriction is difficult to achieve in many parts of the world. Dietary sodium restriction requires lifestyle modifications that are difficult to implement, particularly over the long term [56]. Nevertheless, Özkahya *et al.* [57] have impressively demonstrated that a dietary salt restriction for >36 months results in a reduction of IDWG (from 2.9 ± 1.3 to 1.8 ± 1.2 kg), systolic BP (from 173 ± 17 to 114 ± 10 mmHg) and diastolic BP (from 102 ± 9 to 71 ± 7 mmHg) in maintenance HD patients. Restricting dialysate sodium can also reduce thirst, limit inter-dialytic weight gain and assist the achievement of dry-weight [56]. Strict volume control makes antihypertensive drug treatment often unnecessary and even dangerous [20]. Kayikcioglu *et al.* [58] assessed the effectiveness and cardiac consequences of two different strategies for BP control in maintenance HD patients. Centre A ($n = 190$) practised the salt restriction (5 g/day) strategy, while Centre B ($n = 204$) practised the antihypertensive-based strategy. Antihypertensive drugs were used in 7% of the HD patients in Centre A, but in 42% of the HD patients in Centre B. Patients of Centre A had significantly lower IDWG, lower left ventricular mass, lower frequency of left ventricular hypertrophy, better preserved systolic and diastolic functions, and lower episodes of intra-dialytic hypotension than patients of Centre B, despite similar systolic and diastolic BP values [58].

As mentioned before, antihypertensive drugs may interfere with the compensatory vasoconstriction in BP maintenance in the face of rapid changes in intravascular volume during conventional HD [20]. In addition, based on the haemodynamic response to ultrafiltration-induced

hypovolaemia, HD patients can be classified as hypotension prone or hypotension resistant. Hypotension-prone patients show a defective arteriovenous tone adjustment to plasma volume changes. Reduced cardiac pre-load with both atrial and ventricular underfilling may explain why these patients are unable to maintain adequate output despite abnormal sympathetic activation [59].

Pulse pressure as a risk factor

Augmented volume removal therapy evokes parallel reductions in awake and sleep BP without restoring a nocturnal dipping in HD patients. Since reduction of systolic BP by volume removal therapy exceeds that of diastolic BP, a reduction of PP occurs with the potential to impact survival in HD patients [60]. There is increased death risk associated with post-dialysis PP >60 mmHg but also for pre-dialysis PP <55 mmHg [20]. Change in PP during HD was investigated as a risk factor for hospitalization and mortality among prevalent HD patients. Patients who had the least change in PP from before to after HD had clinical characteristics of volume overload. Lowering of PP from before to after HD was associated with lower hospitalization and lower mortality outcomes [61]. The PP (by virtue of low diastolic BP) was greater in patients initiating dialysis who developed stroke than in those who did not. Comparing the BP values of patients with and without stroke, there was no difference [62].

Intra-dialytic hypertension

Intra-dialytic hypertension may be a sign of volume excess and should trigger an evaluation of dry-weight [63]. Intra-dialytic BP can also rise due to endothelin excess, sympathetic overactivity, activation of the renin-angiotensin-aldosterone system, or dialysis-specific factors such as net sodium gain, high dialysate calcium, hypokalaemia or removal of hypertensive medications. Intra-dialytic hypertension is mostly defined by a MAP \geq 15 mmHg during or immediately after HD or an increase in systolic BP > 10 mmHg from pre- to post-dialysis. Many recommendations have been proposed to treat intra-dialytic hypertension. Most of these recommendations are not validated by respective studies [64,65].

Effects of dialysis regimen

Long, slow, home HD or frequent, short HD sessions or nocturnal HD also result in reduction of BP and left ventricular hypertrophy in ESRD patients (for review see [1]). For example, thrice-weekly in-centre nocturnal HD is an effective strategy to optimize blood pressure. Cravedi *et al.* [66] found a decrease of systolic BP from 149.4 ± 16.6 to 128.4 ± 26.0 mmHg ($P < 0.001$) and a decrease of diastolic BP from 87.7 ± 11.1 to 79.6 ± 16.7 mmHg ($P < 0.05$) in seven maintenance HD patients at 2 years after starting nocturnal HD. Interestingly, normalization of BP associated with a significant reduction in the use of per pa-

tient antihypertensive agents (1.17 ± 1.19 versus 0.47 ± 0.89 ; $P < 0.05$) despite an increase in dry body weight from 61.4 ± 21.8 to 67.1 ± 16.4 kg ($P < 0.001$).

Renal replacement therapy (RRT) allows not only the removal of uraemic toxins and water but also the removal of sodium and salt which accumulates in between treatments. During HD, patient sodium levels equilibrate with the described dialysate sodium levels. As a consequence of a negative sodium gradient during HD, >10% of total body sodium is removed. On the other hand, upon HD with a positive sodium gradient, sodium and weight gain will occur [67]. IDWG is associated with cardiovascular mortality [68]. Thus, lowering dialysate sodium might prevent IDWG and possibly decrease mortality.

Conclusions

Hypertension affects the vast majority of HD patients, suggesting that this complication should be treated effectively. There is, however, no consensus (at present) how BP should best possibly be recorded (in daily practice) and which BP levels should be targeted. Normovolaemia is the key therapeutic target for hypertension in HD patients, achieved by additional ultrafiltration combined with daily dietary salt restriction (or reduced dialysate sodium concentration). Antihypertensive drugs may reduce cardiovascular complications, but it is still premature (or even impossible) to make general recommendations for the very heterogeneous population undergoing maintenance HD.

Conflict of interest statement. None declared.

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