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**REVIEW ARTICLE**

# Hypertension in patients on chronic hemodialysis: pathophysiology and treatment

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The incidence of end-stage renal disease (ESRD) has been doubled over the past 10 years and the leading causes of ESRD are hypertension and diabetes. The prevalence of arterial hypertension among dialysis patients is high and approximately 80-90% of patients are hypertensive by the time chronic renal failure progresses to ESRD. Recently, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) have published their guidelines for the management of arterial hypertension. Chronic kidney disease (CKD) and ESRD are associated with an increased prevalence of cardiovascular (CV) disease[1].

The main pathophysiological mechanism of hypertension in dialysis patients is extracellular volume expansion, which is tipically sodium sensitive, given the loss of renal function.

All recommendations for management of hypertension in dialysis patients focuses on the CV risk factor in dialysis patients because of hypertension. Hypertension is discussed in the new light of modern CV risk assessment.

The first goal of hypertension treatment in dialysis patients is the achievement of dry body weight and dietary sodium and water restriction.The second goal is pharmacological treatment of hypertension, if it still exists, after the achievement of the first goal.
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Hypertension is a major risk factor for progression of renal disease and it is both cause and consequence of chronic kidney disease. Chronic kidney disease has emerged as a public health problem.The data justify the need for an adequate prevention and *treatment* of renal damage in the population. Progression of renal failure is associated with increased prevalence of CV disease.

Common risk factors for CV disease present in general population are also present in dialysis patients. Hypertension is a major CV risk factor. There are uncommon – uraemia related risk factors for cardiovascular disease[2] (Table 1).

Many studies show that elevated systolic blood pressure is a more significant CV risk factor than diastolic blood pressure. High systolic blood pressure is associated with an elevated pulse pressure, which has been shown to be a major predictor of mortality in dialysis patients. Recently, studies have associated uncontrolled hypertension with shorter survival and excellent blood pressure (BP) control with increased survival. Pulse pressure was a better predictor of mortality rate than systolic or diastolic BP.

Extracellular volume (ECV) overload plays an important role in the pathogenesis of dialysis-associated hypertension. Hypoalbuminemia has also been recognized in many studies as a potent risk factor for mortality. There is the relationship between albumin levels, intravascular volume, and cardiac risk[3]. Control of the ECV in the prevention of hypertension in HD patients has been provided by studies in *Tassin*: Patients were treated with long slow hemodialysis (18 hours per week). They had higher 10-year survival rates as opposed to similar populations who underwent conventional hemodialysis (12 hours per week)[4,5]. The *Tassin* experience provided us with an important physiologic principal: There is a nonlinear relationship between ECV status and BP. A proposed explanation for this mechanism is in altered auto-regulation and circulating factors in ESRD (Na+, K+ ATPase inhibitor-increase intracellular Ca, and vascular smooth muscle contraction and inhibitor of nitric oxide).

## Pathogenesis

Patients with ESRD are very susceptible to the adverse effects of salt, as their ability to excrete sodium is lost. The adverse effects of salt in renal patients are predominantly due to combined water and sodium overload because the body tries to maintain the osmolarity of the extracellular compartment. There is the salt sensitivity concept in the pathogenesis of essential hypertension. Salt-sensitive patients and salt-resistant patients show different behavior to salt loading and restriction. The activity of Na+-K+ ATPase inhibitors was found to be increased in animal models and humans with salt-sensitive hypertension, which may lead to an increase of intracellular calcium and hence an increase of vascular resistance. In salt-sensitive patients with essential hypertension, blood pressure changes after salt loading were inversely related to changes in nitric oxide (NO) activity, which was in turn inversely related to changes in the endogenous NO inhibitor, asymmetric dimethylarginine (1-ADMA)[6-8].

**Table 1.** *Cardiovascular risk factors in dialysis patients*

| Common CV risk factors | Uncommon – uraemia related risk factors |
|---|---|
| Male gender | Micro-inflammatory state |
| Hypertension | Anaemia |
| Diabetes mellitus | Left ventricular hyperthrophy |
| High LDL-cholesterol | Salt and water overload |
| Low HDL-cholesterol | Malnutrition |
| High lipoprotein | Increased oxidative stress |
| High Lp(a) | Reduced vascular compliance |
| Family history of CV disease | Secondary hyperparathyroidism |
| Smoking | Hyperphosphataemia |
| Obesity | Physical inactivity |

In patients with chronic kidney disease, the blood pressure response to salt loading is generally augmented. The activity of the sympathetic nervous system is increased in patients with advanced renal disease[9-11].

The removal of excess water and sodium improves blood pressure control in patients with advanced renal disease. Also, a complete normalization of blood pressure regulation has been achieved by the use of prolonged dialysis times, such as in the centre in Tassin and in the case of nocturnal dialysis. Pathophysiological mechanisms are associated with volume expansion in hemodialysis patients. Hemodialysis patients also lose the normal circadian flactuation of blood pressure. It is well known that nocturnal blood pressure normally decreases in general population, while it remains elevated in dialysis patients. Pathogenesis of hypertension in hemodialysis patients is multifactorial, but the majority of cases are considered to be volume dependent and determined by sodium balance (Table 2).

**Relationship between ECV and blood pressure**

Correct estimation of dry body weight is very important for dialysis patients and overestimation of dry weight will contribute to hypertension. The "lag phenomenon" is an observation that adequate blood pressure control often does not immediately occur after ultrafiltration to the dry weight, especially in patients who are chronically volume overloaded. Study from Tassin comparing body weight and blood pressure showed a steady reduction in mean arterial pressure (111.3 ± 2.5 to 94.4± 1.7 mmHg) after reduction to the targeted dry weight over the first 6 months[12-14].

**Table 2.** *Mechanisms of Hypertension in Hemodialysis Patients*

| |
|---|
| *Renal – dependent mechanisms* : dysregulation of renin-angiotensin system sympathetic hyperactivity, loss of inherent renal vasodilatory factors |
| *Vascular mechanisms* : elevated calcium/phosphate product, Secondary hyperparathyroidism ,vascular calcification and stiffening |
| *Circulating factors* : endogenous inhibitors of nitric oxide system Endogenous inhibitors of vascular Na+ K+- ATPase, Parathyroid hormone, "Uremic toxins" |
| *ECV expansion*: Blood volume – related vasoactive substances, dietary salt noncompliance |
| *Hemodialysis prescription* : dialysate Na and K concentrations, shorter dialysis sessions, over estimation of dry weight |

**Dysregulation of renin-angiotensin system**

Several studies have been used to approach the link between angiotensin II and oxidative stress and the consequences of oxidative stress at tissue level. Animal model and in vitro cell culture studies have discussed the implication of angiotensin II, by activation of AT1 receptors, in the pathogenesis of oxidative stress in chronic kidney disease.

The production of reactive oxygen species (ROS), especially superoxide and hydrogen peroxide, are important signaling molecules.They are regulated by enzyme nicotin-amide adenine dinucleotide phosphate (NADPH) oxidases, and their catabolism by antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase. ROS participate in vascular smooth muscle cell growth and migration, modulation of endothelial function and expression of adhesion molecules. Angiotensin II stimulates oxidative stress. The kidney has a rich expression of NADPH oxidase that generates superoxide anion, which is important in transducing the signal of angiotensin II to oxidative stress. The angiotensinogen gene, which provides the precursor for angiotensin production, is stimulated by NF-kappa B activation, which is sensitive to the redox ratio. Many vasoconstrictor mechanisms, as blockade of nitric oxide synthase, and activation of angiotensin II type 1 (AT1) receptors can induce oxidative stress in hypertension[15,16].

**Circulating Factors**

There is inhibition of nitric oxide in subjects with chronic kidney disease and end stage renal disease. NO is an important vasodilatator and it is synthesized from L-arginine in an enzymatic reaction mediated by endothelial NO synthase. Blockade of NO production causes vasoconstriction and hypertension in animals. Recently, an endogenous inhibitor of NO production has been discovered and has been shown to be elevated in subjects with chronic kidney disease and ESRD. The asymmetrical dimethyl-l-arginine (ADMA), acts by competing with L-arginine. Salt loading has been shown to cause a decrease in plasma NO production in patients with essential hypertension. The highest levels of ADMA are found in subjects with ESRD, especially if they are on dialysis and the severity of the levels has been correlated with increased CV events.

**Treatment**

The high prevalence of LVH among HD pts may be a consequence of inadequate treatment of arterial hy-

pertension. Blood pressure should be assessed by clinical measurements on a routine basis and 24h monitoring for only selected cases. The target of blood pressure control should be recommended by the present guidelines below 140/90 mmHg.

The first of these, published 1993. by *Cannella* et al, demonstrated that strict BP control can induce a reduction in the LVH. In these pts anemia was also corrected and dialysis adequacy improved, but the reduction of SBP appeared as the most important predictor of LVH reduction[17].

The prevalence of arterial hypertension among dialysis patients is high: more than 70% of patients are hypertensive (HEMO study)[18]. The majority of patients are resistant to antihypertensive medication. Uncontrolled hypertension during dialysis will lead to progression of left ventricular hyperthrophy, which is a strong predictor for ischemic heart disease, cardiac failure and death. Uncontrolled hypertension is associated with increased risk for stroke**.** The first step in treatment is clinical assessment of volume status and dietary salt restriction (less than 5 g/d). Anti-hypertensive drugs in HD patients are indicated only after ECV normalization and an adequate dialysis prescription[19,20]. The indication of a given class of anti-hypertensive drugs may depends on associated pathology (Table 3).

Pharmacological antihypertensive treatment should be the last-choice option, after achievement of ideal dry body weight, optimal dialysis duration, optimal sodium balance and blood purification adequacy.

ACE-I and angiotensin II receptor antagonists (AT1RA) may be agents of first choice. In patients with congestive heart failure and ischaemic cardiomyopathy b-blockers are good choice in treatment of hypertension.

Most studies have demonstrated an association between hypertension and risk of death in HD patients. The main goal is obtaining optimal dry weight, reduced IDWG, salt restriction and optimal dialysis duration.

For the management of hypertension, systolic blood pressure value below 140 mmHg and diastolic blood pressure below 90 mmHg is recommended.

Blood pressure should be measured by average predialysis BP levels, while ABPM should only be used to examine patients with highly pathological circadian variability (nocturnal hypertension)[20].

**Table 3.** *Anti-hypertensive drugs in dialysis patients*

| Clinical situation | Drugs of choice | Not recommended |
|---|---|---|
| Heart failure | AT1RA, ACE-I, b-blockers | |
| Post-MI | ACE-I, b-blockers | Direct vasodilators |
| Hypertrophic cardiomyopathy | Diltiazem, verapamil, b-blockers | Direct vasodilators alfa-blockers |
| Chronic obstructive pulmonary disease | AT1RA,ACE-I, CCB | b-blockers |
| Ischaemic cardiomyopathy, angina | b-blockers, ACE-I,AT1RA, CCB | Direct vasodilators |

No specific class of anti-hypertensive drugs has proved to be more beneficial than others in dialysis patients. ACE-I and AT1RA may be agents of first choice as they have CV protective effect[21-23].

Beneficial effects of beta-blockers have also been demonstrated in controlled trials in pts with congestive heart failure and ischemic cardiomiopathy.

The new knowledge of the pathophysiology of atherogenesis may have a profound impact on the management of patients at risk of CV disease and hypertension. Treatment of endothelial activation by statins and ACE-inhibitors improve endothelium-dependent vasodilatation and reduce inflammation. Beta-blockers and calcium channel blockers have also been used in hemodialysis patients.

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