Hemodynamic stability during hemodialysis
Ettema, Esmee Marlien

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Chapter 1

Introduction
Hemodialysis and its consequences

The kidneys are the mainstay in the control of volume and composition of body fluids. When kidney function deteriorates, fluid and uremic toxins accumulate, eventually leading to the need for renal replacement therapies such as hemodialysis, peritoneal dialysis or renal transplantation. In the Netherlands, almost 5600 patients were treated with hemodialysis in 2015.

Unfortunately, hemodialysis treatment is not without adverse effects. One of the most common complications of hemodialysis is intradialytic hypotension (IDH), which is estimated to occur in up to 30% of the hemodialysis treatments. IDH can lead to transitory complaints like muscle cramping, nausea and dizziness but also to far more serious events like mesenteric, cardiac or cerebral ischemia. Frequent IDH is associated with underdialysis and chronic volume overload and might also be associated with higher mortality.

Acute treatment of IDH is aimed at raising blood pressure to an acceptable level in order to guarantee blood flow to vital organs. Since a drop in blood volume plays an important role in the pathophysiology of IDH, most of the measures aim to increase the intravascular volume, e.g. by temporarily interrupting ultrafiltration or the administration of saline. Placing the patient in the Trendelenburg position increases the venous return to the heart, resulting in an temporarily increased filling pressure of the left ventricle, which allows the cardiac output to rise. To prevent IDH, several measures can be undertaken, like lowering the dialysate temperature, limiting food intake during dialysis, intradialytic exercise and the use of sodium and ultrafiltration profiling.

Pathophysiology of IDH

During hemodialysis, excess fluid volume is withdrawn during a relatively short period of time. Since the ultrafiltration rate generally exceeds the plasma refill rate, hemodialysis with ultrafiltration leads to hypovolemia. Cardiovascular compensating mechanisms such as venous and arterial vasoconstriction, redistribution of blood from peripheral or splanchnic vascular beds to the central blood compartment and increases in heart rate and cardiac contractility help to maintain blood pressure during hypovolemia. IDH can occur when the cardiovascular compensatory mechanisms cannot adequately compensate for the intradialytic decrease in blood volume.

Decrease in blood volume and blood pressure activates cardiovascular compensatory mechanisms such as the autonomic nervous system. Dysfunction of the autonomic nervous system is prevalent in patients with end stage renal disease and is considered to play a pivotal role in the occurrence of IDH. Besides autonomic dysfunction, also increased NO production has been suggested to contribute to the onset of IDH. Synthesized from the precursor L-arginine by the enzyme NO synthase (NOS), NO is continuously formed in small amounts by endothelial cells. From the endothelial cells, NO diffuses to vascular smooth
muscle cells, causing vasodilation. The endothelial NO formation is allegedly stimulated in uremic conditions and also the hemodialysis procedure enhances NO production through blood-membrane contact and shear stress to blood cells in dialysis equipment. Additionally, shear stress to blood and endothelial cells by fluid diffusing from the interstitial to the intravascular space (e.g. plasma refill) can induce NO production. In addition to autonomic dysfunction and enhanced NO production, insufficient release of the vasoconstrictor vasopressin might contribute to the occurrence of IDH. Vasopressin has the ability to increase blood pressure through vasoconstriction by acting on V1 receptors of smooth muscle myocytes, independent of the endothelium. Vasopressin is considered important for maintaining blood pressure specifically when hemodynamic stability is endangered. Already in 1988, Faber and Dumler proposed that insufficient vasopressin release might contribute to hypotension in dialysis patients. This has subsequently been supported by other groups.

**Ultrafiltration and sodium profiling: the Hemocontrol biofeedback system**

Dialyzing with a high dialysate sodium concentration is advocated to improve hemodynamic stability, but supportive data are scarce. A major disadvantage of dialyzing with a high dialysate conductivity is the potential diffusive sodium load it might induce, resulting in elevated postdialysis plasma sodium levels, thirst, and an increase in interdialytic weight gain. A system that uses controlled sodium profiling in addition to ultrafiltration profiling is the Hemocontrol biofeedback system. This system ensures identical sodium removal compared with standard hemodialysis by using a so-called equivalent conductivity. The equivalent sodium concentration equals the constant dialysate sodium setting by compensating periods with a high dialysate conductivity by a low dialysate conductivity. Several studies have indeed shown that the postdialysis plasma sodium levels during Hemocontrol were not elevated compared to standard hemodialysis.

Hemodialysis with Hemocontrol is associated with better intradialytic hemodynamic stability and a lower frequency of IDH. The Hemocontrol system is designed to prevent large and sudden decreases in blood volume, in order to improve intradialytic hemodynamic stability. The system guides the patients’ blood volume along a predefined ideal relative blood volume trajectory, by continuously adjusting ultrafiltration volume and dialysate conductivity. Changes in blood volume are calculated from changes in hematocrit measured by Hemoscan, a dialysis machine-integrated relative blood volume monitor. The ideal blood volume trajectory is based on the ratio of the relative blood volume decrease per unit of ultrafiltrated fluid (expressed as %/kg) in relation to the development of IDH. This patient-specific ratio is derived from several ‘test sessions’ during which the blood volume is monitored in relation to the intradialytic blood pressure course and symptoms. The pre-set ideal blood volume curve has a marked decrease in the beginning of the dialysis...
session, whereas it is more stable during the second half of the treatment. Hallmark of the Hemocontrol system is the combination of a higher ultrafiltration rate and higher dialysate conductivity during the first half of the dialysis session. This results in a more pronounced initial decrease in blood volume and higher plasma sodium levels during the first half of the dialysis session. Hemocontrol uses higher ultrafiltration rates during the first half of treatment. Therefore, less fluid has to be withdrawn during the second half of the dialysis session, which is considered to be the hemodynamically the most critical part of the treatment.

The actual mechanism behind the improved hemodynamic stability with the Hemocontrol system has not been fully delineated. The general believe is that higher dialysate sodium levels increase plasma refilling from the interstitial tissue and that blood volume is better preserved with Hemocontrol in comparison with standard hemodialysis. However, previous studies showed that the improved hemodynamic stability with Hemocontrol did not coincide with better blood volume preservation compared with standard hemodialysis with constant conductivity and ultrafiltration rate. Thus, although the Hemocontrol system might prevent sudden fluctuations in the blood volume, other mechanisms may also play a role in the observed improved hemodynamic stability, as discussed below.

**Endothelial (dys)function**

The endothelium, the layer covering the luminal side of the blood vessels, plays a role in blood pressure regulation. Upon stimulation, presynthesized and stored vasoactive substances like the vasoconstrictor endothelin-1 and the vascular growth factor angiopoietin-2 are released into the blood within seconds to minutes from endothelial-specific storage granules, called Weibel-Palade bodies. Triggers for endothelium activation include hypoxia and altered shear stress. By balancing the production of the vasodilator NO and the vasoconstrictor endothelin-1, the endothelium plays a major role in the regulation of vascular tone and blood pressure control. Endothelial NO production is considered to be the hallmark of endothelial function.

Endothelium-derived factors such as endothelin-1 and angiopoietins, vascular growth factors, can be measured in the systemic circulation as a reflection of endothelial function. Angiopoietin-1 promotes the resting state of the endothelium and prevents secretion of angiopoietin-2 by the endothelium. Angiopoietin-2, on the other hand, activates the endothelium and triggers an inflammatory response. Measurement of NO is difficult since NO is extremely volatile with an estimated in-vivo half-life of 0.1 second. When released by the endothelium, NO subsequently reacts with oxyhemoglobin (oxy-Hb) to produce methemoglobin (metHb) and nitrite (NO$_2^-$), which is quickly converted to nitrate (NO$_3^-$). Small changes in extracellular sodium concentration alter the function of endothelial cells in-vitro and it has been suggested that this may be relevant to dialysis.
patients. Results from in-vitro and in-vivo studies suggest that sodium down-regulates NO production. An increase in plasma sodium levels during hemodialysis might cause a temporary dysfunction of the endothelium, with less production of NO. This could ameliorate the intradialytic blood pressure fall and could, therefore, have a beneficial effect in patients that frequently experience IDH.

**Autonomic nervous system**

For several years it has been suggested that sodium not only increases blood pressure via a volume-dependent effect, but also through enhanced sympathetic activity. Accumulating evidence suggests that hyperosmolality can stimulate sympathetic nerve activity. Increases in plasma osmolality, induced by infusion of hypertonic saline, were associated with an (initial) increase in sympathetic outflow in healthy volunteers, quantified by measurement of peroneal nerve activity. An increase in plasma osmolality was also associated with increased sensitivity of baroreflex control, which was assessed by the relationship between the beat-to-beat (R-R) interval and systolic blood pressure. The translation of hyperosmolality to increased sympathetic activity is mediated by neurons that sense changes in plasma osmolality, located in the brain (the organum vasculosum of the laminae terminalis). The osmolality-sensing neurons project on the hypothalamic paraventricular nucleus, that is connected to sympathetic-regulatory regions (the rostral ventrolateral medulla and spinal intermediolateral cell column).

**Vasopressin**

Vasopressin is a nonapeptide (i.e. consisting of 9 amino acids) with a molecular weight of 1084 Dalton (Da). It is synthesized as the prohormone preprovasopressin in the paraventricular and supraoptic nuclei hypothalamus and stored in granules in the posterior pituitary, from where it is released in the systemic circulation upon stimulation. Vasopressin secretion is controlled by two systems, the baroreflex arc and osmoreceptors. Baroreceptors are located in the carotid sinus, the atria and the aortic arch. Vasopressin is released upon a decreased stretch of the vascular wall at the site of the baroreceptors, e.g. when blood pressure and/or blood volume fall. Signals from the baroreceptors in the carotid arteries (via the glossopharyngeal nerve) and aortic arch (via the vagal nerve) reach the hypothalamus via the nucleus solitarius in the medulla.

Vasopressin secretion is also controlled by input from central osmoreceptors in the organ vasculosum, and peripheral osmoreceptors, located in the hepatic portal vein. The central osmoreceptors project directly on the paraventricular and supraoptic nuclei in the hypothalamus, whereas the afferent nerves from the peripheral osmoreceptors reach the hypothalamus via the nucleus tractus solitarius through the vagal nerve. The osmo- and baroregulation influence each other’s effects on vasopressin release and
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during pronounced hypovolemia, osmoregulation is overridden by baroregulation\textsuperscript{80,84}.
At lower vasopressin levels, i.e. below 10 pmol/L, the antidiuretic effects of vasopressin prevail. Vasopressin induces water reabsorption in the distal tubule and collecting duct via V2 receptor binding. This action of vasopressin is presumably less or not at all relevant in hemodialysis patients since most of these patients have little or no residual diuresis. At higher vasopressin plasma concentrations the vasoconstrictive effects via V1 receptors become more dominant\textsuperscript{84}.

Copeptin as surrogate marker for vasopressin

Besides vasopressin, the synthesized prohormone preprovasopressin contains copeptin (Figure 1). Copeptin is a 39-aminoacid glycopeptide of approximately 5000 Da. In contrast to vasopressin, little is known about the physiological function of copeptin. It has been suggested that copeptin is of importance in folding of vasopressin\textsuperscript{85} by preventing misfolded proteins from being exported from the endoplasmatic reticulum\textsuperscript{86}. Upon stimulation, vasopressin is released together with copeptin from the posterior pituitary in an alleged 1:1 ratio\textsuperscript{87}, after a calcium influx followed by neurosecretory granule movement\textsuperscript{36}.

Figure 1. Precursor peptide preprovasopressin.

<table>
<thead>
<tr>
<th>Signal</th>
<th>Vasopressin</th>
<th>Neurophysin II</th>
<th>Copeptin</th>
</tr>
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</table>

Adapted from Morgenthaler et al. 2008\textsuperscript{87}

It has been argued in the literature that reliable measurement of vasopressin in blood is hampered by (pre-)analytical factors like instability in the circulation and binding to platelets\textsuperscript{85,86,88}. Copeptin is stated to be more stable and easier to measure in comparison with vasopressin\textsuperscript{85}. Although copeptin and vasopressin correlated well in in vivo studies in healthy individuals\textsuperscript{88-90} and in critically ill patients\textsuperscript{91,92}, studies that have directly compared the stability of vasopressin and copeptin are lacking. Impaired renal function in patients with chronic kidney disease could affect the clearance of copeptin and vasopressin, since both are thought to be partially metabolized by the kidneys\textsuperscript{86,93,94}. An inverse association between copeptin and renal function has been found in several studies\textsuperscript{95-98}. Most of these studies have been conducted in patients with mild renal impairment. Literature on the effect of advanced renal failure on copeptin and vasopressin is scarce with only one published study\textsuperscript{80}. Also the impact of hemodialysis on plasma levels of copeptin and vasopressin has not been studied before. Since vasopressin and copeptin
differ considerably in molecular weight (1 kDa versus 5 kDa) it is conceivable that removal by dialysis also differs between these peptides. Removal of vasopressin by hemodialysis has been suggested previously\textsuperscript{99}, but has never been studied, nor has it been investigated for copeptin.

**Interplay between vasopressin, sympathetic activity and nitric oxide?**

The blood pressure regulating systems autonomic nervous system, the endothelium and vasopressin are not isolated entities but interact with each other. In dialysis patients, the sympathetic nervous system is generally overactive\textsuperscript{18,100-102}. One of the proposed mechanisms is that the NO inhibitor asymmetric dimethylarginine (ADMA) accumulates in renal insufficiency, resulting in less NO production\textsuperscript{57,103} with subsequent increased sympathetic activity since NO is a physiological antagonist of sympathetic activity\textsuperscript{18,104}. On the other hand, it is stated that dialysis also removes the inhibitors of NO synthase, the enzyme that facilitates conversion from the NO precursor L-arginine to NO, and thus enhances NO production\textsuperscript{105}.

Besides an effect on sympathetic activity, NO might also have a directly inhibiting effect on the release of vasopressin by the pituitary gland\textsuperscript{83} and hypothalamus\textsuperscript{106}. Blockade of NO synthesis presumably increases vasopressin secretion\textsuperscript{106}. Vasopressin, in turn, antagonizes endogenous NO\textsuperscript{105} but might also stimulate NO release, since stimulation of the V1 receptor induces production of NO in coronary vessels\textsuperscript{84}.

Also a number of interactions between the sympathetic nervous system and vasopressin is reported. At low concentrations, catecholamines activate $\alpha_1$ receptors, inducing vasopressin release. At higher concentration, catecholamines act on $\alpha_2$ and $\beta$ receptors and inhibit vasopressin release\textsuperscript{83}. Furthermore, vasopressin is stated to enhance the sensitivity of the vasculature to the vasoconstrictive effect of catecholamines\textsuperscript{80}.

It is not clear whether vasopressin mediates the stimulating effect of sodium on sympathetic nervous system activity. In a recent study in rats, it was concluded that vasopressin is one of the key neurotransmitters in the control of sympathetic activity when plasma osmolality is increased\textsuperscript{107}. Blockade of spinal vasopressin receptors eliminated the sympatho-excitatory response to increased systemic osmolality\textsuperscript{75}, indicating a role for vasopressin in the effect of osmolality on sympathetic activity. In contrast, in another study in rats it was concluded that the relationship between osmolality and sympathetic activity was independent of vasopressin concentration\textsuperscript{108}.

A simplified overview of the interplay between NO, sympathetic activity and vasopressin is depicted in Figure 2. Studying these mechanisms in a ‘stress situation’ like hemodialysis, in which the compensatory mechanisms of the body are challenged, could provide insight in the interplay between these blood pressure regulating systems.
Figure 2. Simplified and partial overview of the interplay between three major blood pressure regulating systems.

- **Vasopressin release**
  - Vasopressin levels are higher in end stage renal disease patients but generally do not change during hemodialysis.
  - At higher concentration, catecholamines inhibit vasopressin release via α2 and β receptors.
  - At lower concentrations, catecholamines stimulate vasopressin release via α1 receptors.
  - Vasopressin increases vascular sensitivity to catecholamines.
  - Vasopressin potentially mediates the effect of sodium on sympathetic activity.

- **NO production**
  - NO inhibits vasopressin release at the level of the posterior pituitary.
  - V1 stimulation in coronary vessels induces NO production.
  - NO production decreases in renal failure via accumulation of ADMA (NO inhibitor).
  - NO production increases in hemodialysis via removal of NO synthase inhibitors, shear stress and blood-membrane contact.

- **Sympathetic activity**
  - Autonomic dysfunction is present in end stage renal disease and hemodialysis patients.
Aim and outline of this thesis

In this thesis, we focus on the role of vasopressin in maintaining hemodynamic stability during hemodialysis. In chapter 2, we performed a systematic review of studies in which plasma vasopressin levels was measured during conventional hemodialysis or other hemodialysis techniques. In chapter 3, we compared the course of plasma vasopressin levels during standard hemodialysis and during Hemocontrol hemodialysis to test the hypothesis that Hemocontrol hemodialysis is associated with higher intradialytic plasma vasopressin levels. In chapter 4, we studied the course of plasma vasopressin during standard hemodialysis and Hemocontrol hemodialysis in a larger cohort of patients. In addition to vasopressin, we also compared the course of various markers of sympathetic activity and endothelial function between both dialysis techniques, to explore whether the transient increase in plasma sodium levels seen in dialysis with the Hemocontrol system affected these blood pressure regulating systems. In chapter 5, we studied whether the physiological stimuli for vasopressin release, e.g. osmotic and volume stimuli, are active in dialysis patients. In this study we used copeptin as a surrogate marker for vasopressin release. In chapter 6, we investigated the ex vivo stability of vasopressin and its surrogate marker copeptin in whole blood and plasma under different storage temperatures and durations. Also the effect of centrifugation speed of blood samples and the effect of repeated freezing and thawing on vasopressin and copeptin levels was explored. In chapter 7, we investigated the effect of renal function on copeptin, vasopressin and the copeptin/vasopressin ratio to delineate to what extent copeptin and vasopressin levels are influenced by (impaired) renal function. In addition, we compared the intradialytic course of vasopressin and copeptin as well as its clearances by hemodialysis. In chapter 8, the main findings of the studies in this thesis are summarized and discussed along with future perspectives.
References

Introduction


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