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Blood Volume Regulation During Hemodialysis

Regulatie van bloedvolume tijdens hemodialyse

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Regulatie van bloedvolume tijdens hemodialyse

Proefschrift

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Aan mijn ouders

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Chapter 1: General Introduction

1.1 Principles of hemodialysis

During hemodialysis treatment, many solutes, such as urea, sodium and potassium, which have accumulated as a result of renal failure, have to be removed. Due to reduced diuresis approximately 1.5-4.5 liters of water has to be removed during each treatment. During the procedure, blood is led through an extracorporeal circuit with an artificial kidney, and then returned to the patient, as first reported by Kolff (Figure 1)[1,2].

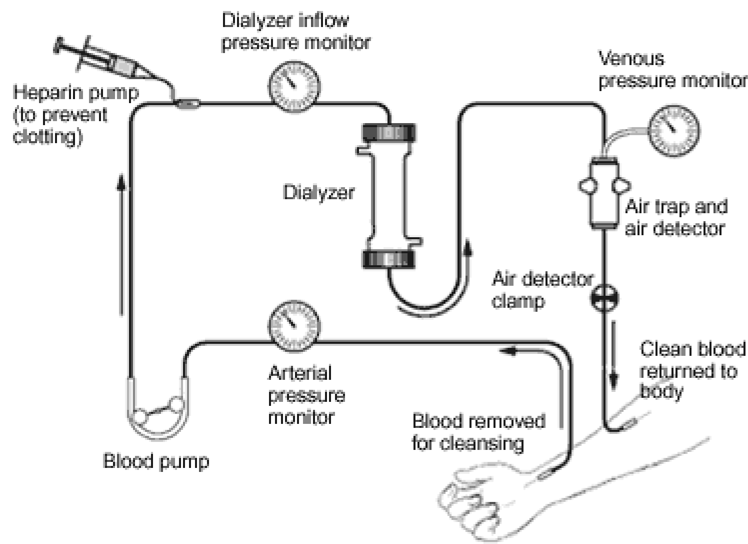
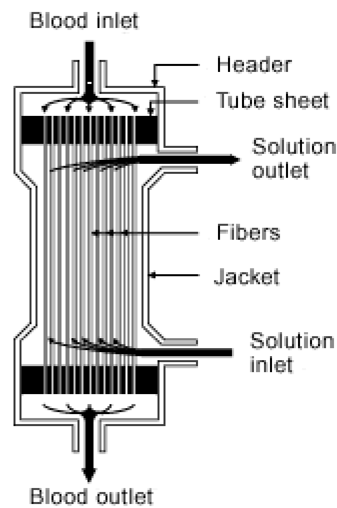


Figure 1. Hemodialysis block diagram

In the artificial kidney, blood is separated from the dialysate by a semi-permeable membrane. This membrane is permeable to solutes up to several thousand Dalton, which allows fluid and waste products to pass through, but prevents the exchange of blood components, microorganisms and endotoxins. Dialysate, flows on the other side of the membrane and in the opposite direction (Figure 2).

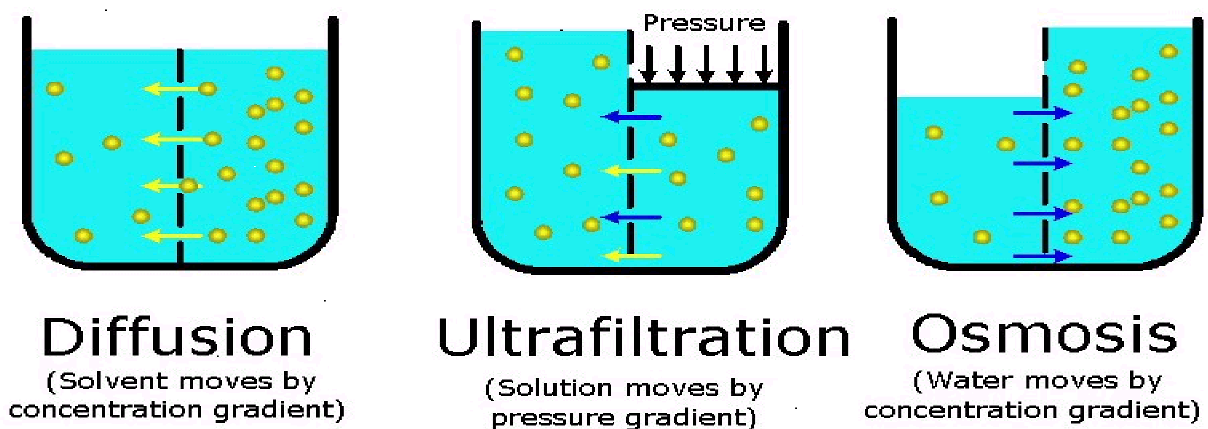
Figure 2. The Artificial kidney



Four processes control the transmembrane exchange of water and solutes: diffusion, ultrafiltration, convection and osmosis. When blood and dialysate flow through the dialyzer a transmembrane concentration gradient is formed. As governed by Fick's law this results in *diffusion* of the accumulated solutes from the intravascular space to the dialysate compartment (Figure 3). By controlling the composition of the dialysate, the concentration gradient can be altered, resulting in an appropriate transfer of solutes. Excess water is removed by *ultrafiltration*. During this process, a trans-membrane pressure (TMP) gradient is generated between the blood and dialysate compartments (Figure 3). This results in the movement of plasma water to the dialysate compartment. As water moves across the dialyzer membrane it drags along solutes (*convection)*, while solutes with a greater molecule mass, such as proteins (colloid solutes), remain within the vascular space [3,4]. The ratio of the amount of solute transported to the ultrafiltrate to the amount retained in plasma water is called the sieving coefficient. The sieving coefficient depends on the properties of the membrane (diameter of membrane pores), and on the molecular size and the chemical properties of the solute. The sieving coefficient of urea equals one and that of proteins is zero [5]. Cations, such as sodium, have a sieving coefficient slightly lower than one. This is caused by the fact that the negatively charged proteins in plasma attract cations, resulting in a decreased trans-membrane movement. This is called the Donnan effect [6-8].

Ultrafiltration can be performed in combination with hemodialysis, or without concomitant diffusive hemodialysis, i.e. isolated ultrafiltration. *Osmosis* is the net movement of water across a selectively permeable membrane, driven by a difference in the concentration of a non permeating solute on the two sides of the membrane (Figure 3). The water shift during osmosis depends on the overall concentration- and hydrostatic pressure gradients across the membrane. When fluid moves to the compartment with the lowest concentration, the hydrostatic pressure in this compartment rises, until equilibrium is reached. The difference in hydrostatic pressure between both compartments in equilibrium is called osmotic pressure. When osmotic pressure is caused by colloids, it is called colloid osmotic (oncotic) pressure. During dialysis, this process does not determine water movement across the dialyzer membrane but it is of major importance in the distribution of water between the fluid compartments [9]. During hemodialysis, fluid is withdrawn from the intravascular space. However, the excess of fluid is distributed over all fluid compartments of the body, e.g. plasma volume, interstitial volume, and intracellular volume. During ultrafiltration, plasma volume is refilled with fluid from the other compartments, as intravascular colloid osmotic pressure increases and hydrostatic pressure decreases. Nevertheless, as the result of a delay in plasma refilling, a decrease in plasma volume is inevitable when a substantial amount of fluid is rapidly removed from the relatively small intravascular space. Consequently, intermittent hemodialysis is often complicated by hypotension, which occurs in one third of the dialysis procedures [10-12].

Figure 3. Principles of hemodialysis



1.2 Hemodialysis related hypotension

Dialysis-induced hypotension has been defined as a decrease in systolic blood pressure (SBP) to below 100 mmHg and/or a decrease in SBP of 25% or more during the dialysis session [13]. Hypotension is a major cause of morbidity such as dizziness, vomiting and lightheadedness [14], but also affects the prognosis of the patient through cardiac, cerebral and mesenteric ischaemia [15-17]. The decrease in blood volume, caused by ultrafiltration and delayed *plasma refilling* from the interstitial space plays a pivotal role in the pathogenesis of dialysis related hypotension [18-21]. Moreover, compensatory mechanisms, such as *vasoconstriction*, that mobilizes blood to the central active blood volume that participates in maintaining blood pressure, may be inadequate during hemodialysis [22-25]. As it is desirable to minimize the frequency of dialysis associated hypotension, the physiology of these compensatory mechanisms during dialysis and ultrafiltration needs to be studied and strategies to improve blood volume preservation and the cardiovascular response during dialysis needs to be devised.

1.3 Blood and plasma volume during hemodialysis

Plasma Volume

During ultrafiltration, the driving forces for *plasma refilling* (J ref) are the decrease in hydrostatic pressure and the increase in colloid osmotic pressure gradients over the capillary membrane, as given by the formula of Starling:

$$J\ ref = Lp\ (\Delta\pi - \Delta p)$$ [26,27].

Thus, plasma refilling is determined by the water filtration coefficient (Lp), which depends on the total membrane surface area and the permeability of the capillary membrane. The colloid osmotic pressure gradient ($\Delta\pi$) and the hydrostatic pressure gradient (Δp) also determine capillary refilling.

Active blood volume

During hypovolemia, the compensatory response to maintain Mean Arterial blood Pressure (MAP) must act on total peripheral resistance (TPR) or on cardiac output (CO = Stroke Volume (SV) x Heart Rate (HR)) as:

$$MAP = TPR \times SV \times HR$$

A substantial percentage of the total blood volume is located in the venous system and its capacity can change markedly. This blood volume is "inactive" and does not contribute to blood pressure. During hypovolemic hypotension, *venoconstriction* mobilizes blood towards the central circulation. This increases stroke volume and helps to maintain blood pressure [28]. Both vasoactive hormones and the sympathetic nervous system regulate venous tone. However, venous tone also interacts with arterial pressure by means of the *de Jager Krogh phenomenon*. As arteriolar vasoconstriction decreases filling and reduces blood flow of the vascular bed, venous recoil of the compliant venous system reduces venous capacity and venous blood is translocated to the heart [29,30]. Arteriolar vasoconstriction, like venous vasoconstriction, results from sympathetic activation. An afferent signal to the medulla oblongata is given by the cardiopulmonary receptors (located in the atria and the pulmonary veins) and the baropressor receptors (located in the aorta and in the carotid artery) [31]. Norepinephrine (NE) is then released by the efferent nerves and causes vasoconstriction [32]. During sympathetic activation *cardiac contractility (systolic function) and heart rate* are increased [31,32]. However, from animal studies and studies using beta blockade and cardiac denervation, it can be concluded that during hypovolemia cardiac output is predominantly determined by cardiac filling [33,34]. Therefore, *diastolic left ventricular function* is of major importance in maintaining adequate cardiac output during hypovolemia. Diastolic function is the capacity of the ventricles to relax and to accept blood without a disproportionate change in ventricular pressure. When diastolic function is inadequate, stroke volume decreases rapidly during an ultrafiltration-induced reduction in cardiac filling [35].

1.4 Patient related factors affecting the blood pressure response to hemodialysis

The incidence of hypotension is not uniform in all patients on hemodialysis. Some patients appear to be hypotension prone, whereas others are hypotension-resistant. In the hypotension prone patients, not all dialysis sessions lead to hypotension.

Fluid status

In hypervolemic patients hydrostatic interstitial pressure is high. This will induce a rapid fluid shift from the interstitial intravascular compartment during ultrafiltration. Conversely, when

the patient is near normovolemia, or at hypovolemia, refilling is diminished, as fluid in the interstitial space is depleted and interstitial hydrostatic pressure is low [36-39].

It is important to determine the fluid status of the individual patient. Normovolemia is difficult to determine and clinically normovolemia is defined as the lowest possible body weight after dialysis (dry weight) without the occurrence of intradialytic symptoms. However, as some patients need antihypertensive drugs to control interdialytic hypertension a more objective measure of normovolemic weight is required. The diameter of the inferior caval vein has been proposed as a more objective measure of dry weight. Underhydration is defined as a vena cava diameter < 8 mm/m^2 body surface area, and overhydration as an inferior caval diameter >11.4 mm/m^2 body surface area [40]. In some patients, increasing the target weight to clearly hypervolemic levels may be the only way to provide a therapy without recurrent dialysis hypotension. However, overhydration has unfavorable cardiovascular effects, such as left ventricular hypertrophy leading to diastolic dysfunction.

Autonomic function

Renal failure often results from diabetes and/or hypertension, which lead to cardiovascular abnormalities, such as heart failure [41,42]. Moreover, an increasing proportion of the dialysis patients are elderly. In diabetics [43], in patients with congestive heart failure [44,45], and the elderly [46,47] cardiopulmonary and pressoreflex function are often impaired, leading to inadequate vasoconstriction and cardiac contractility. Renal failure per se could also lead to autonomic insufficiency due to accumulation of metabolic waste products [48-51]. Impaired vasoconstriction could directly affect plasma volume preservation by a change in hydraulic pressure (Δp) the total surface area (Lp) in Starling's formula. However, in most studies, a causal relation between a diminished baroreceptor function and dialysis related hypotension could not be shown [52-55].

Systolic and diastolic left ventricular function

The volume and pressure overload caused by overhydration, anemia and arterio-venous shunts lead to arterial stiffness and left ventricular hypertrophy. Both will affect the cardiovascular response during hypovolemia [56-59]. Structural abnormalities of the cardiac wall such as left ventricular hypertrophy or coronary ischaemia could lead to impaired cardiac

relaxation, which in turn results in a reduction of the compliance of the left ventricle (diastolic dysfunction) [60-61]. In clinical studies it has been shown that dialysis patients with an impaired left ventricular relaxation are particularly sensitive to hemodialysis induced hypotension [62]. ACE inhibitors or calcium antagonists may improve diastolic function in the long term, but these drugs may also induce hypotension. The most important strategy remains the prevention of left ventricular hypertrophy through timely and adequate treatment of hypertension, anemia and overhydration in the pre-dialysis phase.

1.5 Dialysis related factors affecting the blood pressure response to hemodialysis

Ultrafiltration

The total ultrafiltration volume required during a dialysis treatment is determined by the patient's interdialytic weight gain, which is related to the interdialytic sodium intake. High ultrafiltration rates will exceed the plasma refilling capacity [63-66]. Hypotensive episodes during dialysis are generally treated by stopping ultrafiltration and/or administering intravenous fluids. However, this will lead to a less than adequate treatment with overhydration and consequently cardiac failure. Cardiovascular morbidity is the major cause of death in dialysis patients [67-68]. The problem of sustained fluid overload can be solved by increasing treatment time, but this increases the infringement on the normal lifestyle of the patient, as generally three sessions a week are needed with a total treatment time of 12 to 15 hours. Frequent nocturnal dialysis could improve the tolerability of frequent fluid removal.

Dialysate sodium concentration

Lower dialysate sodium concentrations are associated with an increased incidence of hypotensive periods as compared to higher sodium concentrations [69-71]. This could be explained by the fact that high dialysate sodium concentrations increase plasma osmolarity. The increased plasma osmolarity improves plasma refilling, by inducing an osmotic fluid shift (change in $\Delta\pi$) from the intracellular to the extracellular space [71-75]. The extent to which plasma volume changes at a given dialysate sodium concentration depends on the trans-membrane sodium gradient, which is also determined by the plasma sodium concentration and the plasma concentration of anionic proteins (Donnan effect). [76,77]. On the other hand, the effect of a positive sodium gradient on hemodynamic stability could also be due to a direct

effect of sodium on vascular resistance [78]. Moreover, it is reported that dialysate sodium could increase stroke volume without any effect on total blood volume [79].
However, a positive sodium gradient increases sodium load and thereby thirst and increased inter dialytic weight gain. This results in fluid overload and consequently left ventricular hypertrophy [80]. A positive sodium gradient can therefore be applied during a limited time only. Moreover, in order to avoid a positive sodium balance, a low dialysate sodium concentration must be applied at other phases of the dialysis session.

Diffusive dialysis

It has been shown by Bergström that ultrafiltration is better tolerated when dialysis is not performed simultaneously [81-83]. Several mechanisms could explain the improved hemodynamic stability during isolated ultrafiltration, such as an increased refilling, improved cardiac function and increased vasoconstriction. During diffusive dialysis, the decrease in plasma osmolarity, due to the removal of accumulated solutes, such as urea, influences the intercompartmental fluid shifts and could delay refilling. However, urea rapidly equilibrates between the intracellular and extracellular compartments and some studies failed to observe significant differences in plasma volume preservation between ultrafiltration and ultrafiltration combined with hemodialysis [84-85]. Diffusive dialysis could worsen hemodynamic stability in hypovolemic state, as a result of a diminished ability to increase vascular tone. A change in calcium concentration due to calcium shifts could impair either myocardial contraction and relaxation [86]. Hypokalemia may also impair protective circulatory reflexes needed to avoid hypotension [87]. Moreover, diffusive dialysis impairs the ability to increase vascular tone by an increase in body temperature.

Regional blood flow

Regional blood flow affects both the distribution of blood between pooled and active blood volumes and plasma refilling. The two vascular beds that are of particular importance in the regulation of the active blood volume are the splanchnic and cutaneous circulation [88]. During ultrafiltration, the perfusion of these vascular beds is decreased by sympathical vasoconstriction. This maintains blood pressure, either directly or through the de Jager Krogh phenomenon. When having a meal, blood is pooled in the splanchnic vascular bed, and active

blood volume is consequently decreased [89]. For that reason, ingestion of food should be avoided during dialysis in patients prone to hypotension.
Blood pressure can be stabilized by cold dialysate, as this induced cutaneous vasoconstriction and blood is pooled from the cutaneous to the central active blood volume [90-94]. Therefore, an active control of body temperature can significantly improve intradialytic tolerance in hypotension prone patients [95].
A change in regional blood flow during dialysis may also affect vascular refilling by a change in both Lp and Δp in Starling's formula. Peripheral pooling could decrease vascular refilling, which could contribute to the pathogenesis of hypotension during hemodialysis.

Vasodilators
During dialysis, vasodilatory substances could be released as a result of the interaction of blood with the membrane of the artificial kidney [96]. During these interactions complement activation takes place resulting in production of interleukin-1 and tumor necrosis factor in monocytes [97-101]. These cytokines stimulate the NO synthesis from l-arginine [102,103]. NO produces cyclic guanosine 3'5' monophosphate (cGMP) in smooth muscle cells, which results in relaxation. Moreover, Endothelin-1, which has a potent vasoconstriction action, is decreased by NO [104]. L-arginine and NO synthesis are higher in uremic patients [105]. Increased NO production also directly decreases sympathetic tone [106]. However, there is no evidence that, with the exception of anaphylactic reactions, blood pressure is affected by the type of dialyzer used [98]. Apart from the direct effects of Nitric Oxide on blood pressure, the impaired vasoconstriction could also affect plasma volume by a change in hydraulic pressure and the total capillary surface area.

1.6 Strategies to improve blood pressure stability during hemodialysis

The absolute change in blood volume depends on the amount of ultrafiltration and the compensatory plasma refilling. Relative changes in total blood volume can be estimated from changes in hematocrit or total plasma protein concentration measurements, which can be measured continuously during hemodialysis [107,108].
Monitoring relative blood volume during hemodialysis and discontinuing ultrafiltration when a critical level of relative blood volume reduction is reached, has been advocated in order to

improve hemodynamic stability during dialysis [109,110]. In order to prevent hypotensive episodes, the reduction in blood volume during dialysis to critical levels can be prevented by deliberately changing the dialysate sodium concentration in order to combine an efficient ultrafiltration with a balanced sodium handling [111-118].

Blood returning from the extracorporeal circuit to the patient is cooled by the ambient temperature. This cooling of the blood is prevented by the contact of blood with heated dialysate [119,120]. The cooling effect of the extracorporeal circulation on blood temperature during isolated ultrafiltration could prevent cutaneous vasodilatation. Cooling of blood could also increase systolic left ventricular function [121]. Differences in hemodynamic stability between combined ultrafiltration/dialysis and isolated ultrafiltration disappear when treatment modalities are matched for the extracorporeal energy transfer, suggesting that this is the most important factor for the divergent vascular response [122,123].

Current limitations of blood volume modeling

At present, blood volume modeling lacks an adequate basis for several reasons. An absolute and objectively critical level of Relative Blood Volume at which hypotension occurs does not exist. Any change in patients serum osmolarity, protein concentrations or hydration status can modify the critical level. Each patient should therefore be studied several times in order to assess his or her own critical threshold. Moreover, the critical level of Relative Blood Volume depends on the cardiovascular status of the patient. During blood volume modeling an increase in relative blood volume does not prevent dialysis related hypotension when it does not result in an increase of the central active blood volume. An increase in relative blood volume during blood volume modeling could be induced by sodium profiling, and this would prevent the relative blood volume to reach the critical level at which hypotension occurs. However, the increase in relative blood volume by sodium profiling is relatively small as compared to the decrease in blood volume by ultrafiltration [124,125]. Alternatively, the effect of sodium profiling on hemodynamic stability could also result from an improved cardiovascular response. Thus, sodium profiling could lower the critical blood volume level, rather than increasing relative blood volume. Also other factors during dialysis could induce a change in critical blood level, such as temperature and changes in splanchnic blood sequestration following meals [95-101]. Therefore, for adequate blood volume modeling, it

must be known in what way these factors affect both blood volume and the critical level of relative blood volume at which hypotension occurs. Changes in vascular resistance could also alter the whole body filtration coefficient, as well as the hydrostatic capillary pressure. The direct relation between vasoconstriction and plasma refilling has previously received little attention.

1.7 Aim of the thesis

The blood pressure response during dialysis depends on blood volume preservation and/on changes in vascular tone. However, these two are not independent. In order to delineate the role of blood volume profiling in the prevention of intradialytic hypotension, more information is needed on the relationship between these physiological defense mechanisms. Therefore, we performed several studies to clarify this relationship and to improve the understanding of dialysis related hypotension. Such understanding is desperately needed before preventive measures can be initiated.

In Chapter 2, a mathematical model is constructed that simulates the intercompartmental fluid shifts during combined hemodialysis, diffusive hemodialysis, and isolated ultrafiltration. The relative theoretical effect of hydration status, dialysate sodium concentration, initial plasma concentrations of sodium and urea, and the tissue permeation capacity (change in regional blood flow) on changes in relative blood volume are analyzed.

In Chapter 3, the reproducibility of the measurement of relative blood volume during standard hemodialysis sessions, with a standard dialysate sodium concentration, and in which the decrease in relative blood volume was corrected for the amount of ultrafiltration volume, is analyzed. This study is unique in its setting, as both intra- and inter-individual differences are studied. As it is essential for blood volume modeling that the critical level of reduction in relative blood volume can be predicted in individual cases, the relationship between the occurrence of hypotension and the decrease in relative blood volume is studied.

In Chapter 4, the change in relative blood volume during diffusive dialysis without ultrafiltration is analyzed and compared with the predictions from the mathematical model. It

is unclear whether the negative effect of diffusive dialysis on hemodynamic stability results from reduced blood volume preservation or from reduced vascular reactivity. The mathematical model does not account for a decrease in vascular tone during diffusive dialysis.

In Chapter 5, the effect of isotonic saline (0.9 %), isotonic glucose (5%), hypertonic saline (3%), mannitol (20%) and glucose (20%) on relative blood volume are compared. The effect of changes in osmolarity on hemodynamic stability could be related to an effect on vascular refilling and/or changes in cardiovascular reactivity.

In Chapter 6, the pathophysiology of hemodialysis related hypotension is studied. Hypotension can be due to dialysis-related factors such as changes in osmolarity and diffusive dialysis, but also to patient related factors such as diastolic and autonomic dysfunction. In order to distinguish between dialysis related and patient related factors hypotensive dialysis sessions are compared with Lower Body Negative Pressure experiments.

In *Chapter 7*, we study the relationship between changes total peripheral resistance, and relative blood volume following pharmacological intervention. Some studies indicate that, vasoconstriction can increase relative blood volume, whereas other studies suggest a decrease in plasma volume during vasoconstriction.

In *Chapter 8*, we attempt to answer the question why some patients are hypotension prone in hypovolemic state and why others are hypotension resistant. In order to study the isolated effect of a reduction in cardiac filling, we compared the hemodynamic response to Lower Body Negative Pressure (LBNP) in hypotensive prone and hypotensive resistant patients.

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Chapter 2: A Simulation Study on the Intercompartmental Fluid Shifts during Hemodialysis.

Abstract

Hypotension is the most frequent complication during hemodialysis. An important cause of hypotension is the decrease in the intravascular volume. In addition, a decrease in plasma osmolarity may be a contributing factor. Modeling of sodium and ultrafiltration (UF) may help in the understanding of underlying relationships. We therefore simulated in a mathematical model the intercompartmental fluid shifts during standard hemodialysis (SHD), diffusive hemodialysis (DHD), and isolated ultrafiltration (IU). We analyzed the relative theoretical effect of hydration status, dialysate sodium concentration, the initial plasma concentrations of sodium and urea, and the tissue permeation to solutes on the magnitude and direction of intracellular and intravascular volume changes.

This theoretical analysis show that the transcellular fluid shifts taking place during hemodialysis treatment are for a great part due to an inhomogeneous distribution of regional blood flow and tissue fluid volumes. During hemodialysis treatment, the cellular fluid shift in tissue group with a relative high perfusion of blood and a small volume fraction occurs from the intra- to the extracellular spaces. However, the fluid shift in the tissue group with a relative low perfusion of blood and a great volume fraction takes place in the opposite direction. The UF volume and rates, and the size of sodium (Na+) gradient between the dialysate and blood side of the dialyzer membrane are the most important factors influencing the fluid shifts. Higher UF volumes and flow rates cause an increasing decline in the plasma volume in both SHD and IU. High dialysate sodium concentration (150 mEq L-1) helps plasma refilling slightly when compared with a normal dialysate sodium concentration (140 mEq L-1). However, a high dialysate sodium concentration is associated with a high plasma sodium rebound, which in turn lead to interdialytic water intake resulting from thirst and may cause increased weight gain and hypertension.

Introduction

The most frequent complication of hemodialysis is hypotension [1]. An important cause of hypotension is the decrease in intravascular volume resulting from ultrafiltration (UF). Moreover, the changes in plasma osmolarity induced by dialysis may result in intercompartmental fluid shifts [2-5]. Mathematical models were proposed to predict such volume changes by considering a 2-pool kinetic of water, urea and sodium [6-8]. More comprehensive mathematical models, including a 3-pool water kinetic have also been proposed [9-11]. These models, which differ from each other in assumptions and parametric details, have led the to conclusion that the transcellular fluid shifts caused by a rapid fall in the plasma osmolarity are relatively small and not significant as compared with the transcapillary volume shifts caused by ultrafiltration. In contrast, others [12,13] have suggested that, even with low or moderate UF, dialysis might cause severe hypovolemia by inducing a significant water shift from the plasma volume toward the intracellular space.

We simulated the intercompartmental fluid shifts during standard hemodialysis (SHD), diffusive hemodialysis (DHD) without ultrafiltration, and during isolated ultrafiltration (IU). Furthermore the relative importance of ultrafiltration volume (and flow rate), dialysate Na+ concentration, the initial plasma concentrations of Na+ and urea, and the tissue permeation capacity were determined.

Our mathematical model is based on the concept of regional blood flow [14], in which the body tissues have been categorized according to their fractions of fluid volume and blood perfusion. The tissue group (internal organs) with a relative small volume and high blood perfusion is called as the high flow system (HFS). The tissue group (skin, muscle, etc.) with a relative great volume and low blood perfusion is called as the low flow system (LFS) [14]. In each tissue group, a 2-pool model of both urea and non-urea (Na+, K+, and their accompanying anions) kinetics is combined with a 3-pool model of water kinetic. This model differs from previous classical models in that the classical two-compartment model of solute kinetic has been combined with the model of regional blood flow [14,15]. The effect of cardiopulmonary and blood access re-circulation on the dialyzer clearance has been taken into account. The present model is suitable for profiled hemodialysis.

Mathematical Model

Model description and assumptions

The model incorporates differential equations describing solute and water kinetics as a function of time (t) during hemodialysis. All symbols and units are summarized in the Appendix. The model equations and the initial values of variables are based on the following assumptions:

1. The initial volume fraction of HFS tissue group (f_v^H) equals 20% of the total body water. The volume fraction of LFS tissue group equals $1\text{-}f_v^H$. The volume fraction equals the ratio of tissue volume to that of total body water. The HFS blood perfusion fraction (f_q^H) equals 80% of the systemic arterial blood, whereas the LFS tissue group equals $1\text{-}f_q^H$ [14,15]. The perfusion fraction equals the ratio of flow rate of arterial blood, that enters the HFS tissue group, to that of the systemic arterial blood (minus the flow of blood entering the arterial blood access).
2. During hemodialysis with or without ultrafiltration, solute mass and excess water are removed from circulating arterial blood; e.g., blood is accessed through an arterio-venous device (fistula). At a flow rate of 0.3 L min^{-1}, the access re-circulation ratio equals approximately 3% of the blood flow entering the dialyzer. However, the access re-circulation depends on the flow rate of blood entering the dialyzer and the functionality of the access device.
3. The solute concentrations in arterial blood entering the tissue groups and blood access are equal. Urea, Na^+, K^+ and other unspecified non-urea blood enter the extracellular space directly. The solute mass transfer from tissue EC space to the circulating venous blood takes place by convection and diffusion. The tissue permeation coefficient (product of permeability and surface area) is constant during the whole dialysis session. However, it is likely that the tissue permeation alters during hemodialysis sessions.
4. Within each tissue group, the solute exchange through the capillary wall is neglected because of rapid diffusive exchange of small substances and high permeability of the capillary wall [10]. Consequently, small solutes are evenly distributed over both the interstitial and plasma spaces. One exception is that for charged substances the interstitial concentration is corrected for the Gibbs-Donnan effect. On calculating the solute concentrations in plasma water, the plasma water concentrations of both Na^+ and K^+

become very close to those in interstitial space. This is a result of the fact that the ratio of Donnan factor to the free water fraction is very close to1. The only barrier to solute mass exchange within each tissue group is the cell membrane. Therefore, the solute kinetic within each tissue group is described by means of a 2-pool compartment model [11].

5. The changes in osmolarity are based on the transcellular exchange and removal rates of water, urea, Na^+, K^+ and unspecified osmotically active solutes. For modeling, all unspecified solutes are lumped together as a single solute. K^+, Na^+, their accompanying anions (Cl^-) and other unspecified substances (such as Mg^{2+}, PO_4^-) are called non-urea.
6. Transvascular water exchanges according to the Starling forces. The hydraulic permeability and the compliance of intra- and extravascular spaces are constant parameters. However, it is likely that they might vary with the hydration status of the patient. They may also depend on vasoconstriction or vasodilatation. Transvascular protein mass exchange is neglected; e.g., the plasma together with interstitial space forms one single compartment for indiffusable proteins. Proteins, which enter to the interstitium by capillary filtration, return to the venous blood through the lymphatic circulation.
7. Initial hematocrit (Ht) in both tissue group is equal. The water volume of red blood cells (RBC) varies only because of the volume change of intracellular space. This is a consequence of 2-pool compartment model [10].
8. The relative change in the plasma volume represents the relative change in both the arterial and venous plasma volumes. The ratio of the arterial to the venous plasma volume is 1:4 [16]. The initial ratio of IC to EC volumes is 5:3 [16] and the initial plasma volume is 24% of the initial EC volume [17]. The initial value of total body water is 58% of the sum of patients dry weight and the weight gain [16,17]. These assumptions are true for non-overhydrated patients only.
9. The residual renal function is considered negligible.

Solute Kinetics

Intracellular solute kinetics

Whole body intracellular mass ($M_{i,j}$) of solute *j* consists of the sum of solute masses in each tissue groups intracellular spaces. The mass transfer rates of intracellular substances of both tissue groups ($J^t_{i,j}$) are equal to the sum of mass transfer rate by diffusion and convection:

$$\frac{dM^t_{i,j}(t)}{dt} = \gamma_j C^t_{i,j}(t) J^t_i(t) + f^t_v D_j [Z_j F_w(t) C^t_{e,j}(t) - C^t_{i,j}(t)] \equiv J^t_{i,j}(t) \quad (1)$$

Here, the tissue groups are distinguished by the superscript *t* that refers to *H* representing the HFS-tissue group or to *L* representing the LFS-tissue group. The subscripts *i* and *j* represent respectively the intracellular space and the solute standing for *Na* (sodium), *K* (potassium), *u* (urea), *X* (other unspecified solutes) or *n* (non-urea). The first term on the right-hand side of Equation 1 stands for the mass transfer rate by convection from the IC to the EC space, and the second term for the diffusive mass transfer rate. Convective transport takes place by solvent drag with a volume flow rate (Q^t_i), which equals the exchange rate of intracellular fluid volume. Solute sieving (γ_j) determines the rate of convective mass transport. We consider the sieving coefficient for urea (γ_u) to be one and those for K^+, Na^+ and other unspecified substances to be zero. The diffusive mass transfer rate across the cell membrane is equal to the product of the diffusive mass exchange coefficient (D_j) and the concentration gradient between both spaces. The whole body cellular mass exchange coefficient represents the product of diffusive permeability and the whole body cell surface area. The whole body mass transfer coefficients of urea, Na^+ and K^+ are 0.8 L min^{-1} [8], 1.5 L min^{-1} and 4.02×10^{-3} L min^{-1}, [11] respectively. The solute concentration in extracellular space ($C_{e,j}$) is corrected by a factor (F_w) as a result of the time-dependent change in the free water fraction of blood plasma during hemodialysis, and by a factor (Z_j) representing the solute distribution coefficient at equilibrium between IC and EC spaces. Both passive electro-diffusive and active transport via ATP-ase pumps affect the dynamic of Na^+ and K^+ transport through cellular membrane. Because Na^+ is actively transported from IC to the EC space, the equilibrium distribution coefficient Z_{Na} (= 0.0713) is less than 1. For K^+ the coefficient Z_K (= 28.2) is greater than one because K^+ is counter transported from EC into the IC space. In contrast, the IC urea depends

upon the passive transport by diffusion and convection and it is not affected by active transport. At equilibrium, the IC urea concentration equals the EC urea concentration. Therefore, the urea distribution coefficient (Z_u) equals 1.

Extracellular solute kinetics

Whole body mass ($M_{e,j}$) of solute *j* in EC space consists of the sum of solute masses in each tissue group's EC space. The solute concentration ($C^t_{e,j}$) in EC volume (V^t_e) is considered to be distributed in blood plasma, in red blood cells, and in tissue interstitial spaces. The interstitial solute concentration differs slightly from that in blood plasma ($C^t_{p,j}$) because of the Gibbs-Donnan ratio between plasma and interstitium, which is assumed 0.95 for Na^+, K^+, and 1.0 for urea and for other unspecified substance [11]. For the sake of simplicity, the RBC concentration gradients of Na^+, K^+, urea, and other unspecified substances are considered 0. Consequently, the EC solute mass is taken as the solute mass in blood plasma plus that in the interstitium. During hemodialysis, the mass transfer rates of substances in the EC spaces ($J^t_{e,j}$) of both tissue groups vary according to the following relationship:

$$\frac{dM^t_{e,j}(t)}{dt} = -J^t_{i,j}(t) + J^t_{av,j}(t) + f^t_v G_j(t) \equiv J^t_{e,j}(t) \quad (2)$$

The first term on the right-hand side of Equation 2 represents the IC mass transfer ($J^t_{i,j}$), the second term represents the mass transfer rate of solute from tissues' extracellular space to the venous blood ($J^t_{av,j}$), and the third term is the rate of the generation or intake (G_j). In this simulation work, we stipulate that urea is produced in the liver and directly enters the EC space (the whole body G_u = 0.083 mmol min^{-1} [8]. Also is considered that neither sodium nor potassium is taken (enteral or parenteral) in the EC space (G_{Na}=G_K=0 mEq min^{-1}). The following relationship gives the mass transfer rate of solute from tissue extracellular space to the venous blood:

$$J^t_{av,j}(t) = C_{a,j}(t)Q^t_a(t) - C^t_{v,j}(t)Q^t_v(t) \quad (3)$$

Equation 3 expresses the rate of solute mass gain in venous blood from the tissues EC spaces. The flow rate (Q^t_v) of blood leaving the tissue group equals the blood flow rate (Q^t_a) entering the tissue group increased by the ultrafiltration flow rate (Q_f):

$$Q^t_v(t) = Q^t_a + f^t_v Q_f(t) = f^t_q Q_a + f^t_v Q_f(t) \tag{4}$$

The flow rate of systemic arterial blood (Q_a) equals the cardiac output (CO) minus the flow rate of blood entering the blood access (Q_a^{AC}). The solute concentration in blood leaving the tissue group ($C^t_{v,j}$) is assumed to relate to the tissue EC solute concentration ($C^t_{e,j}$) according to the following relationship [14]:

$$C^t_{v,j}(t) = C^t_{e,j}(t)[1 - \exp(-\frac{f^t_v PS_j}{Q^t_v(t)})] \equiv C^t_{e,j}(t) \cdot m^t_j(t) \tag{5}$$

In Equation 5, the term m^t_j represents the coefficient of concentration equilibration between arterial and venous sides of tissue bed. The m^t_j depends upon the Péclet number, which is the ratio of the tissue permeation coefficient (PS_j) to the flow rate of blood (Q^t_v) leaving the tissue bed. PS stands for the product of permeability and tissue surface area. Solute transport from tissue bed to the venous blood is flow limited if the m^t_j equals 1.0. The solute concentration in arterial blood ($C_{a,j}$) follows from the overall mass balance:

$$C_{a,j}(t)\sum_t Q^t_a - \sum_t C^t_{v,j}(t)Q^t_v(t) = C_{a,j}(t)Q^{AC}_a - C^{AC}_{v,j}(t)Q^{AC}_v(t) \tag{6}$$

with Q_v^{AC} and C_v^{AC} denoting respectively the flow rate of and the solute concentration in blood that returns to the venous limb.

Solute kinetics in blood access and dialyzer

Solute mass in blood entering the arterio-venous access exchanges through the dialyzer membrane with the solute mass in the dialysate compartment. The rate of mass transfer between arterial and venous limbs of the blood access device equals the rate of solute mass

exchange ($J_{dial,j}$) through the dialyzer membrane, which occurs by combined diffusion and convection [7]:

$$J_{dial,j}(t) = J_{dif,j}(t) + [k_j^{CP}(t)R_{D,j}(t)F_w(t)C_{a,j}(t) - \frac{J_{dif,j}(t)}{Q_{wi,j}(t)}]Q_f(t) \qquad (7)$$

The second term on the right-hand side of Equation 7 stands for the mass transfer rate by convection combined with diffusion, in which $Q_{wi,j}$ denotes the flow rate of blood water entering the dialyzer. The solute concentration in blood entering the dialyzer is corrected for the Gibbs-Donnan ratio ($R_{D,j}$) for charged solutes between the blood and dialysate sides of the dialyzer membrane, for the time-dependent change in the free water fraction of blood plasma (F_w), and for the cardiopulmonary re-circulation (k_j^{CP}). The first term on the right-hand side ($J_{dif,j}$) represents the rate of mass transfer through the dialyzer membrane by diffusion without ultrafiltration ($Q_f = 0$) as:

$$J_{dif,j}(t) = CL_j(t)[k_j^{CP}(t)R_{D,j}(t)F_w(t)C_{a,j}(t) - C_{d,j}(t)] \qquad (8)$$

with CL_j the solute dialysance by diffusion and $C_{d,j}$ the solute concentration in the dialysate fluid entering the dialysate compartment of the dialyzer.

Water Kinetics

During hemodialysis with ultrafiltration, the EC fluid volume of both tissue groups changes because of isotonic volume loss (V^t_{uf}) by ultrafiltration (UF) and the transcellular fluid shifts:

$$\frac{dV_e^t(t)}{dt} = -\frac{dV_{uf}^t(t)}{dt} - \frac{dV_i^t(t)}{dt} \equiv Q_e^t(t) \qquad (9)$$

The second term on the right-hand side of Equation 9 stands for the exchange rate of the intracellular volume (Q^t_i) and the first term for the ultrafiltration flow rate (Q_f):

$$Q_f^t(t) \equiv \frac{dV_{uf}^t(t)}{dt} = f_v^t \frac{dV_{uf}(t)}{dt} \equiv f_v^t Q_f(t) \tag{10}$$

The rate of change in the EC volume equals also the sum of rate of change in interstitial volume (V^t_{is}), in water volume of RBC (V^t_{rc}), and in plasma volume (V^t_p):

$$\frac{dV_e^t(t)}{dt} = \frac{dV_p^t(t)}{dt} + \frac{dV_{rc}^t(t)}{dt} + \frac{dV_{is}^t(t)}{dt} \tag{11}$$

The first term on the right-hand side of Equation 11, representing the rate of change in the plasma volume, depends upon both the rate of volume gain (V^t_{pr}) from interstitial space and the rate of volume loss by ultrafiltration:

$$\frac{dV_p^t(t)}{dt} = \frac{dV_{pr}^t(t)}{dt} - f_v^t Q_f(t) \tag{12}$$

The second term on the right-hand side of Equation 11, representing the rate of change in the water volume of RBC, varies as a result of the change in the intracellular volume [10]:

$$\frac{dV_{rc}^t(t)}{dt} = \frac{V_{rc}(0)}{V_i(0)} \frac{dV_i^t(t)}{dt} \equiv Q_{rc}^t(t) \tag{13}$$

$V_i(0)$ and $V_{rc}(0)$ stand, respectively, for the initial IC volume and the initial water volume of red blood cells. The initial water volume of RBC is related to the initial plasma volume, $V_p(0)$, and the initial arterial hematocrit, $Ht(0)$:

$$V_{rc}(0) = \frac{Ht(0)V_p(0)}{1 - Ht(0)} \tag{14}$$

According to Equation 12, during dialysis with ultrafiltration the decline in plasma volume resulting from the volume loss by ultrafiltration is partially compensated for by the volume gain from the interstitial space.

Transcellular fluid shifts

The volume of fluid entering or leaving the IC compartment is referred to as the transcellular fluid shift. The rate of change (Q^t_i) in the intracellular volume (V^t_i), which equals the rate at which the transcellular fluid shift takes place, is taken to be proportional to the net osmotic pressure gradient between both EC and IC spaces:

$$\frac{dV_i^t(t)}{dt} = -f_v^t k_c RT \cdot \Delta Osm^t(t) \equiv Q_i^t(t) \qquad (15)$$

where, k_c (= 19.66x10^{-5} L mmHg^{-1} min^{-1} [8]) is the whole body cellular water exchange coefficient, R (= 62.364x10^{-3} L mmHg K^{-1} mmol^{-1}) is the gas constant, T (= 310 K) is the temperature. ΔOsm^t stands for the net osmolality difference due to the difference between the osmolality of urea (ΔOsm_u) and that of non-urea (ΔOsm_n) on both sides of the cell membrane:

$$\Delta Osm^t(t) = \Delta Osm_u^t(t) + \Delta Osm_n^t(t) \qquad (16)$$

The intra- and extracellular osmolality difference of urea is due to the difference between the IC urea ($C^t_{i,u}$) and EC urea ($C^t_{e,u}$) concentration:

$$\Delta Osm_u^t(t) = \sigma[F_w(t)C_{e,u}^t(t) - C_{i,u}^t(t)] \qquad (17)$$

with σ (=0.95) [8] representing the cellular urea reflection coefficient. In fact, urea causes no osmolality difference at equilibrium. Depending on the removal rate of other osmotically effective substances from EC spaces, there may be regional differences in the urea gradients between IC and EC spaces. The intra- and extracellular osmolality difference of non-urea is due to the non-urea concentration difference between the IC ($C^t_{i,n}$) and EC ($C^t_{e,n}$) spaces:

$$\Delta Osm_n^t(t) = \kappa[F_w(t)C_{e,n}^t(t) - C_{i,n}^t(t)] \qquad (18)$$

where κ (=1.846) [8] is the factor (osmotic coefficient) that converts the molar concentration (free plus bound) of non-urea into its osmotically equivalent osmolar concentration (osmolality). For the sake of simplicity, the osmotic coefficients of Na^+, K^+ and other unspecified non-urea solutes are taken to be equal. The molar concentration of urea is the same (κ=1) as the osmolar concentration because it is uncharged. The EC non-urea is considered to be Na^+ ($C_{e,Na}$), K^+ ($C_{e,K}$) and other unspecified electrolytes X ($C_{e,X}$). The IC non-urea is considered to be K^+ ($C_{i,K}$), Na^+ ($C_{i,Na}$) and other unspecified electrolytes X ($C_{i,X}$). At equilibrium, the osmolality on both side of the cell membrane is the same, and therefore there is no fluid exchange between intra- and extracellular spaces.

Transvascular fluid shifts

The volume (V^t_{pr}) of fluid exchanging between plasma and interstitial spaces is referred to as the transvascular fluid shift. The net rate (Q^t_{pr}) at which the transvascular fluid exchange takes place depends on the rate of water filtration (Q^t_{wf}) at the capillary end and the water reabsorption (Q^t_{wr}) at the venous capillary end:

$$\frac{dV_{pr}^t(t)}{dt} = -Q_{wf}^t(t) + Q_{wr}^t(t) \equiv Q_{pr}^t(t) \qquad (19)$$

Q^t_{pr} is known as the plasma-refilling rate (PRR) when the shift takes place from interstitial to the plasma space. According to Starling concept, water filtration rate from the arterial capillaries into the interstitial space is due to the transcapillary hydraulic and oncotic pressure gradients:

$$Q_{wf}^t(t) = f_v^t L_f \times [P_a^t(t) - P_{is}^t(t) - \Pi_p^t(t) + \Pi_{is}^t(t)] \qquad (20)$$

with L_f (=6x10^{-4} L mmHg^{-1} min^{-1}) [9] representing the whole body hydraulic permeability coefficient of the arterial capillary wall, P^t_a the hydraulic pressure in the arterial capillaries,

P^t_{is} the hydraulic pressure in the interstitial space. The hydraulic pressure in the capillary end varies due to changes in the plasma volume (V^t_p):

$$P^t_a(t) = P_a(0) + \frac{1}{\Omega_a}[\frac{V^t_p(t)}{f^t_v V_p(0)} - 1] \quad (21)$$

where $P_a(0)$ (= 35 mmHg) is the P_a at the start (at t=0) of hemodialysis treatment, $V_p(0)$ the initial V_p, and Ω_a (=0.012×venous compliance) [18] is the arterial compliance. The interstitial hydraulic pressure varies due to the change in the interstitial fluid volume:

$$P^t_{is}(t) = P_{is}(0) + \frac{1}{\Omega_{is}}[\frac{V^t_{is}(t)}{f^t_v V_{is}(0)} - 1] \quad (22)$$

with $P_{is}(0)$ (=1 mmHg) is the initial P_{is}, $V_{is}(0)$ the initial V_{is}, and Ω_{is} (=0.10 per unit interstitial hydraulic pressure) [9] the interstitial volume compliance. The oncotic pressures (Π_p) and (Π_{is}) in Equation 20, exerted respectively by the plasma and interstitial proteins, can be estimated from the following empirical relationships [19]:

$$\Pi^t_p(t) = 0.21C^t_p(t) + 1.6 \cdot 10^{-3} C^t_p(t)^2 + 9 \cdot 10^{-6} C^t_p(t)^3 \quad (23)$$

$$\Pi^t_{is}(t) = 0.28C^t_{is}(t) + 1.8 \cdot 10^{-3} C^t_{is}(t)^2 + 12 \cdot 10^{-6} C^t_{is}(t)^3 \quad (24)$$

in which the plasma (C^t_p) and interstitial (C^t_{is}) protein concentrations in gram per liters are determined from the protein mass balance between plasma and interstitial space. The water reabsorption rate depends on the hydraulic permeability coefficient (L_r =3.7x10^{-3} L mmHg^{-1} min^{-1}) [9] of the venous capillary wall and on the net pressure gradient across the venous capillary wall:

$$Q^t_{wr}(t) = f^t_v L_r \times [\Pi^t_p(t) - \Pi^t_{is}(t) - P^t_v(t) + P^t_{is}(t)] \quad (25)$$

The hydraulic pressure in the venous plasma space (P_v) varies due to the change in the plasma volume:

$$P_v^t(t) = P_v(0) + \frac{1}{\Omega_v}\left[\frac{V_p^t(t)}{f_v^t V_p(0)} - 1\right] \tag{26}$$

in which $P_v(0)$ (=15 mmHg) is the initial hydraulic pressure in the venous plasma, and Ω_v (=0.15 per unit hydraulic pressure) [9] is the venous compliance.

Methods

Predicting the diffusive clearance of K^+, Na^+ and urea

The urea dialysance equals the urea clearance since the urea concentration at the dialyzer inlet of the dialyzer is considered to be zero. However, both Na^+ and K^+ dialysance depends on their dialysate concentrations. In hemodialysis without UF the dialyzer solute clearance (CL_j) can be estimated from the following equation [20]:

$$\frac{CL_j(t)}{Q_{wi,j}(t)} = \frac{1 - \exp\left[\frac{KS_j}{Q_{wi,j}(t)}\left(\frac{Q_{wi,j}(t)}{Q_{di}} - 1\right)\right]}{1 - \frac{Q_{wi,j}(t)}{Q_{di}}\exp\left[\frac{KS_j}{Q_{wi,j}(t)}\left(\frac{Q_{wi,j}(t)}{Q_{di}} - 1\right)\right]} \tag{27}$$

with KS_j the overall (diffusive) permeability coefficient of solute *j*, which is the total membrane surface area times the diffusive mass transfer coefficient of the dialyzer, and Q_{di} the dialysate inlet flow rate that is assumed to be constant during hemodialysis. The overall permeability coefficient (KS_j) of solute *j* is related to the permeability coefficient of urea (KS_u) and that of creatinine (KS_c) [21]:

$$\frac{KS_j}{KS_u} = \frac{KS_c}{KS_u} \times \left[\frac{MW_j}{MW_c}\right]^{-0.42} \tag{28}$$

with MW_j the molecular weight (23 D for Na^+, and 39.1 D for K^+) and MW_c the molecular weight of creatinine (113 D). The ratio of KS_u to KS_c has been experimentally proven to be 1.32 [21]. The relationship given in Equation 28 might also be used to estimate the tissue permeation coefficient (PS_j) in Equation 5 for Na^+, K^+ and other unspecified solutes when the tissue permeation for urea (PS_u = 28 L min^{-1}) is known.

Cardiopulmonary and access re-circulation

The correction factor for cardiopulmonary re-circulation follows from the following relationship[14]:

$$k_j^{CP}(t) = \frac{Q_a + Q_f(t)}{Q_a + k_j^{AC}(t)CL_j(t)} \tag{29}$$

where k_j^{AC} is the correction factor for the solute clearance due to the AV- access recirculation flow rate ($Q_{R,j}^{AC}$) as given by the following expression [14]:

$$k_j^{AC}(t) = \frac{1 - \dfrac{Q_{R,j}^{AC}(t)}{Q_{wi,j}(t)}}{1 - \dfrac{Q_{R,j}^{AC}(t)}{Q_{wi,j}(t)}[1 - \dfrac{CL_j(t)}{Q_{wi,j}(t)}]} \tag{30}$$

The access re-circulation flow is corrected for the blood water fraction. We consider that it is equal for all solutes during hemodialysis.

Blood water flow rate

The blood water flow rate (at the blood inlet) ($Q_{wi\,j}$) differs from the blood flow rate entering the dialyzer (Q_{bi}) because of the time dependent changes in arterial hematocrit (Ht) and in arterial plasma protein concentration (C_p) [22]:

$$Q_{wi,j}(t) = Q_{bi}[1 - Ht(t)][1 - \alpha C_p(0)]\,F_w(t) + f_j Q_{bi} Ht(t) \tag{31}$$

where $1\text{-}\alpha C_p(0)$ is the initial free water fraction of blood plasma with $\alpha = 0.00107\ Lg^{-1}$ representing a factor to calculate the protocrit from the plasma protein concentration, f_j is the fractional volume distribution of solute *j* in blood cells ($f_u = 0.8$ for urea and $f_{Na} = f_K = 0$ for sodium and potassium [22]. The first term on the right-hand side of Equation 31 represents the plasma water flow rate and the second term the flow rate of water in red blood cells. The correction factor (F_w) is the free water fraction of blood during hemodialysis with respect to the initial water fraction:

$$F_w(t) = \frac{1 - \alpha C_p(t)}{1 - \alpha C_p(0)} \tag{32}$$

At the start of hemodialysis, where the water fraction of blood with a plasma protein concentration of $C_p(0) = 70\ g\ L^{-1}$ equals 0.925, the correction factor equals 1.0. The arterial hematocrit (Ht) varies in time according to the following relationship:

$$Ht(t) = \frac{\sum_t V_{rc}^t(t)}{\sum_t V_b^t(t)} = 1 - \frac{\sum_t V_p^t(t)}{\sum_t V_b^t(t)} \tag{33}$$

where the blood volume (V_b) equals the sum of plasma volume (V_p) and the volume of red blood cells (V_{rc}).

The Gibbs-Donnan ratio

The Gibbs-Donnan ratio ($R_{D,j}$) between the blood and dialysate compartments of the dialyzer equals 1 for urea (because it is uncharged) and approximately 0.942 for Na^+ and K^+ [7,8], but also varies due to changes in the plasma protein concentration (C_p) [23]:

$$R_{D,j}(t) = 1.007 - 9 \cdot 10^{-4} \frac{1}{2}[C_{pi}(t) + C_{po}(t)] \tag{34}$$

where the protein concentration at the dialyzer blood outlet (C_{po}) differs from that at the blood inlet ($C_p = C_{pi}$) when UF takes place:

$$C_{po}(t) = \frac{[1 - Ht(t)]C_{pi}(t)Q_{bi}}{[1 - Ht(t)]Q_{bi} - Q_f(t)} \tag{35}$$

Without ultrafiltration (and pre-dilution), the arterial hematocrit and plasma protein concentration in blood leaving the dialyzer equal the hematocrit and plasma protein concentration in blood entering the dialyzer.

Initial solute composition of extra- and intracellular spaces

The whole body initial concentrations of the IC Na^+, K^+ and urea are calculated from their initial plasma concentrations ($C_{p,\,Na}(0)$ = 140 mEq L^{-1}, $C_{p,\,K}(0)$ = 5 mEq L^{-1} and $C_{p,\,u}(0)$ = 30 mmol L^{-1} respectively):

$$C_{i,Na}(0) = Z_{Na}C_{e,Na}(0) = \frac{Z_{NA}C_{p,Na}(0)}{1 - \alpha C_p(0)} \tag{36}$$

$$C_{i,K}(0) = Z_K C_{e,K}(0) = \frac{Z_K C_{p,K}(0)}{1 - \alpha C_p(0)} \tag{37}$$

$$C_{i,u}(0) = C_{e,u}(0) = \frac{C_{p,u}(0)}{1 - \alpha C_p(0)} \tag{38}$$

The initial non-urea plasma osmolarity ($Osm_{p,\,n}$) is considered mainly due to plasma Na^+ ($C_{p,\,Na}$) and to a minor extend due to plasma K^+ ($C_{p,\,K}$) and other unspecified substances ($C_{p,\,X}$):

$$Osm_{p.n}(0) = \kappa[C_{p,Na}(0) + C_{p,K}(0) + C_{p,X}(0)] \tag{39}$$

The initial EC non-urea osmolarity equals the initial non-urea plasma osmolarity divided by the free water fraction:

$$\kappa[C_{e,Na}(0) + C_{e,K}(0) + C_{e,X}(0)] = \frac{Osm_{p,\,n}(0)}{1 - \alpha\, C_p(0)} \qquad (40)$$

Because the normal initial plasma osmolarity due to osmotically active non-urea, which is considered to be 285 mosmol L^{-1}, and the initial plasma Na^+ and K^+ concentrations are given, the unspecified EC non-urea concentration can be calculated as:

$$C_{e,X}(0) = \frac{Osm_{p,\,n}(0)}{\kappa\,[1 - \alpha\, C_p(0)]} - C_{e,Na}(0) - C_{e,K}(0) \qquad (41)$$

The IC non-urea is considered to be mainly K^+ ($C_{i,\,K}$) and to a minor extent Na^+ ($C_{i,\,Na}$) and other unspecified substances ($C_{i,\,X}$). The initial unspecified IC non-urea concentration can be calculated from the following relationship:

$$C_{i,X}(0) = \frac{Osm_{p,n}(0)}{\kappa\,[1 - \alpha C_p(0)]} - C_{i,Na}(0) - C_{i,K}(0) \qquad (42)$$

At equilibrium, the total initial plasma osmolality is equal to 290 mosmol L^{-1} with a normal initial urea concentration of 5 mmol L^{-1}.

Computational methods for solute and protein concentrations

Calling Δt a time element on which all variables are considered to be constant, all the first order differential equations governing the changes in volumes and solute masses are numerically solved in the commercially available spreadsheet MS Excel 97®

For each tissue group, the time-dependent changes in both intracellular mass ($M^t_{i,\,j}$) and extracellular mass ($M^t_{e,\,j}$) of Na^+, K^+ and urea are computed from the following difference equations:

$$M^t_{i,j}(t+\Delta t) = M^t_{i,j}(t) + J^t_{i,j}(t)\cdot\Delta t \tag{43}$$

$$M^t_{e,j}(t+\Delta t) = M^t_{e,j}(t) + J^t_{e,j}(t)\cdot\Delta t \tag{44}$$

The initial value of $M^t_{i,j}$ equals $f^t_v V_i(0) C_{i,j}(0)$ and that of $M^t_{e,j}$ equals $f^t_v V_e(0) C_{e,j}(0)$. $J^t_{i,j}$ and $J^t_{e,j}$ are given by Equation 1 and Equation 2 respectively. Given the exchange rate of intracellular fluid (Q^t_i) as in Equation 15 and the exchange rate of intracellular fluid (Q^t_e) as in Equation 9, the time-dependent changes in both intra- and extracellular volumes can be computed from the following difference equations:

$$V^t_i(t+\Delta t) = V^t_i(t) + Q^t_i(t)\cdot\Delta t \tag{45}$$

$$V^t_e(t+\Delta t) = V^t_e(t) + Q^t_e(t)\cdot\Delta t \tag{46}$$

The initial values of V^t_i and V^t_e equal $f^t_v V_i(0)$ and $f^t_v V_e(0)$ respectively. The time-dependent change in the transcellular fluid shift is calculated as $\Delta V^t_i(t)=V^t_i(0)-V^t_i(t)$. The starting value of whole body V_i (V_e) is estimated as 5/8 (3/8) times the sum of the total body water and the weight gain (excess water volume).
The total body water volume is estimated as 58% of the dry body weight. The time-dependent changes in plasma volume (V^t_p) are calculated as the difference between the plasma refilling rate (Q^t_{pr}) from Equation 19 and the cumulative volume loss (V^t_{uf}) by UF:

$$V^t_p(t+\Delta t) = V^t_p(t) + [Q^t_{pr}(t) - f^t_v Q_f(t)]\cdot\Delta t \tag{47}$$

The initial plasma volume, $V^t_p(0) = f^t_v V_p(0)$, is estimated as 24% of the initial EC volume. The cumulative volume gain by plasma refilling from the interstitial space and the volume loss from the plasma volume by ultrafiltration are computed as follows:

$$V^t_{pr}(t+\Delta t) = V^t_{pr}(t) + Q^t_{pr}(t)\cdot\Delta t \tag{48}$$

$$V^t_{uf}(t+\Delta t) = V^t_{uf}(t) + f^t_v Q_f(t)\cdot\Delta t \tag{49}$$

The initial values of V^t_{pr} and V^t_{uf} equal zero. At the end of dialysis session ($t=T_d$), Equation 48 results in the total plasma water volume gain (loss) from (to) the interstitial space. At $t=T_d$, Equation 49 results in the total volume loss by ultrafiltration that equals the initially determined weight gain (excess water volume). The ultrafiltration flow rate can be profiled as desired. In this simulation work, we utilize a constant ultrafiltration flow rate during hemodialysis and calculate it by dividing the excess water volume by the duration of dialysis session. We calculate the relative time-dependent change in the plasma volume as $RV^t_p(t) = [V^t_p(t)/V^t_p(0)] - 1$. The time-dependent changes in the water volume of RBC are calculated as:

$$V^t_{rc}(t + \Delta t) = V^t_{rc}(t) + Q^t_{rc}(t) \cdot \Delta t \tag{50}$$

where the initial value of $V^t_{rc}(0)=f^t_v V_{rc}(0)$, and Q^t_{rc} is calculated from Equation 13. The interstitial volume is calculated as the EC volume minus the blood volume:

$$V^t_{is}(t) = V^t_e(t) - V^t_b(t) = V^t_e(t) - [V^t_p(t) + V^t_{rc}(t)] \tag{51}$$

On dividing the solute mass by the volume, the intra- and extracellular concentrations of Na^+, K^+ and urea are calculated:

$$C^t_{i,j}(t) = \frac{M^t_{i,j}(t)}{V^t_i(t)} \qquad C^t_{e,j}(t) = \frac{M^t_{e,j}(t)}{V^t_e(t)} \tag{52}$$

The unspecified substances are not removed across the dialyzer membrane. Consequently, their time-dependent changes in both intra- and extracellular spaces are due to changes in volumes:

$$C_{i,X}^{t}(t)=\frac{V_{i}^{t}(0)C_{i,X}^{t}(0)}{V_{i}^{t}(t)} \qquad C_{e,X}^{t}(t)=\frac{V_{e}^{t}(0)C_{e,X}^{t}(0)}{F_{w}(t)V_{e}^{t}(t)} \tag{53}$$

Total plasma protein and interstitial protein concentrations can be computed as:

$$\frac{C_{p}(t)}{C_{p}(0)}=\frac{V_{p}(0)}{\sum_{t}V_{p}^{t}(t)} \qquad \frac{C_{is}(t)}{C_{is}(0)}=\frac{V_{is}(0)}{\sum_{t}V_{is}^{t}(t)} \tag{54}$$

in which the initial plasma and interstitial protein concentration are considered respectively as $C_p(0) = 70$ g L^{-1} and $C_{is}(0) = 19.2$ g L^{-1} to obtain a zero plasma refilling rate at t = 0.

Adequacy of dialysis treatment

To evaluate the adequacy of hemodialysis sessions we calculate the dialysis dose (Dd), which is known as KT/V-value in the literature [24]. An adequate dialysis treatment for urea is achieved if the *total* urea clearance per treatment is higher than the post-dialysis volume of urea distribution (V_i+V_e) in patients who have negligible residual renal function. This statement is characterized by dialysis dose. We calculate the cumulative dialysis dose during hemodialysis by making use of Equation 7:

$$Dd(t+\Delta t)=Dd(t)+\frac{J_{dial,u}(t)\cdot\Delta t}{k_{u}^{CP}(t)F_{w}(t)C_{a,u}(t)\sum_{t}[V_{i}^{t}(t)+V_{e}^{t}(t)]} \tag{55}$$

At t=0 the dialysis dose equals zero. At t=T_d (the end of dialysis session), Equation 55 results in the value of dialysis dose. In general, a dialysis dose of 1.2 to 1.4 achieved at the end of a dialysis session lasting T_d = 4 hours on a trice weekly basis has been shown to be associated with decreased mortality [24].

Results

Simulations

We simulated diffusive hemodialysis (DHD) session with zero UF rate (Q_f = 0) to correct uremia with a dialysis dose of 1.2, isolated ultrafiltration (IU) treatment ($CL_u = CL_{Na} = CL_K$ = 0) to correct excess water, and standard hemodialysis (SHD) session to correct uremia with a dialysis dose of 1.25 and to withdraw excess water simultaneously. All simulated sessions, each lasting 4 hr, were calculated for an adult of 72 Kg dry-weight with an excess water volume of 3.2 L, and with an initial plasma urea concentration of 30 mmol L^{-1} indicating the initial uremic state. The dialysate Na^+ and K^+ concentrations were 140 and 2 mEq L^{-1} respectively. The initial diffusive clearance values of urea, Na^+ and K^+ were calculated as 0.225, 0.19 and 0.186 L min^{-1} respectively from Q_{bi} = 0.3 L min^{-1}, Q_{di} = 0.5 L min^{-1} and SK_u = 0.72 L min^{-1}. The tissue permeation coefficients of Na^+ and K^+ were calculated from that of urea (PS_u = 28 L min^{-1}) according to Equation 28. The cardiac output and the arterial blood access flow rate were 6.3 and 0.8 L min^{-1} respectively. The access flow recirculation ratio was assumed 0.03. The fractions of tissue volume and blood perfusion were $f^H{}_v$ = 0.2, $f^H{}_q$ = 0.8, for HFS, and $f^L{}_v$ = 0.8, $f^L{}_q$ = 0.2 for the LFS, corresponding to m^H = 0.98 and m^L = 0.64 for urea.

Transcellular fluid shifts

Figure 1 shows time courses (bold thick lines) of the exchange rates of IC fluid (Q_i) and the resulting fluid shifts (ΔV_i) in HFS, LFS and HFS+LFS during DHD. Both tissue groups are assumed to have equal fractions of volumes ($f^L{}_v = f^H{}_v = 0.5$) and equal fractions of blood perfusion ($f^L{}_q = f^H{}_q = 0.5$), corresponding to $m^L = m^H = 0.92$. During early hours of DHD, the sum of transcellular osmolar gradients in both tissue groups due to changes in urea and non-urea concentrations result in a negative net osmolar gradient (Q_i <0). This causes a fluid shift from the EC to the IC space. Note that the magnitude of fluid shift equals the area under the net Q_i-curve. After that an equilibrium state (Q_i = 0) is reached, the net osmolar gradients become positive (Q_i >0) and increase gradually to the end of treatment, causing a decrease in the fluid shift from EC to the IC spaces. The osmolar gradients in both tissue groups develop equally.

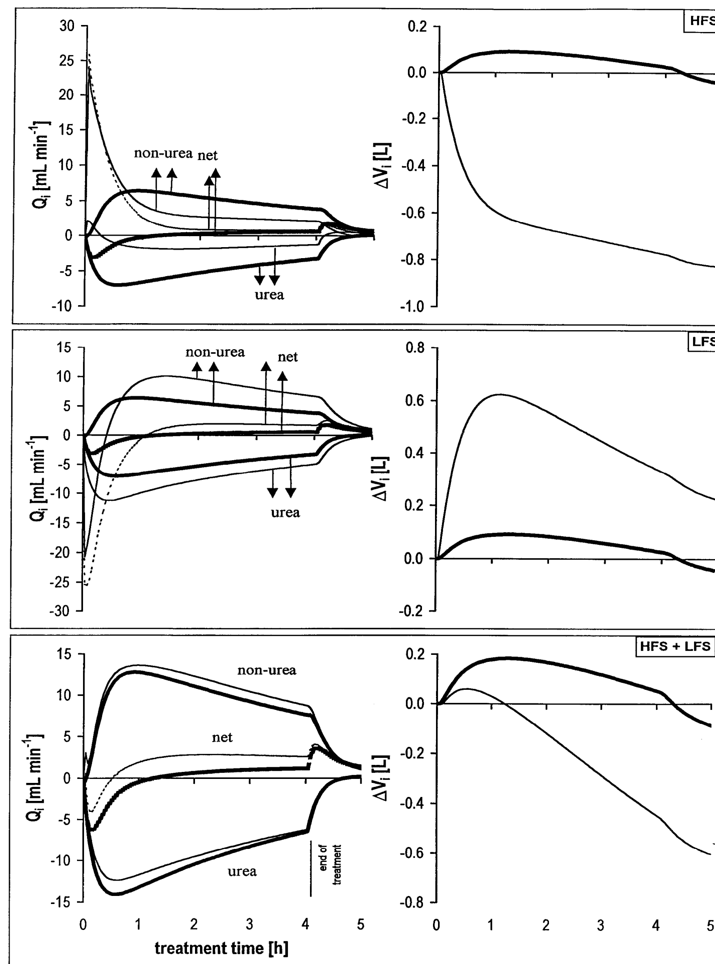

Figure 1

Simulated time changes in the exchange rate of intracellular fluid (Q_i) during diffusive hemodialysis, and the resultant transcellular fluid shifts (ΔV_i). The HFS and LFS tissue groups have different fractions of volume (f^L_v = 0.8, f^H_v = 0.2) and blood perfusion (f^L_q = 0.2, f^H_q = 0.8). The HFS+LFS represents the overall tissue. The bold thick lines represent the changes in Q_i and ΔV_i when the tissue groups are assumed to have equal fractions of volume ($f^L_v = f^H_v$ = 0.5) and blood perfusion ($f^L_q = f^H_q$ = 0.5).

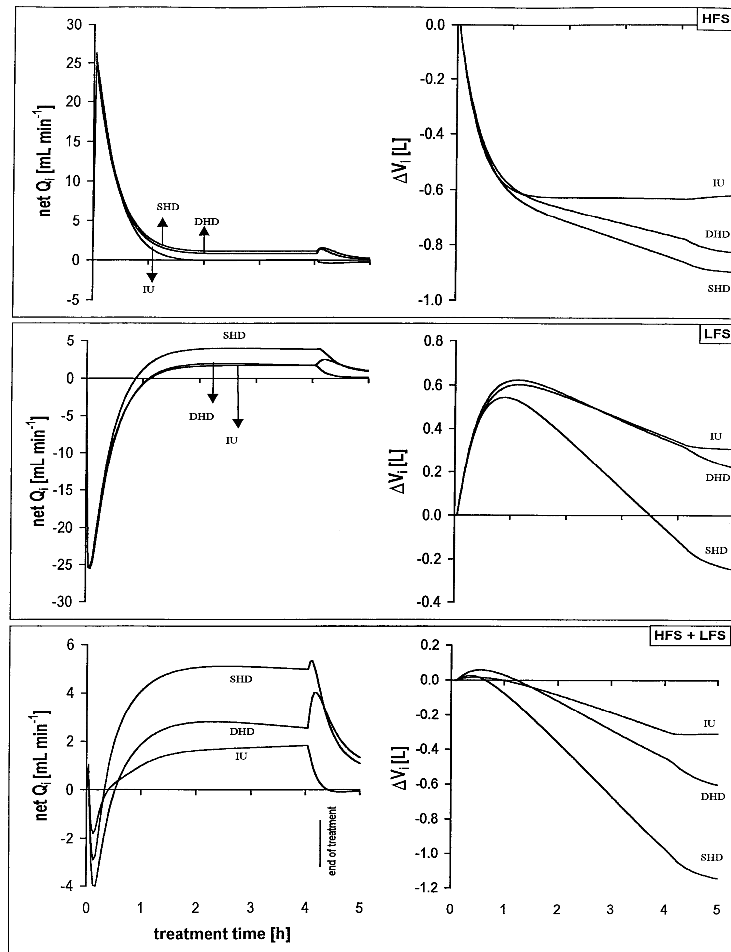

Figure 2 .

Simulated time courses of Q_i during diffusive hemodialysis (DHD), isolated ultrafiltration (IU) and standard hemodialysis (SHD), and the resultant fluid shifts (ΔV_i). The HFS and LFS tissue groups have different fractions of volume ($f^L_v = 0.8$, $f^H_v = 0.2$) and blood perfusion ($f^L_q = 0.2$, $f^H_q = 0.8$).

Consequently, the fluid shifts in both tissue groups are equal (0.027 L in HFS, 0.027 L in LFS, accounting for an overall fluid shift of 0.054 L). After the end of treatment, the net osmolar gradients in both tissue groups tend to disappear, causing the fluid eventually to shift out of the cells. *Figure 1 (thin lines)* shows the time-dependent changes in Q_i and ΔV_i during DHD in the tissue groups with different fractions of volume and blood perfusion. The transcellular fluid in the HFS tissues shifts from IC to the EC space, while that in the LFS tissues takes place in the opposite direction. The overall fluid shift at the end of treatment accounts for 0.45 L out of the cells (0.77 L out of cells in HFS, and of 0.33 L into cells in LFS). This indicates that the transcellular fluid shifts taking place during DHD are, to a great part, due to an inhomogeneous distribution of regional blood flow and tissue fluid volumes.

In Figure 2, the net osmolar gradients and the resulting transcellular fluid shifts during IU and SHD sessions are compared with those during DHD sessions. The magnitudes of net osmolar gradients in HFS during both DHD and SHD sessions are almost equal, indicating that the effect of ultrafiltration on the fluid shift in HFS is relatively small. The magnitudes of net osmolar gradients in LFS during both IU and DHD sessions are almost equal, indicating that the effect of diffusive solute exchange on the fluid shift in LFS is, once again, relatively small. The overall fluid shift at the end of session accounts for –0.29 L (-0.63 L in HFS, 0.34 L in LFS) with IU. Note that $\Delta V_i<0$ indicates a fluid shift from intra- to the extracellular space. With SHD, the overall fluid shift is –0.97 L (-0.85 L in HFL, -0.11 L in LFS).

Plasma refilling rate and depletion of plasma volume

The time courses of the transvascular fluid exchange (Q_{pr}) and the relative changes in the plasma volume (RV_p) during the modeled sessions of IU, DHD and SHD are depicted in *Figure 3*. Although excess water is withdrawn with constant UF flow rates, the plasma volumes of both HFS and LFS tissues groups decrease the fastest within the first hour of UF treatment. One half of the total depletion of plasma volumes occurs in this early hour, as the response of Starling forces to refill the plasma volume is lacking. After reaching its maximum value within the first hour, the Q_{pr} in HFS tissue group decreases slightly during the later treatment, leading to a gradual decline of plasma volume.

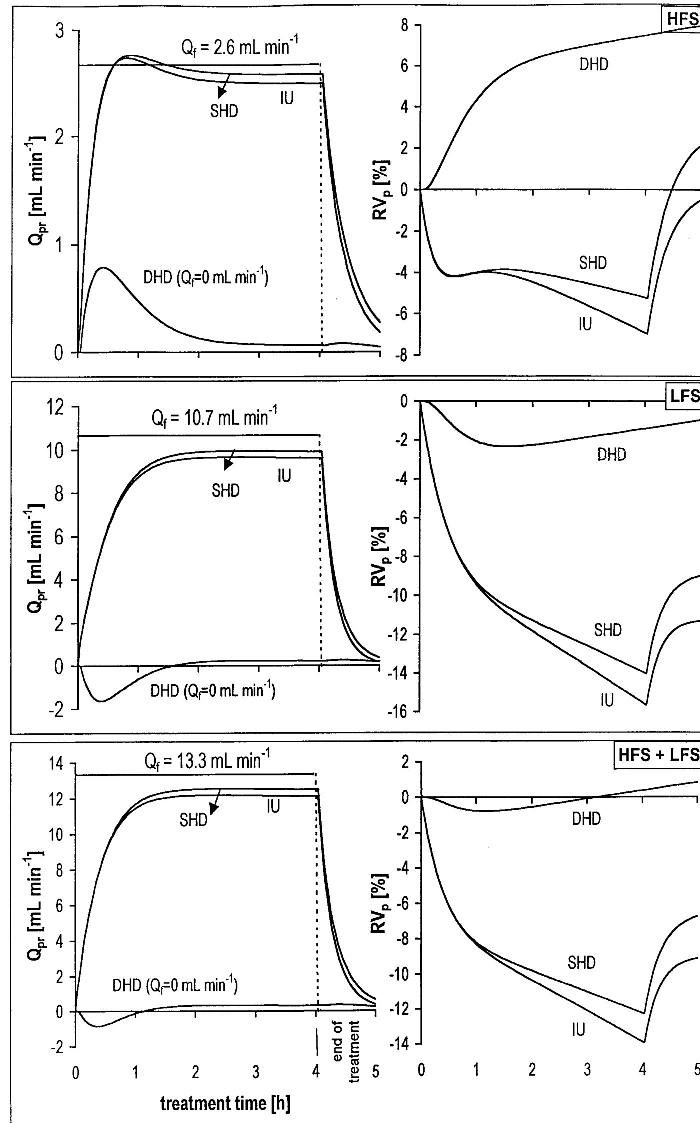

Figure 3

Simulated time changes in the plasma refilling rate (Q_{pr}) and the relative changes in the plasma volumes (RV_p) during DHD, IU and SHD. The HFS and LFS tissue groups have different fractions of volume ($f^L_v = 0.8$, $f^H_v = 0.2$) and blood perfusion ($f^L_q = 0.2$, $f^H_q = 0.8$).

The Q_{pr} in LFS tissue group reaches its maximum slower than that in the LFS tissue group and remains unchanged during the later treatment, leading to a linear decrease in plasma volume. The difference between the area (V_{uf}) under the line representing the UF flow rate and the area (V_{pr}) under the theoretical Q_{pr}-curve corresponds to the depletion of the initial plasma volume due to insufficient refilling from the interstitial space. The smaller the difference between V_{uf} and V_{pr} ,the higher the plasma refilling capacity. The depletion of plasma volume in the HFS tissue group accounts for 7% while that in LFS tissue group is almost two times more (15.6%). After stopping the treatment, the Q_{pr} decreases and returns to 0. During this period, the fluid shift from interstitial space causes the plasma volume to increase. When the same amount of excess water is withdrawn by performing SHD, the degree of depletion of the plasma volume in both tissue groups is slightly smaller (1.7%) than with IU, emphasizing the fact that the diffusive solute removal only has a minor influence on plasma volume depletion. When dialysis is performed without UF, the plasma volume of the HFS tissue group increases up by 7.5% due to the plasma refilling from the interstitial space. In contrary, the plasma volume of the LFS tissue group decreases by 1.4% as a result of volume loss to the interstitial space. Note that the relative depletion of the overall (total) plasma volume is not equal to the linear sum of the relative depletions of plasma volumes of both tissue groups. When both tissue groups are assumed to have equal fractions of volume and blood perfusion, the time-dependent changes in Q_{pr} in both systems develop equally. Consequently, both tissue groups contribute equally to the depletion of the overall plasma volume.

Sensitivity Analysis

We investigated the relative importance of variables such as ultrafiltration flow rate and volume, dialysate Na^+ concentration, initial plasma Na^+ and urea concentrations, and the tissue perfusion (PS) on the exchange rate of intracellular fluid (Q_i) and the plasma refilling rate (Q_{pr}) during SHD, by performing a sensitivity analysis (one variable changes while all others are held unchanged).

Ultrafiltration flow rate and volume.

An UF volume equal to the excess water (several liters of fluid) is removed during the course of a SHD session or by IU with constant or profiled ultrafiltration flow rates. *Figure 4* shows the effect of removing the same amount of excess water (2.4 L) with different (constant) ultrafiltration rates, and the effect of removing different amount of excess water (2.4 L, 4.8 L) within the same duration of SHD (4h) on the transcellular and transvascular fluid shifts during SHD. Withdrawal of an excess volume of 2.4 L in a short (T_d = 2h) and fast (Q_f = 20 mL min^{-1}) hemodialysis causes a fluid shift of –0.49 L (-0.73 L in HFS, 0.24 L in LFS). The same amount of excess water in a long (T_d= 4h) and slow (Q_f = 10 mL min^{-1}) hemodialysis results in a fluid shift of –0.83 L (-0.82 L in HFS, -0.01 L in LFS). It is evident that the shorter the session (thus the higher the UF flow rate) the harder the net osmolar gradient develops, and consequently the greatest the amount of fluid shift to the EC space. However, due to diffuison a higher amount of solute (urea, Na^+, K^+) is removed in longer than in shorter hemodialysis, leading to a greater fluid shift at the end of a longer session than that with a shorter session. At the end of session lasting 4 h, the slow UF together with the fluid shift to the EC space improves the plasma refilling capacity by 4.7% (6.2% in HFS, 4.4% in LFS). By prolonging the duration of treatment session with a high UF flow rate (Q_f = 20 mL min^{-1}) 2 hours longer, an excess volume of 4.8 L is withdrawn, causing an increased fluid shift to the EC space (–1.25 L, -0.92 L in HFS, -0.33 L in LFS). Nevertheless, despite this increased fluid shift to the EC space, the capacity to refill the plasma volume decreases by 3.6% (2% in HFS, 4% in LFS). The response of Starling forces to refill the plasma volume decreases with the increasing volume of ultrafiltration.

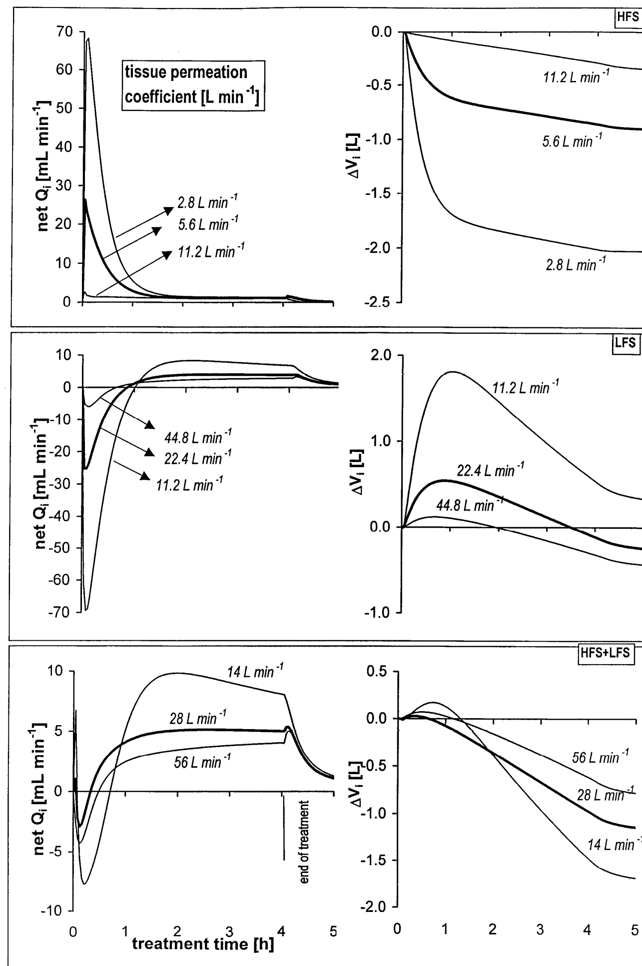

Figure 4

Simulated time courses of the net Q_i (a), the resultant ΔV_i (b), the Q_{pr} (c), and the RV_p (d) in the HFS+LFS during SHD for three cases of ultrafiltration. 1) An excess water volume of 2.4 L is withdrawn in a short (2 h) and rapid (Q_f = 20 mL min^{-1}) hemodialysis (bold thick lines). 2) The same volume of excess water (2.4 L) is withdrawn in a relative long (4 h) and slow (Q_f = 10 mL min^{-1}) hemodialysis. 3) The rapid (Q_f = 20 mL min^{-1}) hemodialysis is prolonged to 4 h to withdraw an excess water volume of 4.8 L.

Dialysate sodium concentration.

Figure 5 shows the time courses of Q_i and Q_{pr} during SHD with different dialysate Na^+ concentrations and with an initial plasma Na^+ concentration of 140 mEq L^{-1}. At the low (120 mEq L^{-1}) dialysate Na^+ concentration, the plasma Na^+ concentration at the end of session is changed by 3.6% (17.4% in HFS, -0.9% in LFS). The net osmolar gradient reaches an equilibrium state almost at the end of the session, causing a fluid shift of 0.82 L (-0.47 L in HFS, 1.29 L in LFS). The plasma refilling is 5% (3% in HFS, 5.4% in LFS) less than when a dialysate Na^+ concentration of 140 mEq L^{-1} (normal) is used. At the high (150 mEq L^{-1}) dialysate Na^+ concentration, the overall plasma Na^+ concentration at the end of the session of SHD is changed by 8.1% (22.7% in HFS, 3.4% in LFS). The net osmolar gradient at the end of the session causes a fluid shift of -1.81 L (-1.03 L in HFS, -0.78 L in LFS). Due to the fluid shift to the EC space, the plasma refilling is improved by 2.1% (1.3% in HFS, 2.4% in LFS), when compared to the normal dialysate Na^+ concentration.

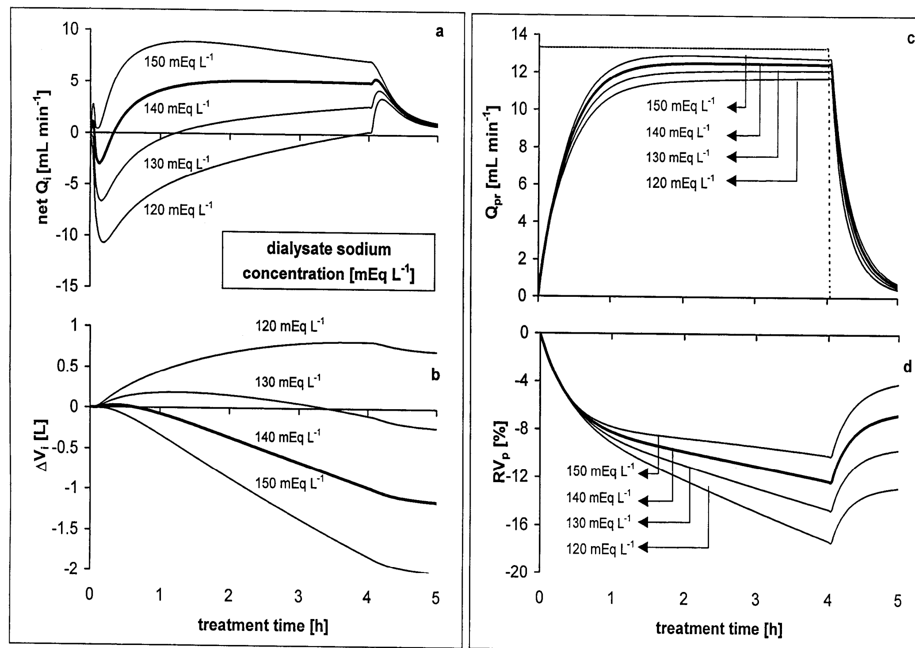

Figure 5

Simulated time changes in the net Q_i (a), the resultant ΔV_i (b), the Q_{pr} (c), and the changes in RV_p (d) in the HFS+LFS during SHD. Initial plasma Na^+ concentration (140 mEq L^{-1}) is fixed and dialysate Na^+ concentration is varied from 120 mEq L^{-1} to 150 mEq L^{-1}.

Initial plasma sodium concentration

The changes in Q_i and RV_p due to different initial plasma Na^+ concentrations during SHD (with C_{dNa} = 140 mEq L^{-1}) are shown in *Figure 6*. The initial plasma Na^+ concentration was varied by ±3.6% from 140 mEq L^{-1}. Hereby, the initial IC Na^+ concentration was calculated so that at the start of each session the osmolality on both sides of the cell membrane is equal. At 135 mEq L^{-1}, a fluid shift of 1.44 L (0.9 L in HFS, 0.54 L in LFS) takes place out of the cells due to an increased plasma Na^+ concentration. The plasma refilling is 1.6% (0.4% in HFS and 1.9% in LHF) more than at a normal plasma Na^+ concentration (140 mEq L^{-1}). However, at 145 mEq L^{-1} the fluid shift accounts for -0.46 L (-0.81 L in HFS, +0.35 L in LFS). The plasma refilling is 1.8% (0.4% in HFS, 2.1% in LFS) less than at a normal plasma Na^+ concentration.

Initial urea concentration

The changes in Q_i and RV_p due to different initial urea concentrations during SHD are also shown in *Figure 6*. The initial plasma urea concentrations (both in the intra- and extracellular space) were varied by ±10 mmol L^{-1} from 30 mmol L^{-1}. In all cases the fluid shift from EC to the IC space occurs in the first hour of treatment. The fluid shift to the EC space decreases slightly with the increasing urea concentration. It varies from 1 L (0.86 L in HFS, 0.14 L in LFS) at 20 mmol L^{-1} to 0.93 L (0.85 L in HFS, 0.08 L in LFS) at 40 mmol L^{-1}. A variation in the initial urea concentration by ±10 mmol L^{-1} from 30 mmol L^{-1} has no remarkable effect on the plasma refilling capacity.

Tissue permeation capacity

An averaged value of 20 L min^{-1} for the tissue urea permeation coefficient was reported in the literature [14]. It is very likely that this quantity might vary from patient to patient, and even during treatment in one patient. The higher the tissue permeation coefficient, the faster the concentration in tissue equilibrates with that in venous blood (flow-limited transport). Figures 7 and 8 show respectively the time-dependent changes in the transcellular and transvascular fluid shifts during SHD, when the tissue permeation coefficient is varied by ±50% from 28 L min^{-1}. The lower the tissue permeation capacity the higher the amount of fluid shift out of the cells in the HFS tissue group, and the higher the plasma refilling capacity. In the LFS tissue

group, a decreased tissue permeation coefficient causes the fluid to move in the cell. The lower the tissue permeation capacity the lower the plasma refilling capacity in the LFS tissue groups. A higher value of the tissue permeation coefficient than 28 L min^{-1} does not affect the overall plasma refilling.

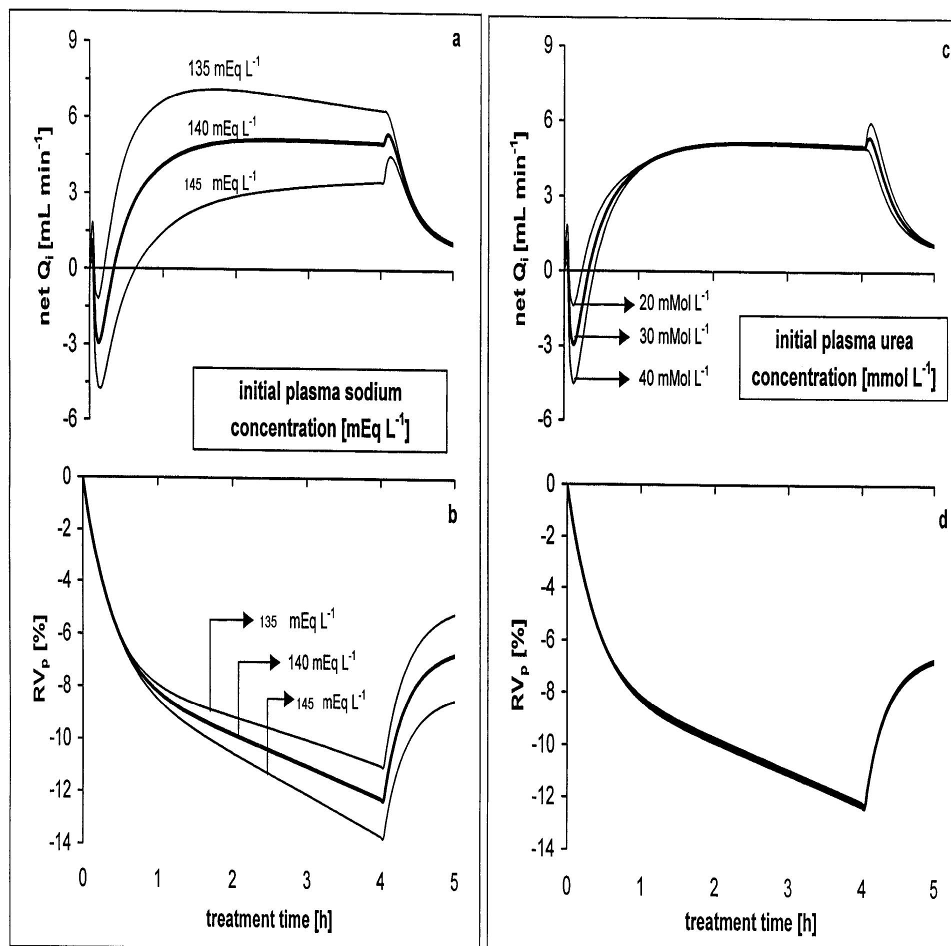

Figure 6

Simulated time courses of the net Q_i (a) and the RV_p (b) in the HFS+LFS during SHD. Dialysate Na^+ concentration (140 mEq L^{-1}) is fixed and initial plasma Na^+ concentration is varied from 135 mEq L^{-1} to 145 mEq L^{-1}. Time courses of the net Q_i (c) and the changes in RV_p (d) when the initial concentration of plasma urea is varied from 20 mmol L^{-1} to 40 mmol L^{-1}.

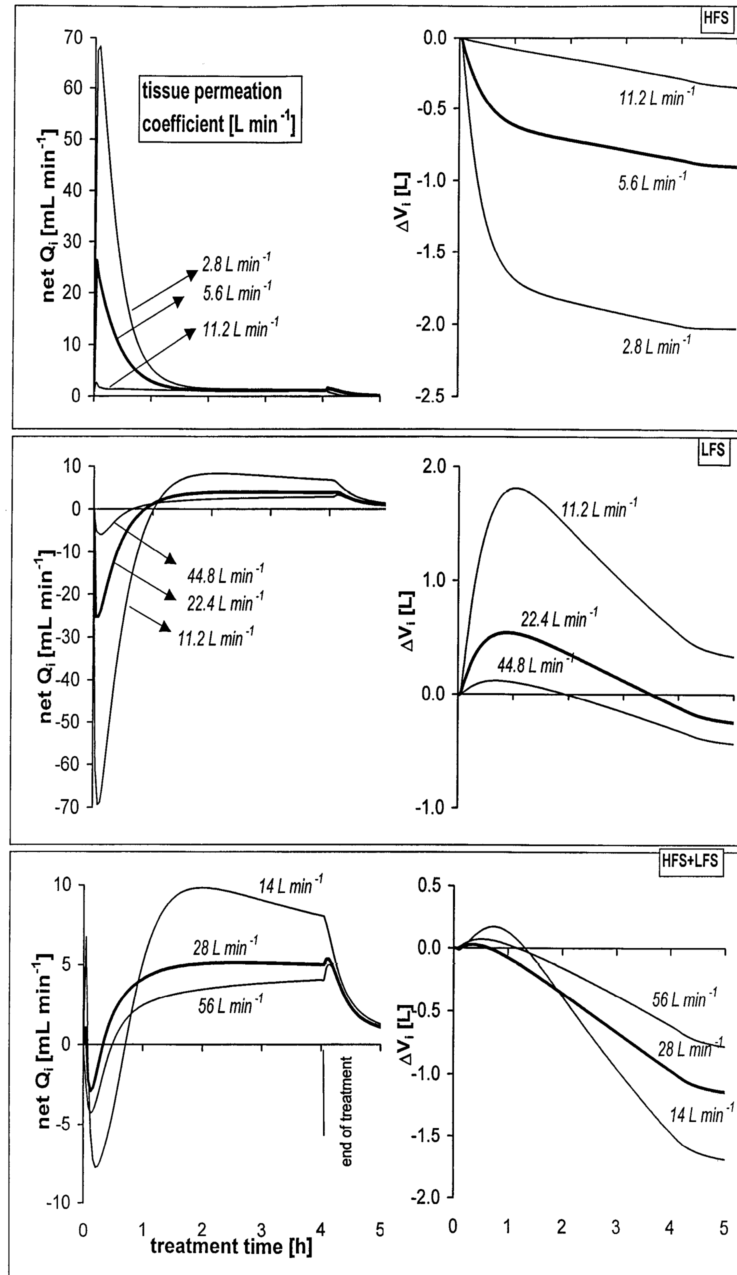

Figure 7

The simulated time changes in the net exchange rate of intracellular fluid (Q_i) and the resultant transcellular fluid shifts (ΔV_i) during SHD. All other parameters are fixed and the tissue permeation coefficient for urea is varied from 14 L min^{-1} to 56 L min^{-1}. Since the HFS and LFS tissue groups have different fractions of volume (f^L_v = 0.8, f^H_v = 0.2), their tissue permeation coefficients for urea are also different.

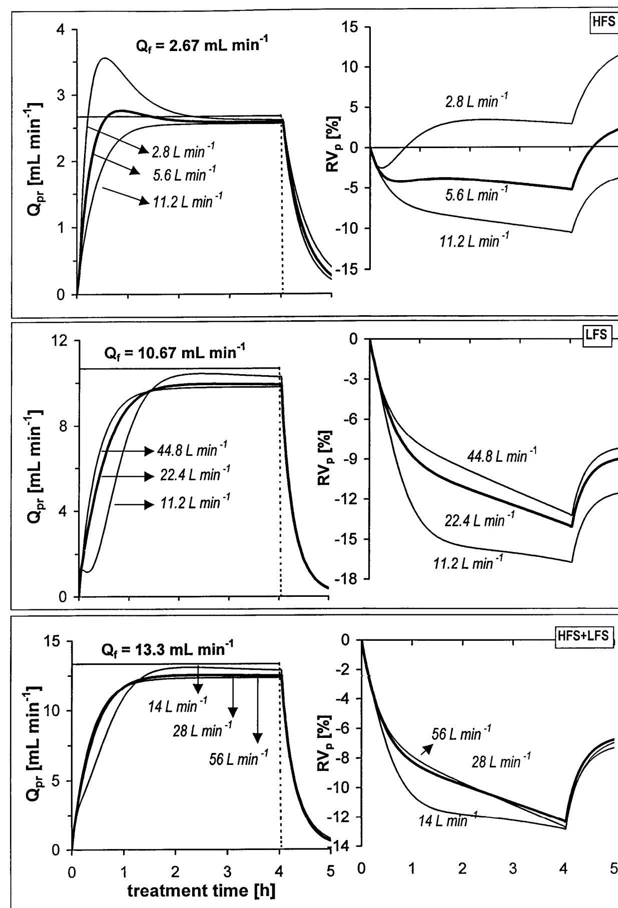

Figure 8.

The simulated time changes in the plasma refilling rate (Q_{pr}) and the relative changes in the plasma volume (RV_p) during SHD. See also Figure 7. All other parameters are fixed and the tissue permeation coefficient for urea is varied from 14 L min^{-1} to 56 L min^{-1}

Discussion

We describe a mathematical model of intercompartmental fluid and solute kinetics during hemodialysis. This model differs from previous models in that the IC and EC solute masses, IC and EC osmolarities, dialysis dose, urea clearance, Na^+ and K^+ dialysance, blood water flow rate, erythrocyte water content, and Donnan factor are all taken as variable in time. Thus, this model may predict changes in solute and water transport throughout the profiled dialysis

session. Further, a regional blood flow model is combined with the classical two-compartment model. Correction factors for the dialyzer performance due to cardiopulmonary and access recirculation, are included. Using a sensitivity analysis we assessed the relative importance of ultrafiltration flow rate and volume, dialysate Na^+ concentration, initial plasma Na^+ concentration and initial urea concentrations, and the tissue permeation capacity on dialysis induced intercompartmental fluid shifts in both HFS and LFS tissue groups.

The greater the amount of UF the greater the amount of fluid shift to the EC space. This fluid shift to the EC space is not sufficient to refill the plasma volume loss by ultrafiltration. In addition, the higher the rates of ultrafiltration flow, the higher the decline of plasma volume. High dialysate Na^+ concentration (150 mEq L^{-1}) causes the cellular fluid (1.8 L) to move to the EC space, enhances the plasma refilling (2.2%) and, therefore, helps the plasma volume preservation during standard hemodialysis when performed with a normal (140 mEq L^{-1}) dialysate Na^+ concentration. A variation in the initial plasma Na^+ concentration by ± 5 mEq L^{-1} from normal plasma Na^+ concentration causes a variation of ±0.45 L in the fluid shift. A variation in the initial plasma urea concentration by ±10 mmol L^{-1} from 30 mmol L^{-1} causes a variation of ±0.03 L in the fluid shift, and it has no remarkable effect on the refilling rate capacity. Low tissue permeation in the LFS tissue group leads to an increase of the fluid shift in the cells, especially in the early hour of treatment, causing a delay in the plasma refilling. In the HFS tissue group, this has a contrary effect on the plasma refilling due to the increased fluid shift from intra- to the extracellular space.

Other factors influencing the transcellular and transvascular fluid shifts, such as solute and fluid distributions, transvascular protein transport, volume compliance, the solute and fluid permeation coefficients, which we cannot measure directly, are given at the start of treatment as parameters. Some factors such as flow rates, dialysate Na^+ and K^+ concentrations, length of dialysis session, and urea clearance are either given at the start of treatment or can be measured directly. However, some other parameters such as the permeability coefficients, compliance and initial ratios of different volume compartments were taken from literature, are likely to change during dialysis therapy, and can only be estimated in vivo. However, differences between this mathematical model and the *in vivo* situation enable us to compare the changes in the fluid and electrolyte fluxes that are predicted, to those observed during actual treatment. This is bound to improve our understanding of such variables, which is

especially relevant, as we must assume that the dialysis treatment itself induces changes in these variables.

We conclude that the magnitudes and direction of fluid shifts induced by hemodialysis treatment are not equal in tissue groups with different fractions of volumes and blood perfusion. The UF volume and flow rate, and the size of Na^+ gradient between the dialysate and blood (EC) side of the dialyzer membrane are the most important factors influencing the magnitude (up to 1.8 L) and direction of transcellular fluid shifts. High dialysate Na^+ concentration helps plasma refilling (by 2.5%). However, a high dialysate Na^+ concentration is associated with a high EC Na^+ rebound, which in turn may lead to interdialytic water intake resulting from thirst and may cause increased weight gain and hypertension.

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Appendix: list of symbols and units

Symbol	***Explanation [units]***
α <ga>	a factor to calculate protocrit from plasma protein concentration [Lg^{-1}]
γ_j <gg>	solute cellular sieving coefficient
ΔOsm	magnitude of the net transcellular osmolar driving force [mosmol L^{-1}]
ΔOsm_n	magnitude of osmolar gradient due to non-urea [mosmol L^{-1}]
ΔOsm_u	magnitude of osmolar gradient due to urea [mosmol L^{-1}]
Δt	a discrete time interval [min(utes)]
ΔV_i	magnitude of transcellular fluid shift [L(iters)]
κ <gk>	conversion factor from molar to equivalent osmolar concentration
Π_{is}, Π_p <gP>	oncotic pressure in intersitial and plasma compartment [mmHg]
σ_u <gs>	transcellular urea reflection coefficient
$\Omega_{a,}$ $\Omega_{v,}$ Ω_{is}	compliance of arterial, venous plasma and interstitial space [% $mmHg^{-1}$]
$C_{d,j}$	inlet dialysate solute concentration [mEq L^{-1}]
$C_{e,j}$, $C_{i,j}$, $C_{p,j}$	EC, IC and plasma solute concentration [mEq L^{-1}, mmol L^{-1}]
$C_{a,j}$, $C_{v,j}$	arterial and venous concentration of solute *j* [mEq L^{-1}, mmol L^{-1}]
C_{is}, C_p	interstitial and plasma protein concentration [g L^{-1}]
CL_j	solute clearance or dialysance by diffusion [L min^{-1} or Lh^{-1}]
CO	cardiac output [L min^{-1}]
Dd	dialysis dose
D_j	whole body cellular diffusion coefficient of solute [L min^{-1}]
f_j	volume distribution of solute in red blood cell volume
f_v^t	volume fraction of tissue group *t*
f_q^t	blood perfusion fraction of tissue group *t*
F_w	correction factor for the free water fraction of EC space
G_j	generation or intake rate [mEq min^{-1}, mmol min^{-1}]
Ht	hematocrit
$J_{dial,j,}$ $J_{dif,j}$	total and diffusive transport rate through dialyzer [mEq min^{-1}, mmol min^{-1}]
$J_{i,j}$, $J_{e,j}$	mass exchange rate of IC and EC solute [mEq min^{-1}, mmol min^{-1}]
$J_{av,j}$	mass transfer rate from tissue to venous blood [mEq min^{-1}, mmol min^{-1}]
k_c	transcellular whole body water exchange coefficient [L min^{-1} $mmHg^{-1}$]
k^{CP}	correction factor for cardiopulmonary recirculation

k^{AC}	correction factor for arterial access blood recirculation
L_f, L_r	arterial and venous capillary hydraulic permeability [L mmHg^{-1} min^{-1}]
m^t	concentration equilibration coefficient in tissue group *t*
$M_{i,j}$, $M_{e,j}$	IC and EC solute mass [mEq, mmol]
MW_j	molecular weight of solute *j* [Dalton]
$Osm_{p,n}$	plasma non-urea osmolality [mosmol L^{-1}]
P_a, P_v, P_{is}	hydraulic pressure in arterial, venous plasma, interstitium [mmHg]
PS_j	whole body tissue permeation coefficient for solute *j* [L min^{-1}]
Q_a	systemic arterial blood flow rate [L min^{-1}]
Q_a^{AC}, Q_v^{AC}	flow rate of blood entering and leaving the dialyzer [L min^{-1}]
Q_a^t, Q_v^t	flow rate of blood entering and leaving the tissue group *t* [L min^{-1}]
Q_{bi}, $Q_{wi,j}$	flow rate of blood and blood water that enters the dialyzer [L min^{-1}]
Q_{di}, Q_f	dialysate inlet and ultrafiltration flow rates [L min^{-1}]
Q_{wf}, Q_{wr}	vascular water filtration and reabsorption rate [L min^{-1}]
Q_i, Q_{pr}, Q_{rc}	exchange rate of IC, transvascular and red blood cell volume [L min^{-1}]
Q_R^{AC}	access recirculation blood (water) flow rate [L min^{-1}]
R	gas constant [L mmHg K^{-1} mmol^{-1}]
R^c_D, $R_{D,j}$	capillary wall and dialyzer membrane Gibbs-Donnan ratio
RV_p	relative change in plasma volume with respect to its initial value [%]
SK_j	dialyzer membrane solute permeation coefficient [L min^{-1}]
T, T_d	temperature [K(elvin)], duration of treatment session [min, hour]
V_e, V_i, V_{is}	volume of EC, IC and interstitial compartment [L]
V_p, V_b	plasma, blood volume [L]
V_{uf}	excess water (weight gain) or ultrafiltration volume [L]
V_{rc},V_{pr}	volume of red blood cells and plasma refilling [L]
Z_j	solute distribution coefficient between EC and IC space at equilibrium

Chapter 3: Variability of Relative Blood Volume during Hemodialysis

Abstract

A decrease in blood volume is thought to play a role in dialysis-related hypotension. Changes in relative blood volume (RBV) can be assessed by means of continuous haematocrit measurement. We studied the variability of RBV changes, and the relation between RBV and ultrafiltration volume (UV), blood pressure, heart rate, and inferior caval vein (ICV) diameter.
In 10 patients on chronic hemodialysis, RBV measurement was performed during a total of one hundred 4-h hemodialysis sessions. Blood pressure and heart rate were measured at 5-min intervals. ICV diameter was assessed at the start and at the end of dialysis using ultrasonography.
The changes in RBV showed considerable inter-individual variability. The average change in RBV ranged from -0.5 to -8.2% at 60 min and from -3.7 to -14.5% at 240 min (coefficient of variation (CV) 0.66 and 0.35 respectively). Intra-individual variability was also high (CV at 60 min 0.93; CV at 240 min 0.33). Inter-individual as well as intra-individual variability showed only minor improvement when RBV was corrected for UV. We found a significant correlation between RBV and UV at 60 ($r = -0.69$; $P<0.001$) and at 240 min ($r = -0.63$; $P<0.001$). There was a significant correlation between RBV and heart rate ($r = -0.39$; $P<0.001$), but not between RBV or UV and blood pressure. The level of RBV reduction at which hypotension occurred was also highly variable. ICV diameter decreased from 10.3±1.7 mm/m^2 to 7.3±1.5 mm/m^2. There was only a slight, although significant, correlation between ICV diameter and RBV ($r = -0.23$; $P<0.05$). The change in ICV-diameter showed a wide variation.
RBV changes during hemodialysis showed a considerable intra- and inter-individual variability that could not be explained by differences in UV. No correlation was observed between UV or changes in RBV and either blood pressure or the incidence of hypotension. Heart rate, however, was significantly correlated with RBV. Moreover, IVC diameter was only poorly correlated with RBV, suggesting a redistribution of blood towards the central venous compartment. These data indicate that RBV monitoring is of limited use in the prevention of dialysis-related hypotension, and that the critical level of reduction in RBV at which hypotension occurs depends on cardiovascular defense mechanisms such as sympathetic drive.

Introduction

Intradialytic hypotension is a common complication in patients on chronic hemodialysis. Many factors have been implicated in its pathogenesis, including autonomic dysfunction, cardiac dysfunction and a reduction in effective blood volume [1,2]. Changes in effective blood volume can be measured by radioisotope dilution techniques [3], but these methods are complicated and not easily applied on a routine basis. Changes in relative blood volume (RBV), however, can be estimated by means of continuous haematocrit measurement [4-6]. Monitoring RBV during hemodialysis and discontinuing ultrafiltration when a critical level of RBV reduction is reached has been advocated in order to improve haemodynamic stability during dialysis [7,8]. For this it is essential that the critical level of RBV reduction can be predicted in individual cases. Therefore we studied the intra- and inter-individual variability of RBV measurement and the correlation of RBV with blood pressure (BP), heart rate (HR), and inferior caval vein (ICV) diameter.

Subjects and methods

Patients and hemodialysis treatments

Ten patients on regular hemodialysis were asked to participate in this study. This study was approved by the ethical committee of the University Hospital Rotterdam–Dijkzigt, and informed consent was obtained from all patients. Age, sex, and dialysis data are given in Table 1. Hemodialysis treatments were performed using bicarbonate buffered dialysate (sodium 138 mmol/l, potassium 2.0 mmol/l, bicarbonate 34 mmol/l), polysulphone membranes (F60, Fresenius, Bad Homburg, Germany) and Fresenius 4008 E hemodialysis monitors. Blood flow ranged from 200 to 250 ml/min, and dialysate flow was 500 ml/min. Treatments were performed on a thrice-weekly basis for 4 h. Only subjects requiring at least 1000 ml of ultrafiltration volume (UV) during each treatment were included.

Table 1. Characteristics of the patient

Age (yrs)	65.5	±	11.9
male/female		5/5	
dry weight (kg)	63.8	±	11.8
time on dialysis (yrs)	5.3	±	2.5
Cardiac index (L/m^2)	2.3	±	1.1
EA ratio	0.9	±	0.3

Food and fluid intake was withheld prior to each investigative dialysis sessions. One hour after starting, one cup of tea and a snack were served. One hour later, another cup of tea was provided.

Blood pressure, inferior caval vein diameter, and cardiac output measurements
During dialysis, BP and HR was measured at 5-min intervals by means of the Accutor 3 oscillometric device (Datascope Co., Montreal NJ, USA). Hypotension was defined as a systolic blood pressure 90 mm Hg. To estimate hydration status before and after dialysis., ICV measurements were performed using ultrasonography (Aloka SDD 1100, 3.75 MHz probe, Aloka Co., Tokyo, Japan). Real-time, two-dimensional ultrasonography was used, with simultaneous ECG monitoring. The longitudinal axis of the ICV was used to measure its diameter at inspiration and at end-expiration, exactly 2 cm below the diaphragm. Using a cine loop memory containing 10 images, an image just before the P wave on the ECG tracing was taken for measurement. In all patients, cardiac function was previously analyzed using precordial ultrasonography. Cardiac output was determined by calculating the stroke volume using the bi-plane discs method. Diastolic left ventricular function was assessed by Doppler evaluation of left ventricular filling. After measuring early (E) and atrial (A) flow over the mitral valve, the E/A ratio was calculated. Diastolic dysfunction was present in all patients.

Relative blood volume measurement
RBV measurement was performed by continuous optical measurement of the haematocrit using the Crit-line device (In-line Diagnostics Co., Riverdale, Utah, USA). Patients were placed in a supine position 30 min before starting RBV measurements, and this position was maintained throughout the investigative dialysis sessions. To ensure an adequate baseline haematocrit without mixture of rinsing saline, RBV measurement was started 5 min after the onset of hemodialysis. RBV measurement was performed during 10 consecutive weeks on the same weekday.

Data collection
Data from the Crit-line device and the Accutor 3 were sent to a personal computer and recorded by a data acquisition program. During the data collection, the occurrence of symptoms and/or changes in the dialysis treatment parameters was instantly recorded.

Statistics

For RBV, means of 10-min periods at 60, 120, 180, and 240 min were used for comparison. Similarly, means of RBV values over a range of 10 ml at 500, 1000, and 1500 ml ultrafiltration volumes were taken. Differences in BP, HR, ICV diameter, and RBV were analyzed using ANOVA for repeated measurements followed by the Newman–Keuls test for multiple comparisons. Differences between patients were analyzed using two-way ANOVA. Variability was assessed by calculating the coefficient of variance. Correlation was assessed using linear correlation by calculating Pearson's correlation coefficient. All data are presented as mean±standard deviation. A *P* value of <0.05 was assumed to indicate statistical significance.

Results

Ultrafiltration volume

Measurements were performed in 100 hemodialysis sessions. UV after 4 h was 2438±457 ml. With a mean body weight of 65.9±9.3 kg; this represents 3.7% of the total body weight. The mean UV corrected for body surface area (BSA) was 1428±311 ml/m^2 (Table 2. In 19 sessions, ultrafiltration was temporarily stopped because of hypotension or other symptoms.

time (minutes)	start			60			120			180			240			F	P
UV (ml/m^2)				386	±	118	746	±	184	1098	±	254	1428	±	311		
ICVD-exp. (mm/m^2)	10.3	±	1.7										7.3	±	1.5		<0.001
SAP (mm Hg)	151.4	±	20.6	151.1	±	14.1	150.5	±	18.6	148.1	±	18.9	140.0	±	17.3	2.4	<0.05
DAP (mm Hg)	84.0	±	7.1	82.7	±	7.7	83.8	±	6.5	83.6	±	7.9	79.8	±	7.7	6.2	<0.001
HR (bpm)	73.9	±	7.9	74.9	±	10.1	76.9	±	9.2	80.0	±	9.2	81.3	±	10.2	33.7	<0.001

Table 2. Weight gain, ICV measurement, blood pressure, RBV, and ultrafiltration volume (mean of all sessions)

Mean systolic blood pressure (SAP) decreased from 151.4±20.6 mmHg at the start of hemodialysis to 140.0±17.3 mmHg at the end (*P*<0.05; Figure 1.) Diastolic blood pressure (DAP) decreased from 84.0±7.1 to 79.8±7.7 mmHg (*P*<0.001), while the heart rate increased from 73.9±7.9 to 81.3±10.2 b.p.m. (*P*<0.001).

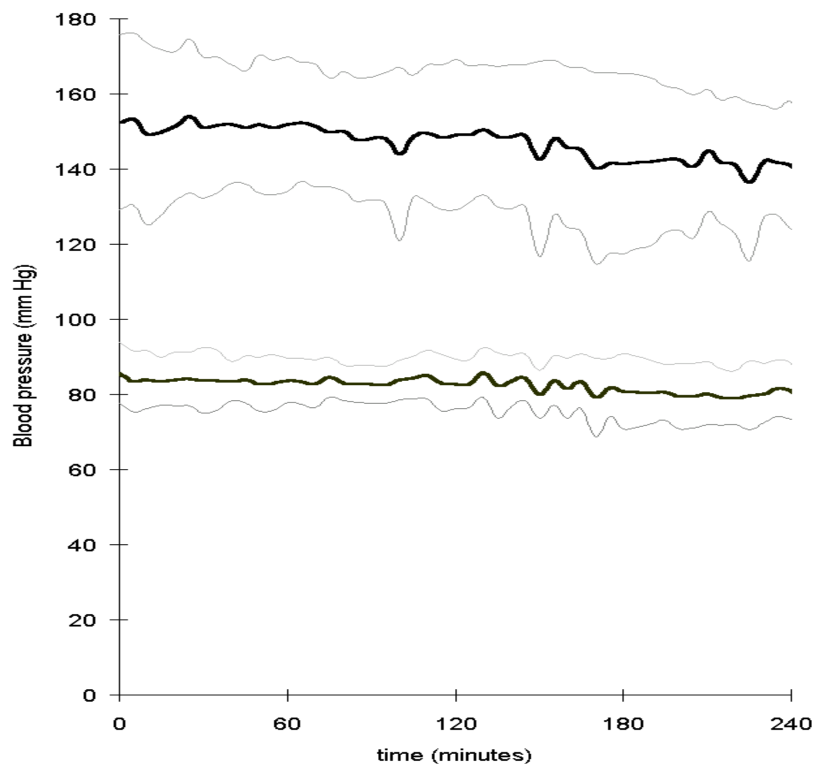

Fig. 1.

Systolic and diastolic blood pressure during 4 h of hemodialysis in 10 patients (thick lines, mean of all patients; thin lines, ±standard deviation).

ICV measurement

At the start of dialysis, mean ICV diameter at end-expiration and at inspiration were 10.3±1.7 mm/m^2 and 8.2±2.2 mm/m^2 respectively. At the end of dialysis, mean ICV diameters had decreased to 7.3±1.5 mm/m^2 at end-expiration and 5.3±1.5 mm/m^2 at inspiration (*P*<0.001; Table 2).

Blood volume monitoring

Changes in RBV showed marked inter-individual variability (*Figure 2a*. For all patients, the change in RBV was -3.8±2.5% at 60 min and -10.3±3.6% at the end of dialysis (*Table 2*. At 60 min, mean RBV of 10 single patients varied between -0.51% and -8.17% (*P*<0.001), and at the end of dialysis, RBV varied between -3.71% and -14.55% (*P*<0.001; Table 3). The

coefficients of variability demonstrate a wide variation in RBV after 60, 120, 180, and 240 min between different patients (CV 0.66, 0.52, 0.41, and 0.35 respectively; Table 3. Within individual patients, changes in RBV were also highly variable. Mean coefficients of intra-individual variability ranged from 0.66 after 60 min to 0.35 at the end of dialysis (Table 3)

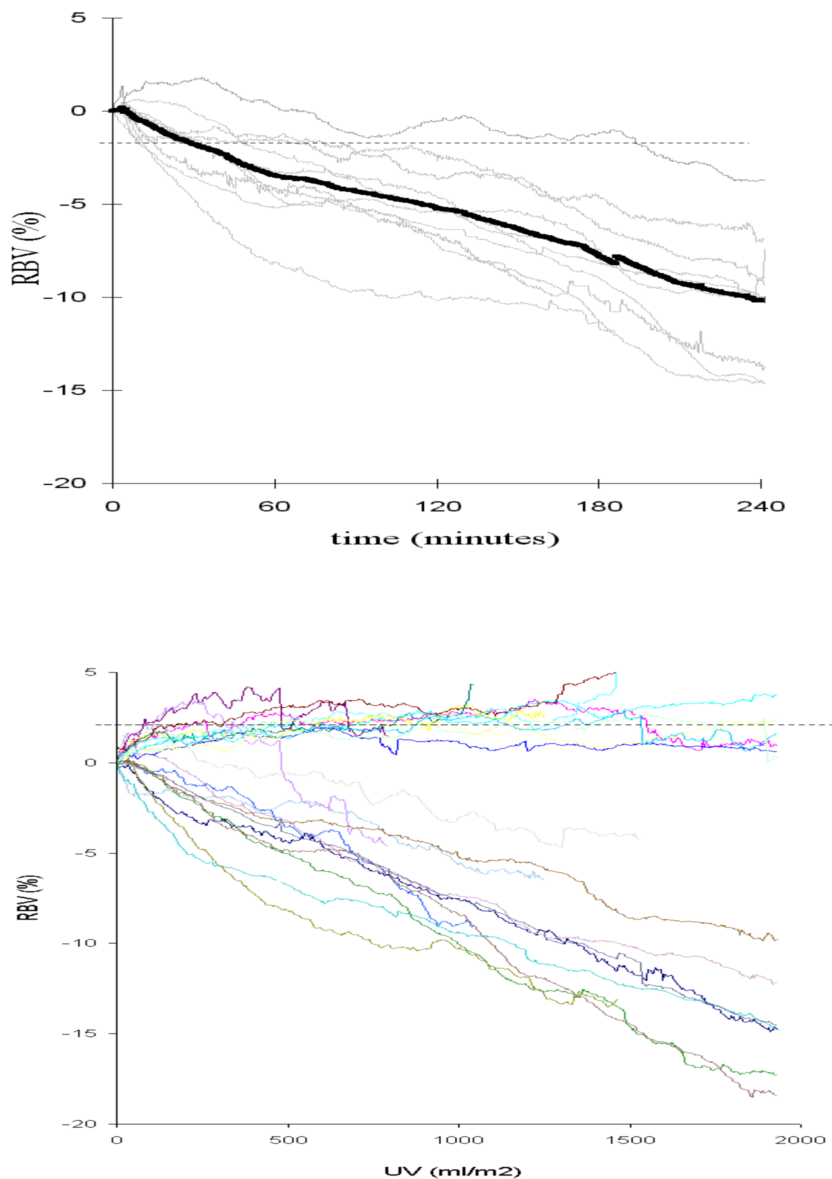

Figure 2.

Mean changes in relative blood volume of 10 patients in 10 hemodialysis sessions (thin lines), and mean of all patients (thick line), plotted (a) against time and (b) against ultrafiltration volume

	RBV at 60 minutes	CV	RBV at 120 minutes	CV	RBV at 180 minutes	CV	RBV at 240 minutes	CV
Patient 1	-4.24	0.57	-6.70	0.32	-10.15	0.33	-13.71	0.19
Patient 2	-2.43	0.67	-3.00	0.74	-5.35	0.33	-6.98	0.30
Patient 3	-2.27	0.68	-5.20	0.46	-7.96	0.38	-9.99	0.31
Patient 4	-0.51	3.65	-0.52	6.41	-1.20	2.83	-3.71	0.87
Patient 5	-1.37	1.58	-3.51	0.76	-6.12	0.55	-8.23	0.37
Patient 6	-4.12	0.43	-7.13	0.35	-11.23	0.22	-14.55	0.23
Patient 7	-8.17	0.29	-10.05	0.27	-10.94	0.25	-8.64	0.42
Patient 8	-7.48	0.29	-8.68	0.27	-11.27	0.16	-12.84	0.17
Patient 9	-2.77	0.70	-3.89	0.74	-6.44	0.59	-9.73	0.20
Patient 10	-4.51	0.40	-5.41	0.59	-9.02	0.37	-14.51	0.22
Mean	-3.79	0.66	-5.41	0.52	-7.97	0.41	-10.29	0.35
Inter-individual CV	0.93		1.09		0.60		0.33	

Table 3. Relative blood volume of 10 patients (mean of 10 hemodialysis sessions) at 60, 120, 180, and 240 min of dialysis

When changes in RBV were plotted against UV corrected for BSA, inter-individual variability remained considerable (Figure 2b). Coefficients of variation ranged from 0.48 to 0.23 (Table 4). Intra-individual variability was also marked (mean intra-individual CV 0.95 to 0.37; Table 4).

Correlation between relative blood volume, ultrafiltration volume, heart rate, blood pressure, and inferior caval vein measurement

The change in RBV was highly correlated with ultrafiltration volume both at 60 min (r= -0.69; P<0.001), and at 240 min (r= -0.63; P<0.0001; Figure 3a). Interestingly, there was no significant correlation between the change in RBV and either systolic or diastolic blood pressure, at 60 min and at 240 min (Figure 3b). Ultrafiltration volume was not correlated with either systolic or diastolic blood pressure. The change in heart rate was correlated with change in RBV at 240 min (r=-0.39; P<0.0001; Figure 3c), but not with ultrafiltration volume. Although there was a marginally significant correlation between the change in RBV and ICV

diameter (*r*=-0.23; *P*<005), there was a considerable variation in the decrease in ICV diameter (Figure 3d).

	RBV at 500 ml UV	CV	RBV at 1000 ml UV	CV	RBV at 1500 ml UV	CV
Patient 1	-4.40	0.60	-7.57	0.36	-11.56	0.24
Patient 2	-2.15	0.80	-5.59	0.55	-	-
Patient 3	-3.22	0.64	-7.36	0.30	-10.16	0.29
Patient 4	-0.60	5.24	-3.03	0.98	-3.96	1.34
Patient 5	-3.52	0.52	-8.95	0.30	-	-
Patient 6	-6.76	0.22	-9.39	0.12	-12.38	0.08
Patient 7	-5.04	0.27	-10.04	0.24	-14.63	0.17
Patient 8	-8.20	0.28	-10.27	0.26	-	-
Patient 9	-3.31	0.47	-5.15	0.32	-8.58	0.29
Patient 10	-4.86	0.48	-8.40	0.23	-14.47	0.08
Mean	-4.20	0.95	-7.57	0.37	-10.81	0.37
Inter-individual CV		0.48		0.31		0.23

Table 4. Relative blood volume of 10 patients (mean of 10 hemodialysis sessions) at 500, 1000, and 1500 ml of ultrafiltration volume/m^2 of body surface area

Incidence of hypotension, and corresponding relative blood volume and haematocrit

The incidence of hypotensive episodes was relatively low. Hypotension occurred in seven hemodialysis sessions, all in two patients. Systolic blood pressure ranged from 63 to 89 mmHg in patient 1 (four sessions), and from 84 to 89 in patient 7 (three sessions). In six sessions, hypotension was accompanied by a heart rate of 60 b.p.m. or less. In both patients, RBV at which hypotension occurred, varied markedly (patient 1, -9.2 to -16.0%; patient 7, -1.4 to -16.5%). In addition, the corresponding haematocrit values showed considerable variation (patient 1, 0.27 to 0.31; patient 7, 0.32 to 0.37). Change in ICV diameter was not significantly different from sessions without hypotensive episodes.

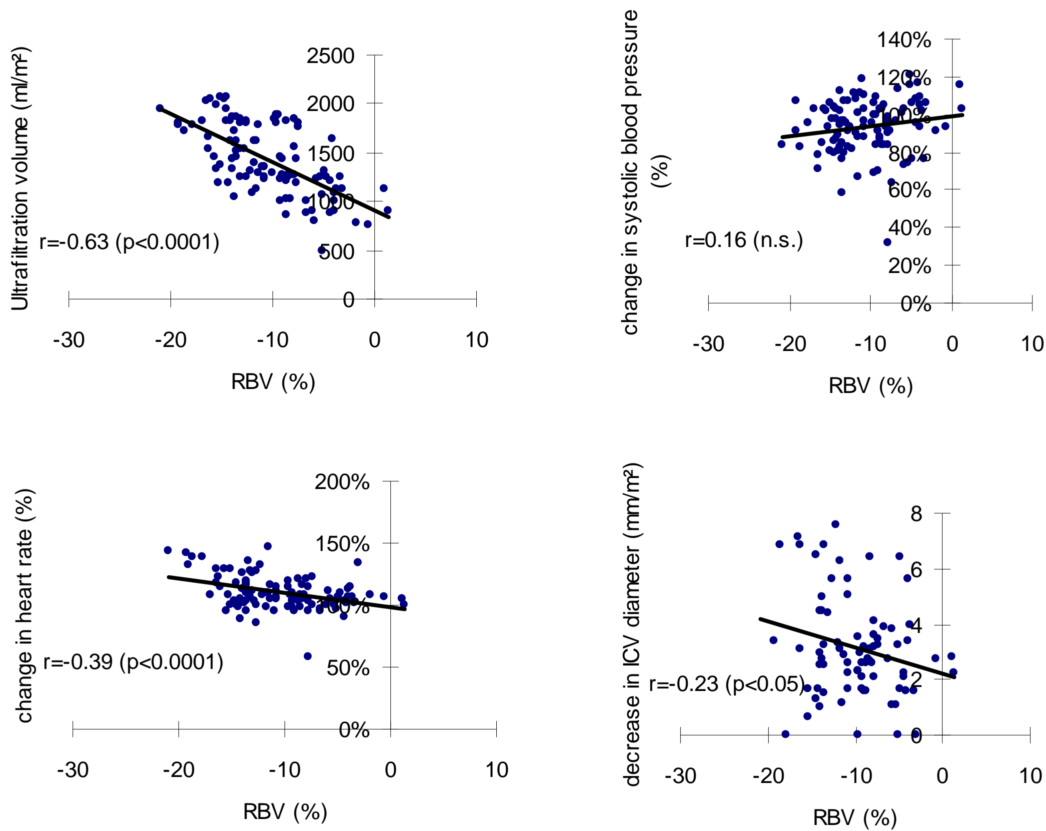

Figure 3.

(a) RBV (%) *vs* ultrafiltration volume after 240 min of hemodialysis. (b) RBV (%) *vs* change in systolic blood pressure after 240 min of hemodialysis. (c) RBV (%) *vs* change in heart rate (%) after 240 min of hemodialysis. (d) RBV (%) *vs* decrease in ICV diameter (end-expiration; mm/m^2) after 240 min of hemodialysis.

Discussion

In this paper, the variability of RBV changes during hemodialysis is reported for the first time. We observed a considerable inter-and intra-individual variability of RBV changes during hemodialysis, even when corrected for UV. Although there was a significant correlation between RBV and ultrafiltration volume, a correlation between RBV and blood pressure was not found. Ultrafiltration volume was not correlated with blood pressure or heart rate. There

was, however, a significant correlation between RBV and heart rate, and a slight correlation between RBV and ICV-diameter.

It is not surprising that we observed high inter-individual variability of RBV changes as differences in body composition, hydration state, and the cardiovascular status are known to affect the course of RBV during dialysis [1,2,9]. However, we found that the intra-individual variability was equally high. In our study, this variability could not be explained by differences in food and fluid intake during dialysis, as these were restricted according to a standardized time and quantity schedule. Also, medication was not changed during the 10-week trial period, and intercurrent changes in the cardiovascular status such as the occurrence of myocardial ischaemia or systemic infection were not observed.

It is tempting to assume that the observed intra-individual variability in RBV changes was caused by differences in ultrafiltration volume, as there was a significant correlation between UV and RBV. However, when the RBV curves were plotted against UV instead of time, we found only a minor improvement of the variation coefficients. Thus, differences in ultrafiltration rate are unlikely to account for the day-to-day variation of the blood volume response to hemodialysis, and other factors must be involved.

There was no correlation between RBV and blood pressure, which is contrary to other observations [6,10,11]. However, a discrepancy between blood pressure and blood volume has been reported before [12]. Blood pressure was also not dependent on UV. There was, however, a significant correlation between RBV and heart rate. This suggests that a reduction in RBV, through ultrafiltration, stimulates the autonomic nervous system, which prevents a decrease in blood pressure by an increase in heart rate. In patients who did develop hypotension during dialysis, we were unable to determine a critical level of RBV reduction. Moreover, in six out of seven hypotensive dialysis sessions, patients were bradycardic instead of tachycardic, indicating that in these patients hypotension was caused rather by a failing cardiovascular response than by critical level of blood volume reduction.

In our study, ICV diameter decreased significantly during dialysis. However, when we studied the relation between the change in ICV diameter and the change in RBV during dialysis, the correlation proved to be poor. This means that filling of the central venous compartment, which is assumed to be represented by the ICV diameter [13], does not change in parallel to changes in RBV. Therefore a redistribution of blood within the vascular compartment must be

assumed. This most probably results from cardiovascular defense mechanisms such as peripheral and/or venous vasoconstriction, or a change in cardiac output.

We conclude that RBV changes have a considerable intra- and inter-individual variability, not only in time but also when plotted against UV. No correlation was observed between UV or changes in RBV and either blood pressure or the incidence of hypotension. Heart rate, however, was significantly correlated with RBV. Moreover, IVC diameter was only poorly correlated with RBV, suggesting a redistribution of blood towards the central venous compartment. These data indicate that RBV monitoring is of limited use in the prevention of dialysis-associated hypotension. The critical level of reduction in RBV at which hypotension occurs may depend more on cardiovascular defense mechanisms such as sympathetic drive, than on the reduction in RBV.

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Chapter 4: Increase in Blood Volume during Dialysis without Ultrafiltration.

Abstract

Combined dialysis and ultrafiltration leads to more frequent episodes of hypotension than isolated ultrafiltration. It has been suggested that decreased plasma volume preservation could be responsible for this phenomenon. The present study evaluates the effects of diffusive dialysis on the changes in relative blood volume. Six stable hemodialysis patients, without the need for ultrafiltration, were studied during ten sessions of diffusive dialysis (bicarbonate) lasting four hours. Relative blood volume (RBV) was monitored continuously by measurement of hematocrit. During the first and second hour RBV increased by 2.4 ± 1.4 and 2.5 ± 0.8 % respectively, returning to baseline levels at the end of dialysis. No changes in blood pressure or heart rate were noted. We conclude that during diffusive dialysis without ultrafiltration relative blood volume is increased. A decrease in vascular resistance, or changes in regional blood distribution could explain the findings.

Introduction

Hypotension is a major complication of hemodialysis, which occurs in approximately one third of the patients [1]. It has been shown that isolated ultrafiltration without simultaneous dialysis is better-tolerated [2]. This could suggest that the hemodynamic instability that occurs during dialysis results from changes in osmolality [3-5]. Using kinetic modelling, the rapid fall in the urea concentration of the extracellular compartment, is predicted to induce a volume shift from the extracellular to the intracellular compartment [6,7,8]. On the other hand, some studies failed to observe differences in plasma volume preservation between ultrafiltration and ultrafiltration combined with hemodialysis [9,10,11]. However, differences between blood volume decrement during isolated ultrafiltration and ultrafiltration combined with dialysis could be masked in these studies, as there is an intra-individual variability in change of blood volume during ultrafiltration, which is relatively large as compared to the expected change in blood volume during diffusive dialysis [12,13]. To avoid these problems, the effect of blood volume can best be studied during dialysis without net ultrafiltration (diffusive dialysis). The effect of diffusive dialysis on changes in blood volume has been only reported by Fleming et al. [14]. However, this study was set up to investigate the effect of different dialysate sodium concentrations on blood volume, rather than the effect of diffusive

dialysis on blood volume. At present, it is therefore unclear whether the negative effect of diffusive dialysis on hemodynamic stability results from reduced blood volume preservation or from altered vascular reactivity. The present study evaluates the effects of diffusive dialysis on blood volume preservation by continuously measuring the change in relative blood volume. In order to correct for intra-individual variability, all subjects were studied during ten dialysis treatments.

Subjects and Methods

Patients

We studied 6 patients, 4 men and 2 women, requiring chronic hemodialysis (time on dialysis 2 months - 5 years) with such a residual diuresis (900ml - 2000 ml/24 hr) that ultrafiltration is not necessary. None of these patients suffered from diabetes mellitus. As there were no further exclusion criteria all six patients were studied. Mean age of the subjects was 59 ± 20 years. Their mean weight was 72 ±16 kg. The local ethics committee approved the study and informed consent was obtained in all subjects. Medication was changed during the experiments.

Dialysis prescription

In this study we examined 10 sessions for each patient. All dialysis sessions were performed on the same day of the week. Dialysis was performed three times a week for four hours using bicarbonate dialysate. Dialysate contained a sodium concentration of 138 mEq/L. Fresenius F-60 high-flux dialyzers (Fresenius AG, Bad Homburg, Germany) and Fresenius 4008E hemodialysis monitors were used to perform the treatments. Patients were connected to the circuit after the priming volume of saline was discarded. Blood and dialysate flow rates were 200-300 ml/min and 500 ml/min respectively. Delivered Kt/V ranged between 1.1 and 1.3 on a trice weekly basis, including residual renal function. All patients remained supine starting from 30 minutes before being connected to the dialysis circuit till the end of the treatment. No intravenous infusions were given during the treatment and the intake of fluids and food was withheld during the treatment.

Measurements

Blood volume was measured optically by means of the CRIT-LINE device (In-line Diagnostics Co., Riverdale Utah). Before dialysis a sterile plastic disposable blood chamber was placed between arterial bloodline and the dialyzer. The CRIT-LINE uses a transmissive photometric technique to determine the hematocrit with a 95 % confidence interval from + 2.32 to – 2.31 hematocrit % and a repeatability 95 % interval from + 0.56 to - 0.55 hematocrit % [15]. The CRIT-LINE device calculates relative blood volumes (RBV) from initial hematocrit and the subsequent changes in wavelength as the erythrocytes pass the through the blood chamber. For each patient, we calculated a mean relative blood volume and standard deviation at 60, 120, and 180 minutes, and at the end of treatment. From all the mean relative blood volumes of each patient, we calculated a grand mean relative blood volume. Blood pressure was measured by means of an oscillometric device (Accutor 3, Datascope Co., Montreal, NY) at 5-minute intervals. Blood pressure and heart rate were calculated as the average of three consecutive measurements. Hypotension was defined as decrease in systolic blood pressure (SBP) of more than 30%. Blood samples were taken before and after the dialysis session for measurement of the sodium and urea concentrations and for the mean corpuscular volume (MCV) of the erythrocytes. We used the ionometric method for determination of the sodium concentrations, because this method refers to the activity of the sodium capable of crossing the membranes of the dialyzer [16].

Statistical analysis

All data are presented as mean ± standard deviation (SD). For changes in relative blood volume 95 % confidence intervals were calculated. Differences between study periods were assessed by means of ANOVA with repeated measures. All calculations were performed using the SPSS statistical software package.

Results

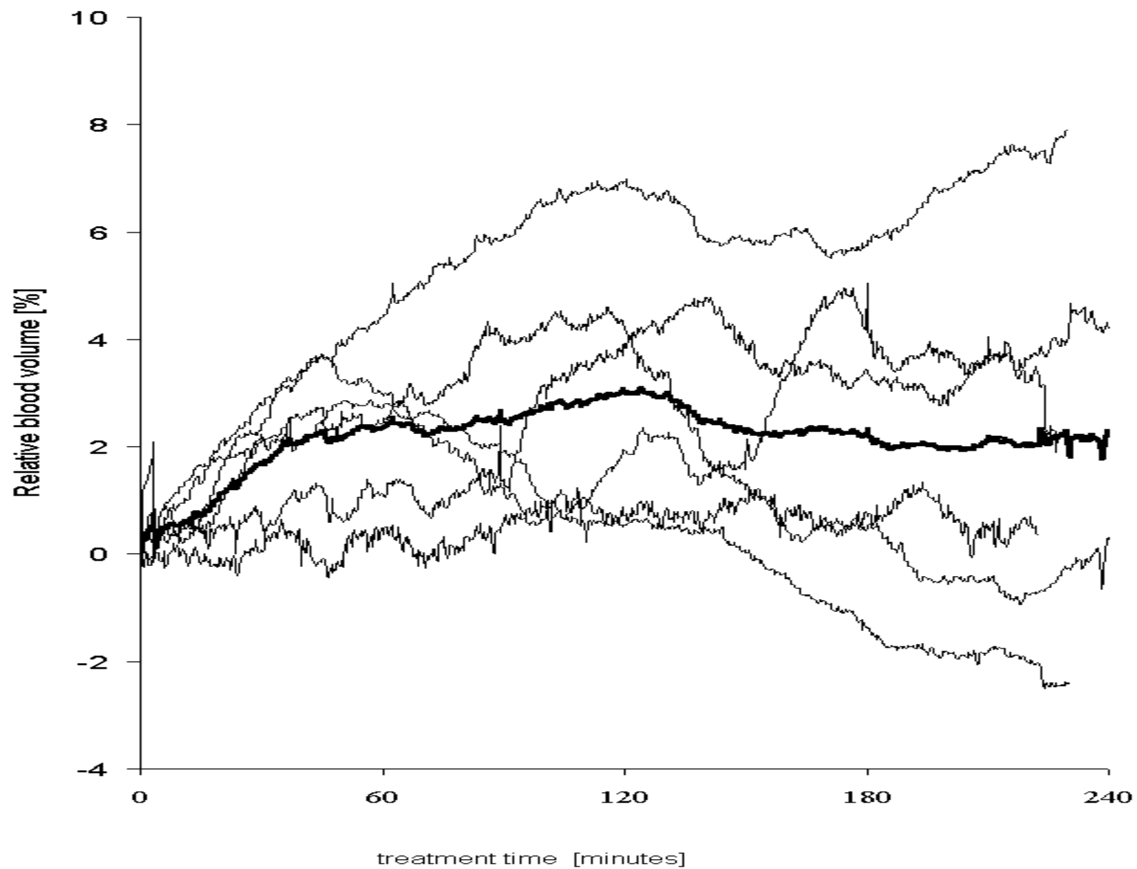
Relative blood volume

RBV increased significantly during the first (+ 2.4 ± 1.4 %; $p < 0.05$) and second hour (+2.5 ± 0.8 %; $p < 0.05$) of the treatment (fig 1.). After reaching a plateau, RBV tended to decrease at the end of the treatment. We observed no correlation between the changes in RBV and plasma urea or sodium concentrations prior to dialysis (table 1). The observed increase in RBV did not result from a change in MCV (91 ± 3.7 vs. 92 ± 2.8 fL). There was a similar pattern of increase in all patients studied. However, there were considerable inter- and intra- individual differences (table 2).

Patient	AHT*	[Na] ± SD	[Urea] ± SD	ΔRBV_{120} ± SD	ΔBP_{120} ± SD
1	A, C, E	142 ± 1	27.4 ± 0.3	0.51 ± 2.71	1 ± 12
2	None	138 ± 2	28.5 ± 3.6	4.35 ± 4.2	10 ± 12
3	B, D	142 ± 1	26.5 ± 0.7	6.90 ± 1.74	-9 ± 28
4	None	141 ± 2	26.4 ± 14	3.70 ± 0.35	2 ± 10
5	D	140 ± 1	31.5 ± 0.7	1.90 ± 0.99	0 ± 9
6	None	134 ± 2	32.1 ± 0.2	0.73 ± 2.16	5 ± 11
Mean		140 ± 3	28.4 ± 3	2.45 ± 1.62	0.55 ± 15.4

Table 1. Relationship between the use of anti-hypertensive drugs, osmolarity, blood pressure and blood volume
Abbreviations are : aHT = antihypertensive drugs, [Na] = mean plasma sodium concentration (mmol/l) , [Urea] = mean plasma urea concentration (mmol/l), SD = standard deviation, ΔBP_{120} = % increase in systolic blood pressure in the first two hours, ΔRBV_{120} = % increase in relative blood volume in the first two hours.
A = Nitates, B = β blocker, C = Calcium antagonist, D = ACE inhibitor, E = α 1 blocker

Figure 1. Relative Blood Volume Changes in 6 patients during diffusive dialysis. Each curve represents the avarage of 10 dialysis sessions. The bold curve represents the avarage of all 6 patients.



	60 minutes		120 minutes		180 minutes		240 minutes	
	RBV (%)	95% conf. Interval	RBV (%)	95% conf. Interval	RBV (%)	95% conf. Interval	RBV (%)	95% conf. Interval
Patient 1	2.71	(0.36-5.06)	0.51	(-2.2-3.22)	-1.36	(-5.07-2.35)	-2.41	(-6.89-2.01)
Patient 2	2.42	(0.84-4.00)	4.35	(0.15-8.55)	3.45	(0.00-6.90)	3.02	(1.04-7.08)
Patient 3	4.40	(3.21-5.59)	6.90	(5.16-8.64)	5.77	(3.45-8.10)	7.51	(5.07-9.93)
Patient 4	1.33	(0.27-2.39)	3.70	(3.35-4.05)	4.17	(2.17-6.17)	2.23	(0.01-4.45)
Patient 5	3.00	(1.69-4.39)	1.90	(0.91-2.89)	0.44	(-1.40-2.28)	-0.29	(-2.07-1.48)
Patient 6	0.48	(-0.43-1.39)	0.73	(-0.26-2.89)	0.80	(-0.78-2.38)	0.32	(-2.21-2.93)
Mean	2.39	(1.03-3.75)	2.45	(1.64-3.26)	2.21	(- 0.46-4.89)	1.73	(-1.69-5.15)

Table 2: Relative blood volume measurements and 95% confidence intervals during four hour

Blood pressure

SBP and heart rate remained unchanged during the procedure (141 ± 35 vs. 148 ± 39 mmHg and 84 ± 9.8 vs. 87 ± 8.8 bpm respectively (table 3). No episodes of symptomatic hypotension

were noted. We observed no relationship between changes in RBV and usage of anti-hypertensive drugs (table 1). There was also no association between serum sodium concentration prior to dialysis and pre- dialysis SBP or change in SBP, although blood pressure tended to increase when initial serum sodium was low (table 1).

	Systolic blood pressure (mmHg)					
	0 min.	60 min.	120 min.	180 min.	240 min.	Significance
Patient 1	179± 7	177± 6	180±10	184± 3	193± 5	n.s
Patient 2	157±40	157±41	167±30	168±30	168±31	n.s
Patient 3	173±27	154±12	166±12	165±17	177±18	n.s.
Patient 4	112±2	112± 6	113±13	108± 7	105± 4	n.s
Patient 5	135± 7	131±10	134± 7	136± 8	144±11	n.s
Patient 6	90± 7	96± 4	97± 7	95± 3	98± 5	n.s.
Total	141±35	138 ±30	143±33	143±36	148±39	n.s.

Table 3: Blood pressure measurement

Discussion

This study demonstrates that a decrease in plasma osmolality by diffusive dialysis (regular dialysis without ultrafiltration) is associated with a significant increase in RBV.
This finding is contrary to predictions derived from mathematical modeling in which RBV is predicted to decrease [6-8] (Figure 2).

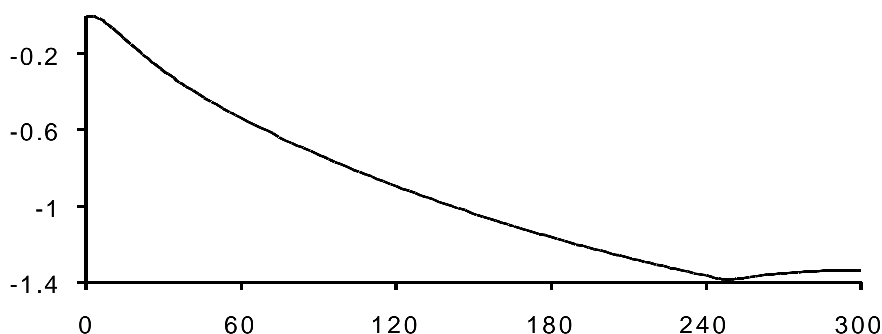


Figure 2. Change in Relative Blood Volume during diffusive dialysis according our Mathematical model

Diffusive dialysis leads to a decreased extracellular osmolarity, as there is an efflux of urea from the extracellular space. Theoretically, such a decrease in extracellular osmolarity would lead to a decreased tonicity of the extracellular space, and this would result in an osmotic fluid shift towards the intracellular space. This fluid shift would in turn lead to a decrease in blood volume [6-8]. As we find an increase in blood volume, the decrease in osmolarity by decreased plasma urea concentrations does not result in a volume shift towards the intracellular compartment. These findings are in accordance with those of Fleming et al, who previously observed that changes in blood volume are not correlated with urea efflux [14]. However, in this study there was a positive correlation between changes in blood volume and the extra cellular sodium concentration. As sodium penetrates the cells much less rapidly than urea it has a far greater impact on tonicity. A small increase in the extracellular sodium concentration during dialysis would thus favor an increase in plasma volume, even when a concomitant efflux of urea exists, that leads to a net decrease in osmolarity.
In our study, the average effective sodium concentration in the blood compartment of the dialyzer accounting for both plasma-water concentration and the Donnan-Gibbs ratio, was 145 mmol/l [7,8]. Using a dialysate sodium concentration of 138 mmol/l would therefore result in a sodium transport towards the dialysate compartment, even if backfiltration were to occur. The observed changes in blood volume can therefore not result from sodium kinetics.
Several other mechanisms could explain the observed blood volume patterns by such as: an increase in the volume of the erythrocytes, an increase in the total amount of intravascular protein, and changes in vascular resistance, especially when the patients are overhydrated.
Blood volume measurements by CRIT-LINE assume the constancy of erythrocyte mass and volume. In theory, the observed decrease in hematocrit could be explained by a fluid shift from the erythrocyte to the intravascular space, thereby reducing erythrocyte volume. However, we observed no differences between MCV measured before and after dialysis, findings that are similar to previous reports [17,18]. Moreover, such a fluid shift from the erythrocyte to the intravascular space is unlikely to occur under these circumstances as the changes in osmolality during dialysis favor a water flux towards the intracellular compartment [8,18].

An increase in the total amount of protein in the intravascular space would also result in an increase in plasma volume. As the total fluid shift between intra- and extra-vascular compartments is determined by the transmural oncotic pressure gradient. The interstitial fluid pressure determines lymph drainage, which increases the back-flow of proteins. However, during dialysis there is a decrease in osmolality in the interstitial space. As this will decrease rather than increase the interstitial volume, it is unlikely that such a backflow of protein would occur.

According to Starlings law, the fluid shift between the vascular and interstitial compartments depends on changes in hydrostatic and oncotic capillary pressure and on the filtration coefficient of the capillary basement membrane [19]. This filtration coefficient varies considerably from one tissue to the other. The whole body filtration coefficient represents the mean value of filtration coefficients of all segments of the regional micro-vascular system, each segment weighted for its fraction in capillary surface area. A change in vascular resistance will alter the blood flow distribution to different sections of the micro-vascular system and could therefore influence the whole body filtration coefficient, as well as hydrostatic capillary pressure. This would result in a different Starling equilibrium between the interstitial and intravascular space.

Wehle et al. [20] observed that diffusive dialysis, using acetate buffered dialysate reduces peripheral resistance. Moreover, several other investigators observed that the increase in peripheral resistance and venous tone during isolated ultrafiltration was significantly reduced by concurrent diffusive bicarbonate dialysis [21, 22]. These results suggest that bicarbonate dialysis reduces peripheral resistance. Wehle et al also observed that, when a dialysate sodium concentration of 140 mmol/L is used, the observed decrease in peripheral resistance during diffusive dialysis is counterbalanced by an increase in cardiac output [23]. This is in accordance with our results that showed no change in blood pressure during diffusive dialysis. Moreover, Wehle et al. found that at a low dialysate sodium concentration, which decreases extracellular sodium concentration, the increase in stroke volume was much smaller and blood pressure dropped [23]. Indeed, in those patients that had a low baseline serum sodium concentration (2 and 6) and hence a relatively high dialysate concentration, we observed a tendency for an increase in blood pressure as compared to the other patients.

When diffusive dialysis without ultrafiltration is performed in overhydrated patients, the decrease in vascular resistance would induce an even greater increase in RBV than in normohydrated patients. It has been shown that during ultrafiltration in overhydrated patients plasma volume preservation is better than in normohydrated patients [24, 25]. As the compliance of the interstitium is high in overhydrated patients a decrease in intra-vascular hydrostatic pressure resulting from ultrafiltration will not lead to a decreased interstitial pressure hence reabsorption of fluid into the capillaries. In our study ultrafiltration was not performed, but a decrease in vascular resistance could also result in a decreased intravascular hydrostatic pressure. Consequently, the high compliance of the interstitial space in overhydrated persons will thus lead to increased absorption of fluid from the capillaries and a greater increase in RBV. Despite the considerable diuresis in our patient group, some patients might have been fluid overloaded, as two patients had elevated systolic blood pressure and several patients used anti-hypertensive medication. In our study, we found no correlation between initial blood pressure or usage of anti hypertensive drugs and RBV during dialysis. However, this does not exclude a relationship between initial fluid overload and the observed increase in RBV.

The relationship between vascular tone and plasma volume expansion was directly assessed by several investigators, who found a plasma volume expansion, following the administration of a vasodilator agent [26,27,28]. Many factors could alter vascular tone during diffusive dialysis, such as induction of cytokine production in the presence of dialysate-derived contaminants or a change in body temperature [29,30]. Cold dialysis results in a greater decrease in relative blood volume, compared to standard treatment [31]. We did not measure body temperature. However, others have shown that body temperature rises during diffusive dialysis and ultrafiltration with a dialysate temperature of 37 °C [32].

The changes in blood volume in this study are small compared to those measured during routine hemodialysis with substantial ultrafiltration rates. Previous studies, in which RBV was studied during dialysis with ultrafiltration and during isolated ultrafiltration showed a tendency for a less pronounced fall in RBV during ultrafiltration combined with dialysis, although this difference was not significant [7,8,9]. However, the relatively large decrement in RBV during ultrafiltration could easily mask the relatively small increase in RBV during diffusive dialysis, as there is a considerable intra-individual variability in RBV during

ultrafiltration [12]. This could explain why these previous studies failed to observe significant differences. Fleming et al [14] studied blood volume changes during diffusive dialysis, and found no significant change in blood volume. However, in this study only twelve sessions with standard sodium concentration were studied, and only 1 or 2 (17 in total) blood volume measurements were done, while in our experiment relative blood volume was measured continuously during 60 sessions.

We conclude that during diffusive dialysis without ultrafiltration relative blood volume is increased. A decrease in vascular resistance or changes in regional blood distribution could explain these findings.

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Chapter 5 : Specific Effect of the Infusion of Glucose on Blood Volume during Hemodialysis.

Abstract

Intradialytic morbid events, such as hypotension and cramps during hemodialysis are generally treated by infusion of iso-or hyper-tonic solutions. However, differences may exist between solutions with respect to plasma refilling and vascular reactivity.

We compared the effect of no infusion (NI), with iso-volumetric infusion of isotonic saline 0.9% (IS), saline 3% (HS), isotonic glucose 5% (IG), glucose 20% (HG) and mannitol 20% (HM), in 6 patients during the first hour of 6 standardized hemodialysis sessions with ultrafiltration. Relative blood volume was monitored continuously by measurement of the intravascular amount of protein. Blood pressure was measured by an oscillometric method, while cardiac output was measured by a thoracic impedance technique.

At baseline no differences in serum urea, sodium, potassium, glucose and osmolarity were found between the various infusion experiments. The maximum increase in relative blood volume directly after infusion was significantly greater with HG (5.1±0.7%) than with all other infusions ($p < 0.05$). Stroke volume increased (21.0±19.2 %, $p < 0.05$) and total peripheral resistance decreased significantly (15.4 ± 16.4 %, $p < 0.05$) after HG infusions.

Infusion of hypertonic glucose during dialysis results in a greater increase in relative blood volume than equal volumes of other solutions. As mannitol has the same osmolarity, molecule mass and charge, the greater increase in RBV following hypertonic glucose appears to be a specific effect, possibly related to a decline in vascular tone. It is therefore uncertain whether the observed increase in plasma volume during hypertonic glucose infusions will be of clinical benefit.

Introduction

Hemodialysis is frequently accompanied by acute symptoms or complications, such as hypotension, severe muscle cramps, dizziness, and lightheadedness [1]. An important contributing factor for these intradialytic morbid events (IME) is hypovolemia due to removal of fluid from the intravascular space by ultrafiltration and inadequate refilling from the extravascular compartment [2]. Inadequate constriction of both arterial and venous vascular beds may also be of importance in the pathogenesis of IME, especially during hypotension [3]. Infusion of fluids to increase blood volume has been advocated to prevent IME. Increasing plasma osmolarity during dialysis has also been shown to reduce IME [4]. The

reduction of symptoms may result from improved refill of the intravascular compartment by the induction of an osmotic gradient between the vascular and the extravascular compartment [4,5], but may also be related to a direct effect of osmolarity on cardiovascular reactivity [6]. In clinical practice isotonic saline (0.9 %) or hypertonic (3%) saline infusions are most frequently used in order to prevent IME. However, increasing the sodium load during dialysis has been shown to increase interdialytic thirst and weight gain [7]. Alternatively, glucose or mannitol solutions can be given. The acute and specific effects of these solutions and their osmolarities on vascular refilling and reactivity are largely unknown. Clear insight into the exact effects of the solutions on hemodynamics and osmolarity is pivotal for the determination which solution should be given during dialysis associated morbidity. We therefore compared the effects of saline 0.9 and 3 %, glucose 5 and 20 %, and mannitol 20 % on vascular refilling and vascular reactivity during combined hemodialysis and ultrafiltration (HD+UF). In order to obtain optimal reproducibility, the dialysis sessions as well as the infusions were standardized. Moreover, the infusions were given during the first hour of the treatment, when variability in blood volume decrement between dialysis sessions is relatively low [8].

Subjects and Methods

Patients

Six clinically stable patients, 3 men and 3 women, requiring chronic hemodialysis were studied. The patients had a mean age of 48 ± 5.9 years and time on hemodialysis averaged 18.5 ± 12.5 months. Renal failure resulted from polycystic kidney disease (2), nephrosclerosis (2), renal artery stenosis (1) and antiglomerular basement membrane nephritis (1). Exclusion criteria were acute infectious diseases, diabetes, severe coronary or valvular heart disease and compromised left ventricular function. The patients did not use anti-hypertensive drugs, except for one patient who used nifedipine. This drug was stopped one week prior to entry in the study. The local ethics committee approved the study and informed consent was obtained from each patient. Dry weight was considered when patients remained without symptoms of dyspnea or edema during the interdialytic period. Moreover, inferior caval vein diameter (VCD) measurements were performed at intervals of three weeks. Overhydration was defined

as a VCD of more than 11.4 and underhydration was defined as a VCD of less than 8 mm/m^2 body surface area [9].

Dialysis prescription

Dialysis was performed three times a week with the procedure normally used at our institution, using bicarbonate dialysate (32 meq/L). Dialysate further contained sodium 138 mmol/L, potassium 2 mmol/L, calcium 1.75mmol/L, glucose 5.5 mmol/L with a total osmolarity of 292 mosm/L, a conductivity of 11.7 mS/cm (Fresenius SK-F213, Fresenius AG, Bad Homburg, Germany) and a temperature of 37 ºC. Fresenius F-60 high flux dialyzers and Fresenius 4008E hemodialysis monitors were used to perform the treatments. Blood and dialysate flow rates were 200-300 ml/min and 500 ml/min respectively. Delivered Kt/V ranged between 1.1 and 1.3, including residual renal function. Patients were connected to the circuit after the priming volume of saline was discarded.

Study protocol

All sessions were performed on the same day of the week during six consecutive weeks. The patients remained supine throughout the experiments and no food or beverages were provided. The investigations were performed during the first hour of six hemodialysis sessions. The ultrafiltration rate was standardized at 20 ml/kg/hr. The study was started after the patients had had a supine rest for 30 min, after which the needles were inserted (t=0). After exactly 10 minutes of UF one of the test solutions was infused by an infusion pump for ten minutes (t=10 to t=20) at the same rate as the ultrafiltration rate (20 ml/kg/hr), so that no net fluid was extracted from the body during the infusion period. In each patient, the effects of no infusion (NI), isotonic saline 0.9% (IS), hypertonic saline 3% (HS), isotonic glucose 5% (IG), hypertonic glucose 20% (HG), and mannitol 20% (HM) (Baxter BV, Utrecht, The Netherlands) were compared. The order in which the solutions were infused was random. The osmolarity of HS (900 mOsmol/L) was roughly comparable to the HM and HG solutions. The HM and HG solutions were iso-osmolar (both 1098 mOsmol/L).

Measurements

Relative Blood Volume (RBV) was measured by means of a blood volume monitor (BVM, Fresenius, Bad Homburg, Germany), which measures the total protein concentration, the sum of hemoglobin and plasma proteins in the vascular space. Changes in total protein concentration during dialysis are used to estimate changes in plasma volume. This method has a very good agreement with a standard reference method involving calculation of RBV from serial measurements of hemoglobin levels (SD 1.7%, $r > 0.96$) and allows precise and reliable measurement of RBV [10]. Moreover, these measurements showed no sensitivity to changes in blood components such as sodium and glucose. Systolic, diastolic and mean arterial blood pressures (SAP, DAP, MAP) and heart rate (HR) were measured in triplicate at 10-minute intervals by means of an oscillometric device (Accutor 3, Datascope Co., Paramus, NJ). The average of three consecutive measurements was used for analysis. Stroke volume (SV) was measured every 10 minutes using electrical impedance cardiography (Cardioscreen Medis, Ilmenau, Germany). Impedance cardiography is based on the fact that when blood is pumped into the aorta from the electrically well isolated heart, the electrical impedance of the thorax changes. SV can be subsequently calculated on the basis of this pulse synchronous change in impedance. This method has proven to give reliable information about the changes in stroke volume during hemodialysis [11]. Moreover, the results of impedance cardiography are highly reproducible (SD 0.36 l/min) [12]. One pair of electrodes was placed on each side of the neck. A third and fourth pair were placed on the lateral thorax at the xiphisternal level. Of each pair one electrode was placed exactly 5 cm above the other. The upper neck and lower xiphisternal electrodes were stimulated by a 60 kHz sinusoidal current and the resulting voltage was monitored from the inner recording electrodes. Two separate electrodes were placed in order to obtain the ECG signal. Stroke volume was calculated with the equation of Bernstein [13]:

$SV = VEPT \times LVET \times (dZ/dt_{max})/TFI$ (ml), where VEPT is the volume of electrically participating tissue, which depends on height and weight of the patient. The weight of the patient at the moment of the measurement was considered as the predialysis weight minus the weight of the net ultrafiltrationvolume. LVET is the left ventricular ejection time (ms), dZ/dt_{max} (Ω /ms) is the magnitude of the peak value of the impedance derivative and TFI (Ω) is the thoracic fluid index, which is given by the basic impedance. At 10- minute intervals the

patients were asked to keep perfectly still and during 20 heart cycles in the course of the examination the impedance curves were transported into a cardioscreen trend softwarepackage (version 3.1) and recorded on a PC screen. A mean impedance curve was calculated by the software program and the curves that varied more than 5% from average were discarded manually. When no more than five curves were discarded stroke volume was calculated from the remaining heart cycles. Total peripheral resistance (TPR) was calculated from, SV, HR and MAP using the following formula: TPR = (MAP/(SV x HR)) x 80 (dyn/sec /cm^{-5}). Before (t=0) and after one hour of treatment (t=60) blood samples were taken for the determination of urea, sodium, potassium, glucose, and osmolarity.
Sodium concentration was measured by ionometry. Osmolalarity was measured by determing the crystallizing temperature of the sample by freezing point depression then using the temperature and calibration curve to determine the osmotic pressure.

Statistical analysis
All data and values are presented as mean ± standard deviation.
Differences in body weight, hemodynamic parameters and laboratory between the procedures were analyzed by one way ANOVA with the post hoc LSD test using the SPSS statistical software package (SPSS version 8.0). Changes in hemodynamic and laboratory parameters compared to baseline were analyzed with a paired t-test.

Results

Body Weight
The average dry weight was 53.8 ± 13.5 kg, while the mean interdialytic weight gain was 4.6 ± 2.0 % of body weight (Table 1). During the 6 weeks period dry weight remained stable in all patients. The average interdialytic weight gain was comparable for all infusion experiments.

However, patient 2 and 3 showed an intra-individual variability in interdialytic weight gain.

Patient	Dry weight (kg)	NI (%)	IS (%)	HS (%)	IG (%)	HG (%)	HM (%)	
1	56.5	6.9	7.6	6.4	6.7	6.5	8.4	
2	32.0	2.5	4.1	8.4	6.2	7.1	4.7	
3	70.0	3.8	3.3	3.2	1.6	1.7	1.6	
4	49.5	4.8	3.2	4.6	3.6	4.4	3.6	
5	65.5	2.4	2.9	2.4	3.5	2.7	2.1	
6	49.5	6.6	6.5	5.6	6.6	4.2	6.5	
Mean	53.8 ±13.5	4.5 ±1.9	4.6 ±1.9	5.1± 2.1	4.7± 2.1	4.4±2.1	4.5±2.6	n.s.

Table 1: Dry weight and interdialytic weight gain. Means are given ± standard deviation n.s.= not significant

	ΔRBV(%) t=20 min	ΔRBV(%) t=30 min	ΔRBV(%) t=40 min	ΔRBV(%) t=50 min	ΔRBV(%) t=60 min
No Infusion	-1.5±0.8 [b]	-1.9±1.1	-3.4±1.9	-4.6±2.3	-6.0±2.3
Isotonic Saline (0.9%)	0.5±1.0	-1.1±1.4	-2.4±2.0	-3.6±2.4	-4.9±2.7
Hypertonic Saline (3%)	1.5±0.8 [a]	-0.8±2.3	-2.4±1.2	-3.6±1.2	–5.0±2.2
Isotonic Glucose (5%)	1.6±1.0 [a]	-0.3±2.4	-1.8±3.5	-3.3±3.9	-4.3±4.7
Hypertonic Glucose (20%)	4.6±0.6 [a b]	2.6±1.4 [a b]	-0.7±2.2	-2.7±1.6	-4.6±3.8
Hypertonic Mannitol (20%)	2.6±1.2 [a]	0.8±1.9	-1.1±1.9	-2.6±2.6	-3.8±3.1

Table 2.Changes in relative blood volume (ΔRBV) compared to the start
of the infusions (t= 10 min.) All values are given as mean standard deviation
[a] =P < 0.05 increase compared to baseline, [b] =P < 0.05 compared to all other infusions.

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Relative blood volume

During ultrafiltration, at a rate of 20 ml/kg/hr, RBV fell by 0.13 % in the first 10 minutes in all patients (Fig 1). A 10-minute infusion at a rate equal to the rate of ultrafiltration prevented a further decrease in RBV, as RBV at the end of the infusion (t=20) was significantly different from the control experiment for all solutions infused (Table 2). With infusion of HG the increase in RBV was significantly greater than the increase observed with all other infusions (Fig 1, Table 2). Moreover, the time at which RBV reached the same level as the

level at which the infusion was started was 18 ± 2 min for HG, which was significantly longer than all other infusion experiments ($p<0.05$, Fig 1). In patient 2, the interdialytic weight gain during the HG and HS infusion session were comparable and RBV increased by 4.8% during the HG infusions whereas RBV increased only 1.8% during the HS infusions (from t=10 to t=20 min). Moreover, RBV increased only by 2.3% during the HM session, despite the fact that interdialytic weight gain was relatively low. The interdialytic weight gain for patient 3 during the HG and HM sessions were comparable. During the HG infusions the increase in blood volume was larger than during the HM infusion (4.1% by HG and 2.3% during HM).

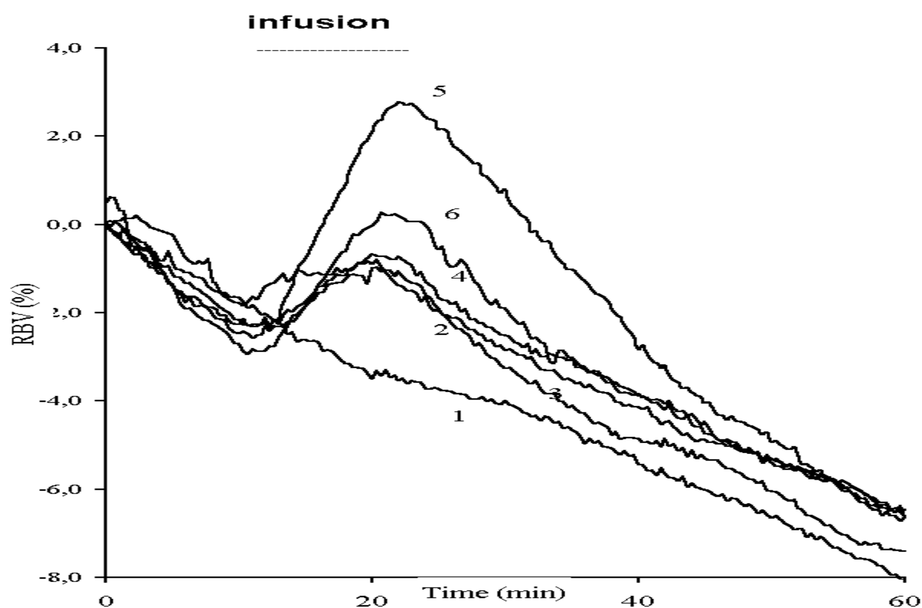

Figure 1: Mean changes in relative blood volume (RBV; %) for all patients during combined dialysis and ultrafiltration (20 ml/kg/hr) following the infusion of different solutions. The increase in RBV is significantly greater during infusion of hypertonic glucose (5). 1= No infusion, 2 = isotonic sodium 3= hypertonic sodium 4= isotonic glucose 5= hypertonic glucose 6= hypertonic glucose

Blood pressure, heart rate and stroke volume.

Blood pressure and heart rate remained unchanged during all experiments (Table 3). No IME events were noted. After infusion of HG blood pressure tended to increase but these changes did not show statistical significance. No episodes of symptomatic hypotension were noted. Stroke volume increased and TPR decreased significantly after the HG infusion.

	ΔSAP (%)	ΔHR (%)	ΔSV (%)	ΔTPR (%)
No Infusion	-0.3 ± 5.0	+2.2 ± 5.6	-6.8 ± 10.6	+9.7 ± 12.6
Isotonic Saline (0.9%)	-1.0 ± 3.6	-1.6 ± 3.7	+4.2 ± 13.4	-1.4 ± 14.6
Hypertonic Saline (3%)	-0.5 ± 4.8	0.0 ± 2.3	+6.0 ± 23.6	0.0 ± 27.0
Isotonic Glucose (5 %)	-1.0 ± 8.1	+3.0 ± 5.0	+6.9 ± 18.4	-1.2 ± 18.2
Hypertonic Glucose (20%)	+7.4 ±10.8	+0.4 ± 5.4	+21.0 ± 19.2 [a b]	-15.4 ± 16.4 [ab]
Hypertonic Mannitol (20%)	+1.3 ± 4.5	-3.8 ± 4.1	+9.3 ± 18.0	-6.1± 17.6

Table 3: Changes in systolic arterial pressure (ΔSAP, %) heart rate (ΔHR, %), stroke volume (ΔSV, %), and total peripheral resistance (ΔTPR, %) between beginning (t=10) and end (t=20) of the infusion period. All values are given as mean ± standard deviation. [a] =P < 0.05 compared to baseline. [b] =P < 0.05 compared to no infusions

Laboratory parameters

At baseline no differences in serum urea, glucose, sodium, potassium, and osmolarity were found between the various infusion experiments (27.9± 6.8 mmol/l, 6.7 ± 1.7 mmol/l, 137 ±2.9 meq/l, 5.37±0.72 meq/l, and 307±8 mOsmol/l respectively). After one hour of dialysis, serum urea concentration was decreased by a similar extent in all experiments (Table 4). Not surprisingly, serum sodium increased significantly after HS (from 137 ± 2.9 to 140.3 ± 3.0 meq/L; p<0.05) and sodium decreased after the HM compared to the most other solutes (136 ±2.5 to 135 ±2.0 meq/l). Serum potassium was lowered significantly during all experiments. The decrease was significantly greater after HG compared to NI, HM and IS experiments (5.4 ± 0.7 to 4.1 ± 0.6 meq/l; p<0.05). Glucose increased significantly after HG infusion only (6.3± 0.9 to 8.2 ±1.2 mmol/L; p<0.05). Plasma osmolarity decreased during NI and IG and tended to decrease in all infusion experiments, but this decrease did not reach statistical significance.

	ΔUrea (mmol/l)	ΔNa^+ (mmol/l)	ΔK^+ (mmol/l)	ΔGlucose (mmol/l)	ΔOsmol (mosmol/l)
No Infusion	-11.9 ± 6.5 [a]	2.5±3.2	-0.85 ± 0.29 [a]	-1.35 ± 2.02	-10.4 ± 5.8 [a]
Isotonic Saline (0.9%)	-11.5 ± 7.9 [a]	2.8±4.8	-0.83 ± 0.41 [a]	-1.12 ± 1.31	-3.8 ± 9.5
Hypertonic Saline (3%)	-11.0 ± 5.3 [a]	3.0 ±1.1 [a]	-0.95 ± 0.11 [a]	-1.07 ± 0.83 [a]	-5.8 ± 7.0
Isotonic Glucose (5%)	-9.4 ± 2.4 [a]	1.3±2.0	-0.98 ± 0.26 [a]	-0.13 ± 1.18 [b]	-8.2 ± 7.2 [a]
Hypertonic Glucose (20%)	-10.1± 3.4 [a]	0.5±1.8	-1.30 ± 0.57 [abce]	1.93 ±1.22 [a f]	-6.9 ± 7.4
Hypertonic Mannitol (20%)	-7.7 ± 1.4 [a]	-1.2±1.5 [bcd]	-0.86 ± 0.40 [a]	-0.17 ± 1.18	-2.2 ± 5.0

Table 4: Changes in laboratory parameters between the start of the dialysis session (t=0) and one hour of dialysis (t=60). All values are given as mean ± standard deviation. [a] =$P < 0.05$ compared to baseline
[b] =$P < 0.05$ compared to no infusions [c] =$P < 0.05$ compared to isotonic saline, [d] =$P < 0.05$ compared to hypertonic saline [e] =$P < 0.05$ compared to mannitol, [f] =$P < 0.05$ compared to all other infusions.

Discussion:

The results of our study demonstrate that during hemodialysis with ultrafiltration, infusion of hypertonic glucose solution (20%) results in a greater preservation of RBV than isovolumetric infusions of either normotonic or hypertonic saline or mannitol. Compared to the other infusion experiments, the increased RBV during hypertonic glucose infusion was associated with an increase in stroke volume and a decrease in vascular resistance. In our study, the finding that infusion of hypertonic glucose is more effective in increasing RBV than infusion of mannitol 20% is remarkable. Van der Sande et al. [14] compared colloids, such as albumin and or hydroxyethylstarch (HES) with saline and found a much greater increase in blood volume and blood pressure after the infusion of colloids. These differences were attributed to an increase in oncotic pressure during the colloid infusions. However, comparing the osmotic agents used in our study, mannitol closely resembles glucose in that it has the same molecular mass and charge and both solutions do not increase the oncotic pressure. Unlike glucose, which is rapidly transported from the extracellular to the intracellular space by insulin, mannitol is slowly eliminated from plasma [15,16]. Thus compared to infusion of mannitol, infusion of glucose is associated with a shorter lasting increase in plasma osmolarity. Indeed, in the present study, osmolarity, 40 minutes after infusions were discontinued, tended to be

slightly higher after administration of mannitol than after administration of glucose. As changes in osmolarity, hence oncotic pressure, do not provide an explanation for the greater increase in RBV after infusion of hypertonic glucose, it is tempting to speculate that glucose-induced vasodilatation accounts for the observed increase in RBV. Compared to other infusions or no infusion at all, infusion of hypertonic glucose was associated with a vasodilator response reflected by a decrease in vascular resistance and an increase in stroke volume. One could argue that the changes in electrolyte composition of the plasma induced by the sudden infusion of hypertonic salt or water directly affect impedance and might cause errors in the estimation of stroke volume and the subsequent calculation of vascular resistance. However, this change will not alter the magnitude of the peak value, as a correction for the baseline impedance is made. Therefore we don't expect problems with the adequacy of the impedance cardiography. Moreover, hypertonic glucose infusion will give a much higher electrical resistance than the infusion of hypertonic saline, which is an electrically active compound. As electrical resistance is inversely related to impedance and stroke volume, changes in stroke volume during hypertonic glucose infusion would be underestimated and those during saline would be overestimated. It has been shown that infusion of hypertonic glucose, but not of normotonic glucose or hypertonic mannitol into the brachial artery, is associated with a forearm vasodilator response [17]. A Study using vasodilator agents demonstrated that vasodilatation is associated with an increase in plasma volume without a concomitant increase in body weight, indicating that redistribution of the extracellular volume between the intravascular and extravascular compartments underlies this increase in plasma volume [18]. Recruitment of capillaries leading to an expansion of the vascular area could explain the vasodilatation- induced increase in RBV. Such a mechanism would be especially favorable for the action of glucose, as it can increase the disposal of glucose to the intracellular compartment [19].

It is uncertain whether the observed increase in RBV is of clinical benefit, as a change in peripheral resistance could induce a change in the critical value of blood volume at which IME occurs. The relatively small increase in blood volume during hypertonic sodium infusion could therefore lead to a more effective RBV and cardiac filling pressure. Previous studies showed that hypertonic saline infusion during hypotension is effective in raising blood pressure and cardiac filling pressure [5.6]. A dissociation between blood volume and vascular

tone would also change the algorithms for those clinical settings, in which RBV measurements are performed with a feed back control in order to prevent IME

We conclude that infusion of hypertonic glucose during dialysis results in a greater increase in RBV than equal volumes of other solutions. As mannitol has the same osmolarity, molecule mass and charge, the greater increase in RBV following hypertonic glucose appears to be a specific effect, possibly related to a decline in vascular tone. It is therefore uncertain whether the observed increase in RBV will be of clinical benefit during IME.

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Chapter 6: Hypotension during Hemodialysis Results From an Impairment of Arteriolar Tone and Left Ventricular Function.

Abstract

Hypotensive episodes are a major complication of hemodialysis. Hypotension during dialysis could be directly related to a reduction in blood volume or to a decrease in cardiovascular activation as a response to decreased cardiac filling. A decreased cardiovascular activation could be due to patient-related or to dialysis-related factors. In order to study the isolated effect of a reduction in filling pressure, lower body negative pressure (LBNP) causes activation of the cardiovascular reactivity with a decrease in cardiac filling, but without the influence of the dialysis procedure that could affect cardiovascular reactivity.

We studied the relationship between Relative Blood Volume (RBV), Central Venous Pressure (CVP), Systolic Arterial Pressure, Heart Rate, Stroke volume Index (SI), and Total Peripheral Resistance Index (TPRI) during a combined dialysis/ ultrafiltration and during LBNP to –40 mmHg in 21 hemodialysis patients with a high incidence of hypotension. Systolic arterial pressure, heart rate, SI, and TPRI were measured by Finapres. CVP was measured after cannulation of the jugular vein. During dialysis RBV was measured by a blood volume monitor (BVM). In order to study the conditions in which hypotension occurred after the dialysis, we divided the patients into two groups: Hypotensive (H) and non-Hypotensive (NH) during dialysis.

Baseline levels did not show any significant differences. During dialysis systolic arterial pressure declined gradually in the H group from 30 minutes before the onset of hypotension. There was a similar decrease of RBV and increase of heart rate in both groups with a large inter-individual variation. At hypotension, H patients showed a significantly smaller increase in TPRI, as compared to NH patients. The reduction in SI tended to be greater at hypotension, while CVP decreased to a similar extent in both groups.

Moreover, during LBNP, a similar reduction in CVP resulted in a much smaller decrease in SI.

Systolic arterial pressure was only slightly lowered due to a much greater increase in TPRI.

We conclude that dialysis related hypotension in our patient group did not result from an inability to maintain blood volume or from decreased cardiac filling. Hypotension appeared to result from the inability to adequately increase arteriolar tone and a reduction in left ventricular function.

Both vascular tone and left ventricular function appeared to be impaired by the dialysis procedure.

Introduction

Hypotensive episodes are a major complication of hemodialysis [1]. Hypovolemia resulting in a decrease in preload has been implicated as a major causative factor. Hypovolemia results from fluid withdrawal from the intravascular space during ultrafiltration and inadequate refilling from the extravascular space [2]. Whether hypovolemia leads to hypotension is dependent on the increase in systemic vascular resistance and maintenance of cardiac output. In response to the decrease in filling pressure adequate cardiac filling and stroke volume (SV) will especially depend on the diastolic function of the left ventricle (LV). Dialysis related hypotension is generally believed to have a multifactorial genesis, involving patient related factors such as sympathetic responsiveness [3], cardiac function [4], age [5] as well as dialysis associated factors such as body heating, [6,7], release of vasodilator agents [8,9], osmolar [10] and electrolyte changes [11].

We studied the relationship between Relative Blood Volume (RBV), Central Venous Pressure (CVP), Stroke volume Index (SI), Heart Rate, Systolic Arterial Pressure, and Total Peripheral Resistance Index (TPRI) during combined dialysis/ ultrafiltration in 21 hemodialysis patients with a high incidence of hypotension. Depending on the blood pressure response during the dialysis session after the dialysis the patients were divided into two groups; those that became hypotensive during dialysis (H) and those that did not (non-hypotensive; NH). However, given the multifactorial genesis, it is difficult to study the contribution of separate factors within the setting of hemodialysis.

The application of negative pressure to the lower part of the body can be used to decrease venous return, thereby simulating hypovolemia. In order to study the isolated effect of a reduction in filling pressure, we compared the hemodynamic circumstances under which hypotension occurred during dialysis with the response to Lower Body Negative Pressure (LBNP) in H patients. During LBNP, we measured the same parameters except for relative blood volume. Moreover, LBNP was performed under identical conditions at the same hydration status.

Methods

Twenty-one patients on chronic hemodialysis with a high incidence of hypotension during dialysis (i.e more than 30 % of their sessions) were studied during a combined dialysis/ultrafiltration session and a LBNP session. The LBNP sessions were performed on the same day as the dialysis session. Following LBNP, patients were allowed to rest for 60 minutes but refrained from fluid intake before the start of dialysis. The ethical committee of the Erasmus Medical Centre Rotterdam had approved the study, and all participants had given written informed consent.

Dialysis procedure

The dialysis procedure was performed with the procedure generally used at our institution, using bicarbonate dialysate (32 mmol/L) and a sodium concentration of 138 mmol/L (Fresenius SK-F213, Fresenius AG, Bad Homburg, Germany) and a temperature of of 37 ºC. The dialysate contained lesser than 50 CFU/ml water and the limulus amoebycyte lysate test was negative. Fresenius 4008H hemodialysis monitors and biocompatible hemophane (MA-12; Kawasumi, Tokyo, Japan) or polysulphone (F-60S; Fresenius MC, Bad Homburg, Germany) hemodialyzers were used to perform the treatments. Blood and dialysate flow rates were 200 ml/min and 500 ml/min respectively. All patients were ultrafiltrated with a constant ultrafiltration rate until dry weight in a 4-hour session. Inferior caval vein measurements were done at intervals of one month and dry weight was adjusted accordingly. Dry weight was considered optimal when patients remained without symptoms of dyspnea or edema during the interdialytic period. Overhydration was defined as a caval vein diameter of more than 11.4 and underhydration as a caval vein diameter of less than 8-mm/m^2 body surface area [12,13]. All patients remained supine starting 30 minutes before being connected to the dialysis circuit until the end of the treatment. No intravenous infusions were given during the treatment and intake of fluids and food was withheld during treatment, unless hypotension occurred. Hypotension was defined as a decline in systolic arterial blood pressure by more than 30 %.

LBNP procedure

During the LBNP procedure, the patients were placed in a box up to the iliac crest, and an airtight connection was attached to the patient's waist. Evacuating air from the box created a lower body negative pressure. After an equilibration period, LBNP of –20 mmHg was applied for 15 minutes. LBNP was subsequently increased to –40 mmHg for 15 minutes. Measurements were taken at the end of each 15 minutes of LBNP.

Measurements

During the LBNP and combined dialysis/ultrafiltration sessions systolic arterial pressure and heart rate were measured continuously by the Finapres device (Ohmeda 2300, Englewood, CO), using the middle finger of the nonfistula arm. This apparatus measures the blood volume under an infrared plethysmograph. When blood volume is kept constant at a set point value by controlling the cuff pressure, Systolic arterial pressure and heart rate can be calculated from these changes in cuff pressure. This method has been validated in many studies against invasive blood pressure measurements [14]. Changes in stroke volume and total peripheral resistance were derived on a beat-to-beat basis from the pulse pressure curve of the Finapres and computed by the Modelflow program (TNO, Amsterdam, the Netherlands) [15]. These parameters have been validated even in patients with shock [16]. However, for highest accuracy and precision a calibration of the model parameters is required [14]. Therefore, before the Finapres measurements were started, all patients underwent an echocardiographic measurement of stroke volume to calibrate the model. The volume of the left ventricle was calculated from the apical two- and four chamber views using a modification of Simpson's rule [17]. The principle of Simpson's rule is to divide the left ventricle into known slices of thickness. The volume of the ventricle is then equal to the sum of the volume of the slices. The endocardial borders of these views were digitally traced at end diastole and end systole. Stroke volume was calculated as the difference between end-diastolic and end-systolic volume. Measurement of CVP was performed continuously with a small bore catheter with a diameter of 0.6 mm, which was inserted in the right jugular vein using the Seldinger technique.

Statistical analysis

Hemodynamic data are given as mean ± standard deviation. SI and TPRI are given per m^2 body surface. Differences in baseline hemodynamics between H and NH were tested with the unpaired two-tailed Student's t-test. Differences in medication were tested with the Fischer's exact test. All changes are given as percentages, except for the changes in CVP, which are given in mmHg. Differences between the groups (H and NH) and procedures (LBNP vs. dialysis) and changes versus baseline were analysed using ANOVA for repeated measurements, and followed by the SNK test for multiple comparisons if appropriate. The level of significance was defined at 0.05.

Results

Baseline characteristics

Eleven of the 21 patients experienced a hypotensive period (H group) during dialysis, while the remaining 10 patients had no such event (NH group). Age, dry weight, time on dialysis, interdialytic weight gain, ultrafiltration rate/kg dry weight, and medication were comparable between the two groups (Table 1). Before dialysis systolic arterial pressure appeared to be lower in the H group, although this was not significant (127±26 vs.151±46 mmHg; Table 2). Baseline values in both groups for heart rate, SI, TPRI and CVP also did not show any significant differences.

Dialysis procedure

During dialysis, hypotension occurred on average 150 minutes after the start of the dialysis session. We therefore compared the 150-min measurements in the NH group with the moment of hypotension in the H group (Table 3). Most hypotensive patients developed severe symptoms, which necessitated intervention. Therefore, as we wanted to make a reliable comparison with the NH group, all data after the occurrence of hypotension were not analyzed.

Table 1. Patient characteristics

	Hypotensive (H)	Non Hypotensive (NH)	p
Number	11	10	
Age (yr.)	60.6 ± 13.3	53.4 ± 12.0	n.s.
M/F	6/5	8/2	n.s.
Time on dialysis (yr.)	2.5 ± 2.1	2.4 ± 1.5	n.s.
Dry weight (kg)	65.7 ± 6.9	67.3 ± 10.4	n.s.
Interdialytic weight gain (kg)	3.0 ± 1.4	3.0 ± 2.5	n.s.
Ultrafiltration rate/ kg dry weight (ml/min/kg)	10.3 ± 2.6	9.0 ± 2.9	n.s.
Medication			
Beta-adrenergic blockers	3	5	n.s.
ACE- inhibitors	1	2	n.s.
Calcium antagonists	3	4	n.s.

Values are mean ± SD n.s. = not significant

Table 2. Baseline hemodynamic data in Hypotensive and Non Hypotensive patients

	Hypotensive	Non Hypotensive	p
SAP (mmHg)	127 ± 26	151 ± 46	n.s.
HR (bpm)	70 ± 10	67 ± 10	n.s.
SI (ml /m^2)	33 ± 8	34 ± 11	n.s.
TPRI (dyne/sec/cm-5)/ m^2)	1225 ± 483	1277 ± 529	n.s.
CVP (mmHg)	11.0 ± 7.0	10.2 ± 4.8	n.s.

Hemodynamic data are mean ± SD n.s. = not significant SAP= Systolic Arterial Pressure; HR= Heart Rate; SI= Stroke volume Index; TPRI= Total Peripheral Resistance Index; CVP= Central Venous Pressure

In most patients systolic arterial pressure declined gradually, starting twenty minutes before the onset of hypotension (Figure 1). Ten minutes before the onset of hypotension blood pressure had already declined significantly compared both to baseline and the NH group (-9 ± 12 vs. +3±6; Table 3). In two patients systolic arterial pressure had dropped by up to 20 % at thirty minutes before the onset of hypotension, whereas in two other patients the drop in systolic arterial pressure occurred in only five minutes (Figure 1). Heart rate increased to a similar extent in both groups (Table 3). During or before hypotension no episodes of bradycardia were observed (Figure 1). During the hypotensive episode SI tended to be lower than at the corresponding time in the NH group (-41±20 vs.-28±18%; Table 3). At

hypotension this difference did not reach statistical significance. However, in the H group, SI had already declined within the first hour of the dialysis session (-20± 15 vs.-4±15%; Table 3). CVP tended to decrease comparable in both groups (Table 3).

Table 3: Hemodynamic changes (%) at each hour, at 30 and 10 minutes before hypotension and at Hypotension (H) or the corresponding moments (NH).

Non Hypotensive group (n=10)						
Time (min)	SAP (%)	HR (%)	SI (%)	TPRI (%)	CVP (mmHg)	RBV (%)
60	2 ± 14	0 ± 7	-4 ± 15	11 ± 32	-1.3 ± 1.3 [a]	-1.5 ± 2.4
120	3 ± 8	5 ± 8	-17 ± 14 [a]	51 ± 71 [a]	-1.5 ± 3.4	-4.1 ± 2.9 [a]
150	3 ± 6	9 ± 14	-28 ± 18 [a]	82 ± 83 [a]	-1.7 ± 2.7	-6.5 ± 3.5 [a]
180	-2 ± 8	11 ± 9 [a]	-28 ± 15 [a]	64 ± 75 [a]	-1.7 ± 3.0	-7.6 ± 4.3 [a]
240	-4 ± 9	13 ± 14 [a]	-40 ± 11 [a]	81 ± 76 [a]	-2.8 ± 2.5 [a]	-9.6 ± 5.3 [a]
Hypotensive group (n=11)						
Time (min)	SAP (%)	HR (%)	SI (%)	TPRI (%)	CVP(mmHg)	RBV (%)
60	2 ± 16	4 ± 9	-20 ± 15 [a, b]	25 ± 31 [a]	-1.5 ± 2.3 [a]	-3.6 ± 2.9 [a]
H-30 (120 ± 60 min)	-4 ± 17	10 ± 16	-27 ± 19 [a]	34 ± 27 [a]	-2.6 ± 2.1 [a]	-6.5 ± 5.2 [a]
H-10 (140 ± 60 min)	-9 ± 12 [a,b]	13 ± 17	-35 ± 13 [a]	35 ± 26 [a]	-2.8 ± 3.0 [a]	-8.5 ± 5.0 [a]
H (150 ± 60 min)	-31 ± 1	16 ± 16 [a]	-41 ± 20 [a]	25 ± 28 [b]	-3.0 ± 2.3 [a]	-8.5 ± 5.3 [a]
240	-22 ± 17	18 ± 20	-35 ± 30 [a]	18 ± 43	-3.3 ± 2.1	-10.5 ± 5.0

All values are expressed as Mean ± Standard Deviation; H= time of hypotension SAP= Systolic Arterial Pressure ;HR = Heart Rate SI=Stroke volume Index; TPRI=Total Peripheral Resistance Index; CVP=Central Venous Pressure; RBV= Relative Blood Volume. a: $p < 0.05$ compared to baseline. b: $p < 0.05$ compared to NH at the corresponding moment (H and H-10 are both compared to 150 min)

In the H group, the increase in TPRI at the moment of hypotension was significantly smaller when compared with NH patients at 150 minutes (25±28 vs. 82±83 %; Table 3).

At the onset of hypotension RBV had dropped by 8.5 % (Table 3). At this point, the ultrafiltration volume was 920 ml/m^2. Mean RBV and ultrafiltration volume for NH at 150 min was not significantly different (-6.5 ±3.5 % and 870 ml/m^2 respectively). At hypotension, there was a huge variation in decline of RBV (Figure1).

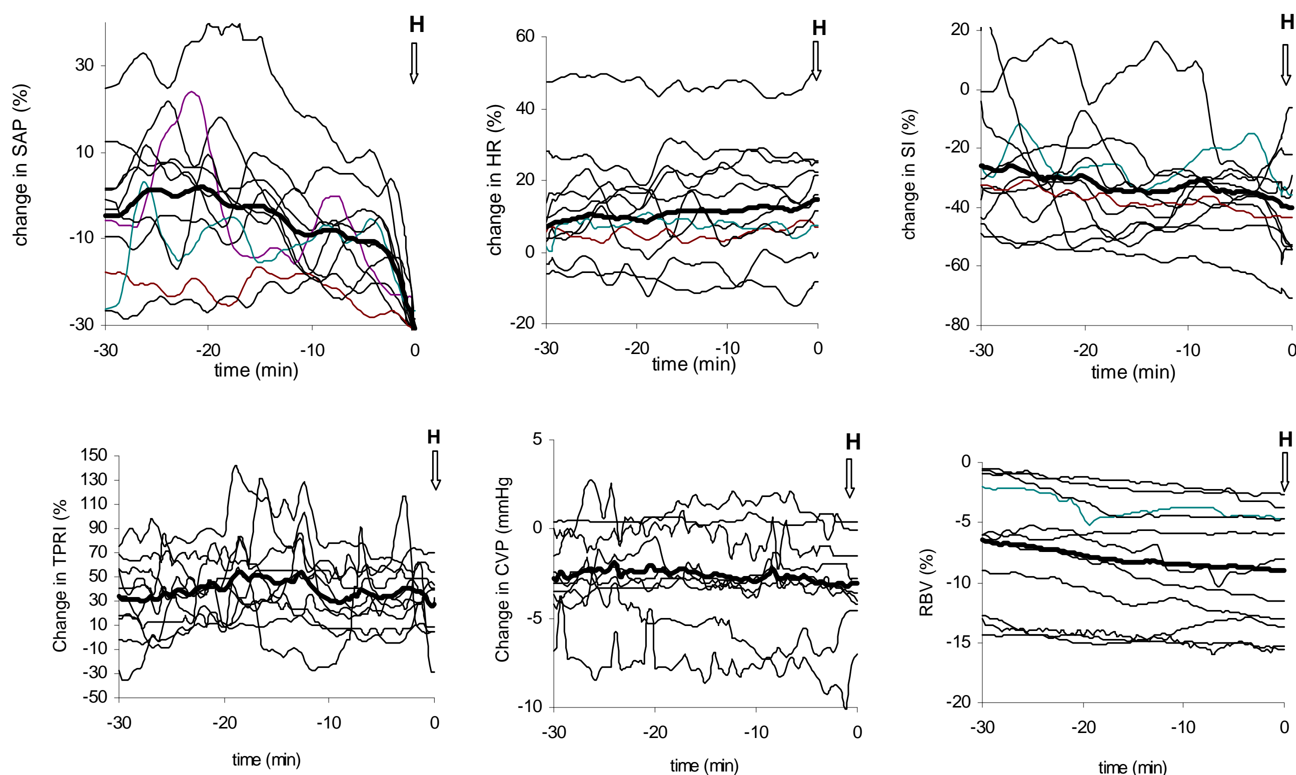

Figure 1 : Hemodynamic changes in hypotensive dialysis sessions from 30 minutes before the onset of hypotension. SAP= Systolic arterial Pressure ; HR = heart rate; SI = Stroke Volume Index; TPRI = Total Peripheral Resistance Index; CVP = Central Venous Pressure, RBV= Relative Blood Volume.

LBNP compared to dialysis procedure

In the patients in which hypotension occurred during dialysis, we compared the hemodynamics with those during the LBNP experiment. The reduction in CVP at which hypotension occurred was achieved by –20 mmHg of LBNP. However, the reduction in systolic arterial pressure at this level of LBNP was markedly lower than during dialysis (4±5 vs. 31±1 % ; Table 4). Moreover, the reduction in SI was significantly less during LBNP (-22±12 vs -41±20%). At –40 mmHg LBNP the reduction in SI was comparable with that during hypotension. However, the systolic arterial pressure was still significantly higher, as TPRI as compared to baseline (Table 4).

Table 4: Changes in hemodynamics in hypotensive patients at moment of hypotension and during LBNP.

	Hypotensive group								
	Dialysis Hypotension			LBNP -20 mmHg			LBNP -40 mmHg		
Hemodynamics									
SAP (%)	-31	±	1	-4	±	5 [a,b]	-15	±	16 [a,b]
HR (%)	16	±	16 [a]	2	±	5	6	±	16
SI (%)	-41	±	20 [a]	-22	±	12 [a,b]	-37	±	16 [a]
TPRI (%)	25	±	28	27	±	19 [a]	53	±	53 [a]
CVP (mmHg)	-3.0	±	2.3 [a]	-3.3	±	2.1 [a]	-5.2	±	4.3 [a]

All values are expressed as Mean ± Standard Deviation SAP=Systolic Arterial Pressure; HR=Heart Rate; SI= Stroke Volume index; TPRI =Total Peripheral Resistance; CVP=Central Venous Pressure; a: $p < 0.05$ compared to baseline b: $p < 0.05$ compared to dialysis hypotension

Discussion

Hypovolemia is generally thought to play an important role in the pathogenesis of intradialytic hypotension [2]. However, in our study hypovolemia did not seem to play a pivotal role in the pathogenesis of hypotension, as the change in blood pressure was not related to the decline in RBV. Moreover, at the onset of hypotension there was a huge variation in decline of RBV. These results are in agreement with our previous results, in which RBV and blood pressure varied significantly during 100 dialysis sessions, even when corrected for ultrafiltration volume [18]. We also found that the change in RBV at the moment of hypotension varied markedly, even within the same patient.

It is known that two essentially different patterns of dialysis related hypotension can be distinguished. One of these has a more or less gradual decrease in blood pressure, whereas the other is characterized by a sudden onset of bradycardia. The bradycardia associated hypertension is presumed to result from a Bezold-Jarish reflex, i.e. paradoxical symphaticoinhibition during severe underfilling [19]. All hypotensive episodes observed in our study were preceded by a gradual increase in heart rate. These findings suggest that the hypotensive episodes did not result from severe underfilling or an inability to increase heart rate, but rather from an incapability to maintain SI and/or to increase vascular tone.

In hypotensive subjects SI was decreased within one hour of the start of dialysis. The reduction in SI also tended to be greater at the moment of hypotension than the

corresponding moment in the non-hypotensive patients. This reduction in SI occurred at a similar reduction in filling pressure, as estimated by CVP. Moreover, when the hypotensive patients were subjected to LBNP, a similar reduction in CVP resulted in a much smaller decrease in SI. Thus the inability to maintain cardiac output appears to be related to the dialysis procedure.

Dialysis may impair either systolic or diastolic left ventricular function. We previously observed a decreased myocardial contractile reserve in hypotension prone patients [20]. Further, previous studies have shown that the dialysis procedure appears to interfere with the systolic left ventricular function [10,11]. However, there is evidence to suggest that increases in cardiac inotropy are not very important during hypovolemic conditions [21,22].

Alternatively diastolic function, can be reduced by the reduction in filling pressure, as a decreased pressure difference between left atrium and ventricle results into a reduced early left ventricular filling [23]. Moreover, diastolic dysfunction during dialysis has been suggested to result from shifts in ionized calcium [24]. Decreased availability of calcium to the myocardium could impair both myocardial contraction and relaxation. Diastolic dysfunction is a complex process that may also be influenced by ventricular interaction.

The observed episodes of hypotension may also have resulted from the inability to adequately increase vascular tone. The increase in vascular resistance at hypotension in the H group, was smaller than the corresponding time in the NH group. During LBNP, the hypotensive subjects were able to increase arteriolar tone and thereby maintain blood pressure despite a similar fall in SI. Therefore, the dialysis procedure appears to interfere with arteriolar tone.

An inadequate increase in arteriolar tone during dialysis is either due to decreased sympathetic activation or to decreased vascular responsiveness. Many previous studies showed that dialysis normally stimulates sympathetic nerve activity during gradual hypotension [25, 26]. On the other hand, it has also been suggested that sympathetic function detoriates during dialysis as plasma norepinephrine levels do not rise appropriately. [27]. Analysis with heart rate variability with spectral analysis also failed to show an increase in sympathetic tone during hemodialysis in hypotensive patients [3,28].

The dialysis sessions in our study lasted for four hours. It is possible that prolonging the dialysis session, as described in the Tassin study, would have resulted in an improved blood pressure profiles during hemodialysis [29].

A decreased vascular response during dialysis could result from a positive thermal balance, due to an inability to dissipate the excess of heat [6,7]. Further, a change in the Nitric Oxide–Endothelin–1 balance as a result of mechanical and chemical stimuli may also be involved in the pathogenesis of dialysis induced hypotension [8,9]. Other dialysis related factors that could cause an impaired vascular response include changes in plasma sodium, potassium, acid base composition and use of anti hypertensive drugs [21].

As the decrease in CVP was comparable in both groups, a decrease in venous tone was unlikely responsible for the occurrence of the hypotensive episodes in our study. This is in agreement with previous study that showed a decreased venoconstriction in stable sessions as well [30,31].

We conclude that dialysis related hypotension in our patient group did not result from an inability to maintain blood volume or from decreased cardiac filling. Hypotension appeared to result from the inability to adequately increase arteriolar tone and a reduction in left ventricular function. Both vascular tone and left ventricular function appeared to be impaired by the dialysis procedure.

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Chapter 7: Norepinephrine-Induced Vasoconstriction Results in Decreased Blood Volume.

Abstract

Hypotension during hemodialysis is due to an inadequate cardiovascular response to ultrafiltration induced hypovolemia. In some studies, it is suggested that plasma volume could decrease by vasoconstriction, whereas several other studies in non dialysis patients observed a decrease in plasma volume. We studied the effect of norepinephrine induced vasoconstriction, compared to no infusion, on Relative Blood Volume in six dialysis patients. During the infusion we measured RBV, blood pressure, Stroke Volume Index, Ejection Fraction , Heart Rate, and body temperature.

At baseline, both groups were comparable. At the end of infusion or at the comparable moment, no significant change in SI (-4 ± 21 vs 0 ± 8 %), HR (-5 ± 19 vs –4 ± 5%), EF (7 ± 14 versus –2 ± 10%) and CI (-10 ± 21 versus –3 ± 6%), and T_{body} (0 ± 2 versus –1 ± 1 %) were observed. However, a significant increase in SAP (27 ± 12 vs 0 ± 8 %; p<0.01) and TPRI (47 ± 47 versus 4 ± 17%; p<0.01) was found. This decrease was concomitant with a significant decrease in RBV (-9±.3 vs. 0±1 % p<0.01).

We conclude that a norepinephrine induced increase in total peripheral resistance results in a decrease in RBV. This indicates that the improved hemodynamic stability during hemodialysis through vasoconstriction can be accompanied by a decrease in RBV, and part of the variability in blood volume may be due to changes in arterial tone.

Introduction

Hypotension is a major complication during hemodialysis (HD) [1]. Decreased plasma volume preservation, due to the fluid withdrawal from the intravascular space and a delay in plasma refilling by ultrafiltration, combined with inadequate compensatory vasoconstriction are directly responsible for this phenomenon [2,3]. The Relative Blood Volume (RBV) can be derived from the measured percentual changes in total protein concentration. Blood volume monitoring (BVM) enables us to measure the relative changes in blood volume (RBV) continuously during hemodialysis in the arterial bloodline [4]. It has been thought that an increase in peripheral arterial resistance during dialysis can increase venous return by means of the DeJagher-Krogh phenomenon [5,6,7]. This implies that when arterial resistance is increased, flow and intra-capillary pressure are reduced and vascular refilling is increased. Moreover, due to passive recoil, venous capacity is decreased and sequestered blood is

translocated back to the heart. Consequently it is suggested that arterial vasoconstriction increases RBV [8-10].

However, evidence for a positive correlation between changes in plasma volume and peripheral resistance has never been found. Evenmore, there is evidence suggesting an inverse relationship. In non-dialysis patients plasma volume decreased as a result of an adrenergically induced vasoconstriction. [11-14]. Moreover, both during diffusive dialysis and glucose infusion, procedures in which vascular resistance is decreased, we observed a concomitant increase in RBV [15,16]. Dialysis, using a lower dialysate temperature, increases peripheral resistance but decreases RBV [17].

In order to clarify the relationship between vascular resistance and plasma volume, we studied the effect of norepinephrine induced vasoconstriction, compared to no infusion, on RBV in six dialysis patients. During the infusion we measured RBV, Blood Pressure, Stroke Volume Index, Ejection Fraction , Heart Rate, and Body Temperature.

Material and methods

Patients

We studied six patients requiring chronic hemodialysis. None of the patients had severe valvular heart disease, heart failure (>NYHA class I) or arrhythmia's. All medication was stopped on the day of the investigation. In the patients using ß blockers, this medication was withdrawn the day before the experiment. The ethical review committee of our hospital approved the study and written informed consent was obtained from all patients.

Study design

Each patient was studied during two dialysis sessions, which were performed on the same day of the week. On arrival, the patients were weighted and were placed in a dialysis chair, where they rested for 30 min (t= -30). During the study, the patients remained supine and no food or beverages were provided throughout the experiment. The patients were connected to the extracorporeal circuit (Fresenius 4008H machines with Fresenius F60-S polysulphone artificial kidneys and BVM/BTM arterial and venous lines; Fresenius MC Bad Homburg; Germany). During connection to the dialysis circuit, the priming volume of saline was discarded. At the start of this procedure blood was drawn from the access for laboratory

measurements. Blood flow was set at 250 ml/min. Neither diffusive dialysis nor ultrafiltration was performed throughout the investigation. After being connected to the dialysis circuit RBV, Systolic, diastolic and mean arterial blood pressures (SAP, DAP, MAP) and heart rate (HR) were measured continuously throughout the experiment. At the start of the experiment (t=0), echocardiography was performed to obtain Stroke Volume, and Ejection Fraction. Directly after these measurements (t=0 min), either Norepinephrine (Nor) was infused or a control experiment was performed in which no infusion was given (Cont). Nor was given at an initial dose of 0.02 μg/kg/min I.V. This was increased with 0.03 μg/kg/min each 5 minutes until after 20 minutes a maximum dose of 0.14 μg/kg/min was reached or until systolic blood pressure was raised by more than 30%. The infusions and control experiments were performed in random order and the patient was blinded to the infusion. Ten and thirty minutes (t=10 and t=30) after the start of the Nor, or at the comparable moments for the Cont experiments, a second and a third echographic measuments were done. Moreover, temperature measurements were performed. After these measurements the study was ended. For safety reasons dialysis was started at least 10 minutes after the infusion was discontinued.

Measurements

RBV was measured continuously throughout the experiment by means of a blood volume monitor (BVM, Fresenius, Bad Homburg, Germany). The blood volume monitor measures the total protein concentration in the arterial bloodline, which is the sum of hemoglobin and plasma proteins in the vascular space. Changes in total protein concentration during dialysis are used to estimate changes in plasma volume. This method has a very good agreement with a standard reference method involving calculation of RBV from serial measurements of hemoglobin levels (SD 1.7%, $r > 0.96$) and allows precise and reliable measurement of RBV [4]. Systolic, diastolic and mean arterial blood pressures (SAP, DAP, MAP) and heart rate (HR) were measured continuously throughout the experiment by the Finapres device (Ohmeda 2300, Englewood, CO), using the middle finger of the nonfistula arm. This apparatus measures the blood volume under an infrared plethysmograph. When blood volume is kept constant at a set point value by controlling the cuff pressure, SAP and HR can be calculated from these changes in cuff pressure. This method has been validated in many studies against invasive blood pressure measurements [18]. Echocardiograms were obtained

using a ultrasound machine (Sonos 5500, Hewlett Packard Medical products, Boston, MA). The volume of the left ventricle was calculated from a two dimensional parasternal view. Endocardial borders of these views were digitally traced at the end of systole and diastole and their volume was calculated. Stroke volume was calculated as the difference between end-diastolic and end-systolic volume. A mean stroke volume of five consecutive beats was taken. Stroke Volume Index (SI) was calculated from stroke volume and body surface area, which was calculated from length and height, according the Dubois formula [19]. Directly after each ultrasonography, SAP, DAP and MAP were also measured by an oscillometric device (Accutor 3, Datascope Co., Paramus, NJ). Body Temperature (T_{body}) was measured by an ear thermometer after each ultrasonography. Total peripheral resistance index (TPRI) was calculated from MAP, measured by datascope, and cardiac index (CI).

Statistical analysis

Hemodynamic data are given as mean ± standard deviation. Differences during the experiments and between groups were tested with the Analysis of Variance with repeated measurements. If significant multiple comparisons were made using the Student Neuman Keuls test. The Graphpad Prism software program was used to perform these calculations. A p-value of less than 0.05 was assumed to indicate statistical significance.

Results

Patients

Six hemodialysis patients, five male and one female participated in the study (Median time on dialysis 2.6 years, range 1.5- 4 years; Table 1). The median age of the subjects was 53 ± 11 years (range; 35-62 years: Table 1). Median residual diuresis was 252 mL/ 24 hr (range 0-950 mL/ 24 hr ml; Table 1). Three patients had a residual diuresis of less than 5 mL/day, while the other three had a rest diuresis of 500 mL/liter or more. One patient with diabetes was included, and two patients were hypertensive. Mean dry weight was 70.6 ± 12.9 kg and interdialytic weight gain was comparable in the two sessions (3.6 ± 1.4 kg versus 3.6 ± 2.3 kg; n.s.; Table 1).

Table 1. Characteristics of the patients

	1	2	3	4	5	6	Mean		SD
M/F	M	M	M	F	M	M			
age (yr)	57	52	54	36	62	35	49	±	11
time on dialysis (yr)	4.0	3.0	1.5	2.5	2.0	2.5	2.6	±	0.9
dry weight (kg)	69.0	75.0	69.0	47.5	77.5	85.5	70.6	±	12.9
IWG(%) Cont	2.9	2.9	5.1	3,4	1.9	5.4	3.6	±	1.4
IWG(%) Nor	2.0	2.8	5.6	2.1	1.2	7.9	3.6	±	2.3
residual diuresis	5	825	0	0	950	500	380	±	440
								Y/N	
Diabetes mellitus	-	-	-	+	-	+		2/4	
hypertension	-	-	-	+	+	-		2/4	
Medication									
beta-adrenergic blockers	-	-	-	-	+	-		1/5	
ACE-inhibitors	-	+	-	+	+	+		4/6	
Calcium antagonists	-	-	-	+	+	-		2/4	
Nitrates	-	-	-	-	+	-		1/5	

IWG, interdialytic weight gain; Cont, control ; Nor, Norepinephrine

Table 2. Baseline Laboratory data

	Control	Norepinephrine	p
urea (mmol/L)	22.9 ± 6.3	22.2 ± 4.7	n.s.
osmolarity (mosmol/L)	298 ± 9	299 ± 10	n.s.
Na (mmol/L)	138 ± 3	138 ± 3	n.s.
K (mmol/L)	4.8 ± 0.9	4.7 ± 0.5	n.s.
Ca (mmol/L)	2.38 ± 0.12	2.43 ± 0.08	n.s.
ionized Ca (mmol/L)	1.24 ± 0.05	1.20 ± 0.07	n.s.
PO4 (mmol/L)	1.47 ± 0.46	1.51 ± 0.48	n.s.
Alb (g/L)	38 ± 2	38 ± 2	n.s.
pH	7.39 ± 0.02	7.40 ± 0.03	n.s.
pCO2 (kPa)	5.2 ± 0.5	4.8 ± 0.6	n.s.
HCO3-	22.7 ± 2.4	23.1 ± 3.2	n.s.
PTH (pmol/L)	93 ± 78	119 ± 74	n.s.
Hb (mmol/L)	7.4 ± 1.2	7.1 ± 1.0	n.s.
Ht (L/L)	0.35 ± 0.06	0.34 ± 0.05	n.s.

Data are ± standard deviation. Na, sodium; K, potassium;Ca, Calcium; PO4, phosphate; Alb, Albumin, pCO2carbon dioxide tension, HCO3-, bicarbonate; PTH, parathormone; Hb, Hemoglobin; Ht, hematocrit n.s., not significant

Table 3. Baseline Hemodynamics

	No infusion			Noradrenaline			p
SAP (mmHg)	165	±	23	139	±	35	n.s.
MAP (mmHg)	113	±	20	101	±	20	n.s.
DAP (mmHg)	84	±	12	71	±	13	n.s.
HR (b.p.m.)	75	±	17	78	±	12	n.s.
CI (ml/m2)	1516	±	458	1283	±	541	n.s.
T body(C)	36,3	±	1,0	36,9	±	0,9	n.s.

n.s., not significant

Baseline Values

At baseline, no differences were found in laboratory data between the Cont and the Nor sessions (Table 2). SAP tended to be lower during the Nor experiment, but this did not reach statistical significance (139 ± 35 versus 165 ± 23 mmHg; Table 3). Datascope blood pressure measurements were comparable to the Finapres measurements and were 165 ± 24 vs 142 ± 34 mmHg for Nor and Cont respectively (Table 3). HR, SI, and TPRI were comparable in both experiments (75±17 vs 78±12 b.p.m., 20 ± 3 vs 18 ± 6 ml/m^2, and 6154 ± 1486 vs 6940 ± 3215 dynes.s m^2/cm^5 respectively; Table 3) Core Temperature (T_{body}) and EF were comparable between both groups (36.3 ± 1.0 vs. 36.9 ± 0.9 °C, and 47±17 vs. 42±7 % respectively; Table 3).

Response to norepinephrine

The patients tolerated the infusion of Norepinephrine well with minor complaints of anxiety and no palpitations. All patients completed the protocol. At 10 minutes SAP tended to increase in the Nor group, RBV decreased as compared to baseline (-3 ± 2 %; $p < 0.05$; Table 3, Figure 1). HR, MAP, SI and TPRI did not change significantly (Figure 1; Table 4).

At 30 minutes both SAP and DAP were increased in the Norepinephrine group both compared to baseline as compared to the Nor group (SAP; 21±12 %, DAP; 18±12 % by finapres and datascope respectively; $p < 0.05$; Table 4, Figure 1).

Table 4. Hemodynamic changes during sessions in the No Infusions and the Norepinephrine group

	Control		Norepineprine	
	t= 10 min	t=30 min	t= 10 min	t=30 min
RBV(%)	0 ± 1	0 ± 1	-3 ± 2 [a]	-9 ± 3 [a,b]
SAP(%)	-6 ± 8	-2 ± 14	12 ± 10 [a b]	24 ± 15 [a,b]
MAP(%)	0 ± 12	4 ± 16	13 ± 15	25 ± 17 [a,b]
DAP (%)	-2 ± 10	4 ± 14	14 ± 5	18 ± 12 [a,b]
HR(%)	-4 ± 2	-4 ± 5	-6 ± 13	-5 ± 19
SI(%)	5 ± 18	0 ± 8	1 ± 10	-4 ± 21
CI(%)	3 ± 19	-3 ± 6	4 ± 18	-10 ± 21
TPRI (%)	1 ± 16	4 ± 17	6 ± 14	47 ± 47 [a]
T body	1 ± 2	0 ± 2	-1 ± 1	-1 ± 1
EF (%)	-5 ± 7	-2 ± 10	3 ± 10	7 ± 14

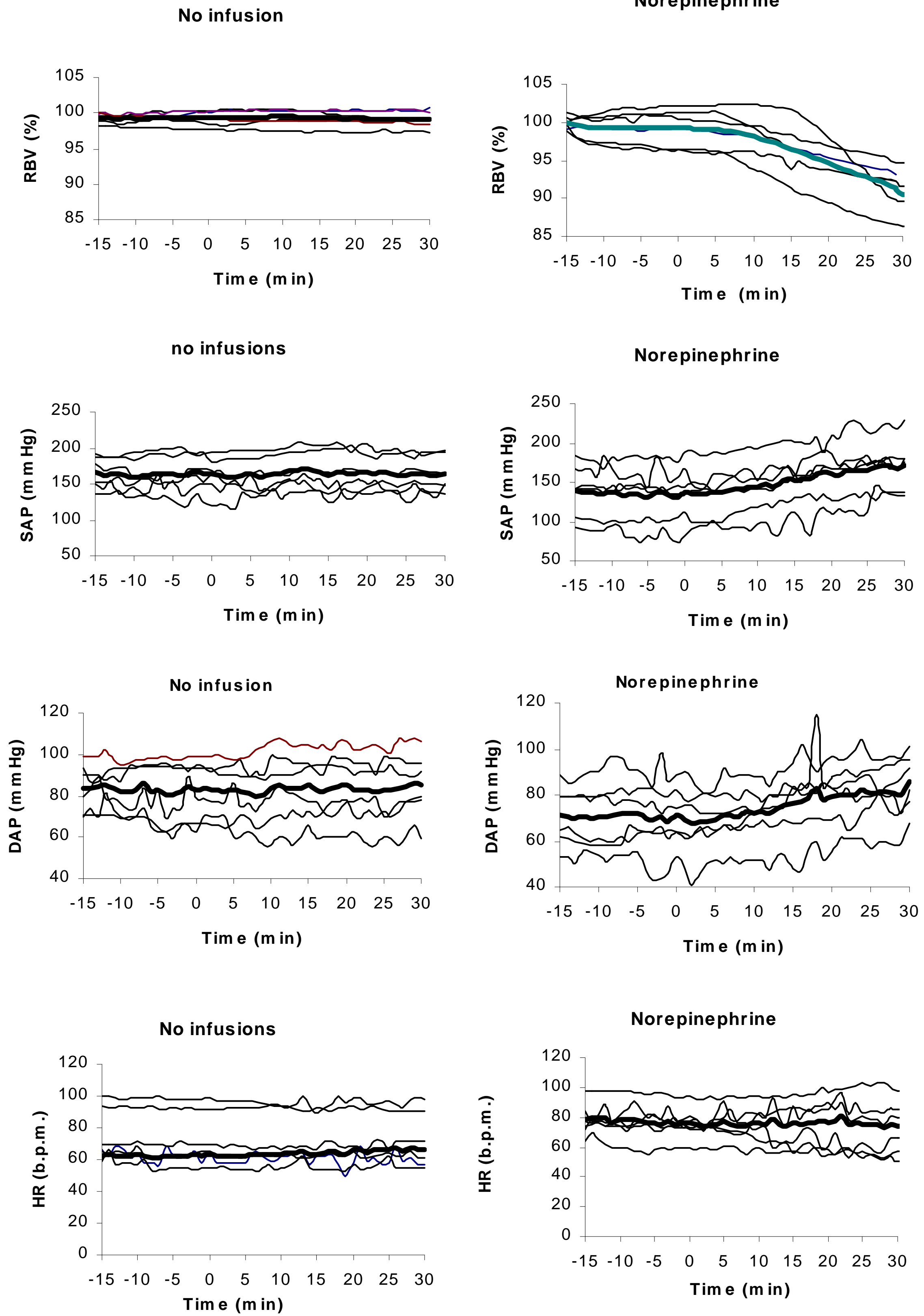
RBV. Relative blood volume; SAP systolic arterial pressure; MAP, Mean arterial pressur; DAP , diastolic arterial pressure; HR, heart rate; SI, Stroke volume Index; CI, Cardiac Index; TPRI, total peripheral resistance index , T body, body temperature; EF, ejection fraction

[a] significant compared to baseline p< 0.05 [b] significant compared to control

There was a good agreement between changes in blood pressure by datascope and by finapres. No significant change in SI (-4 ± 21 vs 0 ± 8 %; p>0.05), HR (-5 ± 19 versus –4 ± 5; p>0.05), EF (7 ± 14 vs –2 ± 10; p>0.05), CI (-10 ± 21 versus –3 ± 6 %; p>0.05) and T_{body} (-1 ±1 vs 0 ± 2% p>0.05) were observed between both groups (Table 4, Figure 1). However, in the Nor group TPRI increased as compared to baseline (47 ± 47 %; p < 0.05), whereas in the Cont group TPRI did not change significantly (4 ± 17 % by finapres; p>0.05) (Table 4).

This increase in vascular resistance decrease was accompanied by a concomitant decrease in RBV (-9±3 vs 0±1 % (p<0.001; Table 4, Figure 1) RBV dropped in all patients and no relation was found between the decrease in RBV and the patient characteristics, such as the presence of hypertension and/or diabetes and the amount of volume overload.

was found. The increase in TPRI did not result from Cooling of blood by the extracorporal circuit, as BT (-1±1 vs 0±2 C) did not decrease significantly.



No infusion
RBV (%)
105
100
95
90
85
-15 -10 -5 0 5 10 15 20 25 30
Time (min)
Norepinephrine
RBV (%)
105
100
95
90
85
-15 -10 -5 0 5 10 15 20 25 30
Time (min)
no infusions
SAP (mmHg)
250
200
150
100
50
-15 -10 -5 0 5 10 15 20 25 30
Time (min)
Norepinephrine
SAP (mmHg)
250
200
150
100
50
-15 -10 -5 0 5 10 15 20 25 30
Time (min)
No infusion
DAP (mmHg)
120
100
80
60
40
-15 -10 -5 0 5 10 15 20 25 30
Time (min)
Norepinephrine
DAP (mmHg)
120
100
80
60
40
-15 -10 -5 0 5 10 15 20 25 30
Time (min)
No infusions
HR (b.p.m.)
120
100
80
60
40
20
0
-15 -10 -5 0 5 10 15 20 25 30
Time (min)
Norepinephrine
HR (b.p.m.)
120
100
80
60
40
20
0
-15 -10 -5 0 5 10 15 20 25 30
Time (min)

Discussion

This study demonstrates that infusion of norepinephrine in patients on dialysis results in a direct and substantial decrease in RBV.

The observed decrease in RBV during the norepinephrine infusions can be either due to a relative increase in the erythrocyte cell mass or to a decrease in the total amount of plasma fluid.

Erythrocyte cell mass could change during vasocontriction, as the erythrocyte cell mass is not uniformly mixed and the hematocrit of the peripheral vascular beds is much lower than that of the large vessels [20,21]. However, it is unlikely that this mechanism could explain the observed decrease in RBV, as during vasoconstriction, blood with a relatively low eryhrocyte content is shifted to the large vessels and arterial bloodline, in which RBV is measured. This would result in an increase in RBV, rather than a decrease.

Erythrocyte cell mass could also be increased by splenic contraction. However, previous studies showed, that in humans, the spleen does not serve as an important reservoir for red blood cells over splenic constraction, could only account for an increase of 1-2% [22,23].

Changes in plasma volume can be explained by Starlings law, which determines the fluid shift between the vascular and the interstitial compartments and depends on changes in hydrostatic and oncotic capillary pressure and on the filtration coefficient of the capillary basement membrane [24]. Reduced perfusion of capillary beds during arteriolar constriction leading to a decrease of the vascular surface area could explain the norepinephrine-induced decline in RBV. A decrease in perfused vascular beds could also increase hydrostatic capillary pressure in the remaining vascular beds. This could in turn lead to a decreased vascular refilling and hence blood volume. However, there is only a slight relation between the change in peripheral resistance and RBV. This can be explained by the fact that total peripheral resistance is calculated from blood pressure and cardiac out put. Each of these measurements varies, and their summed contribution can lead to considerable variability in the calculated TPR. On the other hand, the constriction of the veins could also contribute to the decrease in RBV. When vasoconstriction is more pronounced at the venular than at the arteriolar end of the capillaries, intracapillary hydrostatic pressure will rise, thereby promoting a shift of fluid from the intravasular to the interstitial compartment [25]. Many previous studies lend evidence that blood volume increases after a decrease in total peripheral resistance by arterial vasodilatation

[26-28]. Moreover, the increase in plasma volume after vasodilatation induced by infusion of an alpha-receptor antagonist, was found to be inversely related to the change in CVP [30].
The results of our study are in accordance with most previous studies in which the effect of norepinephrine on plasma volume was studied in non dialysis patients or animals [11-14].
In one study, erythrocyte cell mass increased. However, this study was done in dogs in which the spleen is a far more important red blood cell reservoir [11].
In another study, a norepinephrine-induced increase in peripheral resistance showed no significant change in plasma volume, although hematocrit was increased in three out of four patients [13]. This experiment differs from ours in the fact that norepinephrine was given for six hours, while in our experiment norepinephrine was given for only twenty minutes. It is known that in response to prolonged norepinephrine infusions the cardiac output increases and consequently peripheral resistance decreases, due to the release of endogenous epinephrine [29]. This could diminish the increase in RBV.
The results of our study have major implications for the interpretation of measurements and the applications of a biofeed back control systems in order to prevent dialysis related hypotension. When performing maneuvers to improve vascular stability during dialysis, such as isolated ultrafiltration, or lowering dialysate temperature, RBV decreases and the critical RBV, at which hypotension occurs, will be lowered [17,30]. This can explain the findings of Schneditz et al. who describe improved hemodynamic stability, in spite of a greater reduction in RBV during cold dialysis. Differences in arteriolar tone may also explain the observed variabilility in RBV during hemodialysis and the difficulties to observe a critical value, at which hypotension occurs [31]. Conversely, an increase in RBV does not always lead to an increase in effective plasma volume and cardiac filling pressure. Hypertonic glucose infusions during dialysis result in a greater increase in RBV than equal volumes of mannitol, which has the same osmolarity, molecule mass and charge [16].
These difference could be related to a decline in vascular tone during the glucose infusion. Moreover, during diffusive dialysis, a procedure in which vascular resistance is decreased, we observed an increase in RBV [15].
We conclude that a norepinephrine induced increase in total peripheral resistance results in a decrease in RBV. This indicates that the improved hemodynamic stability during hemodialysis through vasoconstriction can be accompanied by a decrease when n RBV, and

part of the variability in blood volume may be due to changes in arterial tone. Such changes must be taken into account of RBV measurements are used to improve the hemodynamic tolerance of dialysis

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Chapter 8: Hemodynamic response to lower body negative pressure in hemodialysis patients.

Abstract

Hypovolemia is thought to play an important role in the pathogenesis of dialysis-related hypotension. We studied the effect of hypovolemia simulated by lower body negative pressure (LBNP) in 11 hypotension prone (HP) and 11 hypotension resistant (HR) hemodialysis patients. LBNP was applied step-wise from 0, to -20 to -40 mmHg. Systolic arterial pressure, heart rate and central venous pressure (CVP) were recorded continuously after canulation of the right jugular vein. Stroke Volume Index (SI) was measured at each step echocardiographically. At the end of each level of LBNP, blood samples were taken for norepinephrine (NE), epinephrine (E) and atrial natriuretic peptide (ANP) levels. At baseline, CVP (12±5 and 16±7 mmHg), heart rate (72±9 and 70±13 bpm), Cardiac index (2.3±0.6 and 2.5±0.9 l/min), NE (median ,341 pg/mL [range, 198 to 789 pg/mL], and 365 pg/mL [range, 177 to 675 pg./mL] or 2.02 nmol/L [range, 1.17 to 4.66 nmol/L] and 2.16 nmol/L [range, 1.05-4.00 nmol/L]), E (median, 46 pg/mL [range, 18 to 339 pg/mL] and 58 pg/mL [range, 21-122 pg/mL] or 251 pmol/L [range, 98-1951 pmol/L] and 317 pmol/L [range, 115-666 pmol/L]) were similar, whereas systolic arterial pressure (141±26 vs164±22 mmHg) and ANP (441 (152-1330) vs. 804 (517-3560) pg./ml or ng/L) were lower ($p<0.05$) in HP patients. In response to LBNP (-40 mmHg) CVP decreased by 6.5±4.0 mmHg in the HP-group and by 4.9±4.9 mmHg in the HR-group. In HP patients, this decrease was associated with a greater fall in SI (37 ± 16% versus 27 ± 16%) and systolic arterial pressure (19±21% versus 4±14%) than HR patients. Plasma ANP levels did not change, whereas the rise in NE and E was similar in HP and HR patients. We conclude that patients which frequently experience episodes of hypotension during dialysis are also prone to develop hypotension during LBNP, which results from reduced myocardial contractile reserve and/or inadequate sympathetic tone.

Introduction

Hypotension is an important cause of morbidity during hemodialysis treatment and occurs in approximately 30% of the dialysis sessions. Factors that may contribute to the occurrence of hemodialysis-induced hypotension include the reduction in blood volume and the osmotic shifts that occur during dialysis [1]. Failure of the heart and/or the autonomous nervous

system to respond to the hypovolemia induced by hemodialysis may also result in decreased blood pressure preservation [2,3]. The degree in which hypovolemia occurs during dialysis is highly variable. We have demonstrated that both intra- and inter-individual variability of blood volume changes during dialysis is high and cannot be explained by differences in ultrafiltration rate [4]. As these factors may all interact, it is difficult to establish the relative importance of each factor during hemodialysis.

Applying lower body negative pressure (LBNP) allows the isolated manipulation of venous return to the heart [5], thereby mimicking controlled hypovolemia. In healthy volunteers, LBNP causes a reduction in central venous pressure (CVP) starting at –20 mmHg LBNP followed by a reduction in stroke volume index (SI) and cardiac index at higher levels. Blood pressure usually remains unchanged due to an increase in total peripheral resistance and heart rate, but hypotension may occur at levels of -40 mmHg and higher [5-9]. In healthy volunteers, hypovolemia increases the risk for hypotension [8].

In order to determine the importance of hypovolemia in the pathogenesis of dialysis related hypotension, we studied the cardiovascular response to LBNP in hypotension prone and hypotension resistant hemodialysis patients.

Patients and Methods

Patients

Twenty-two patients on chronic hemodialysis, 11 hypotension-prone (HP) and 11 hypotension-resistant (HR), were studied. The ethical committee of the University Hospital Rotterdam-Dijkzigt approved the study, and all participants gave written informed consent. Criteria for classification as hypotension-prone were: decrease of systolic arterial pressure to less then 100 mmHg accompanied by symptoms of hypotension (dizziness and/or syncope) occurring in at least one third of dialysis sessions during the last three months prior to inclusion in the study. Patients with diabetes mellitus were excluded from the study.

Age and sex distribution was not different in both groups (Table 1). Time on dialysis was also not significantly different in HP and HR patients. The average number of antihypertensive drugs was 1.0 in HP patients vs. 1.6 in HR patients (n.s.). All dialysis treatments were performed on a trice-weekly basis, using bicarbonate buffered dialysate and biocompatible membranes (Hemophane or Polysulphone). Dry weight was considered optimal when patients

remained without symptoms of dyspnea or edema during the interdialytic period. Inferior caval vein diameter measurement was performed at intervals of one month. Overhydration was defined as a caval vein diameter of more than 11.4 and underhydration as a caval vein diameter of less than 8 mm/m2 body surface area [10,11]. When inferior caval vein diameter before dialysis was outside the normal limits, dry weight was adjusted accordingly.

Table 1. Characteristics of the patients

	hypotension prone			hypotension resistant			p
n =		11			11		
age (yr)	61.5	±	15	56.8	±	9.4	n.s.
M/F		8/3			8/3		
time on dialysis (yr)	2.82	±	1.65	1.89	±	1.9	n.s.
Interdialytic weight gain (kg)	2.76	±	0.83	3.36	±	1.1	n.s.
Medication							
beta-adrenergic blockers		4			7		n.s.
ACE-inhibitors		2			3		n.s.
Calcium antagonists		3			5		n.s.
Nitrates		2			3		n.s.

Study design

All studies were performed in the morning before hemodialysis, in a quiet room with an ambient temperature of 24 °C. Smoking and beverages containing alcohol or caffeine were avoided for at least 12 hours before the investigation. The patients were placed in a box up to the iliac crest, and an airtight connection was attached to the patient's waist. Evacuating air from the box created LBNP. After local anesthesia, catheter with a diameter of 0.6 mm was inserted into the right jugular vein for measurement of CVP. Blood pressure and heart rate were measured continuously.

After a 45-minute equilibration period, baseline echocardiography was performed and baseline blood samples were collected. Subsequently, LBNP of -20 mmHg was applied for 15 minutes. At the end of this period, echocardiography and blood sampling were repeated. LBNP was subsequently decreased to -40 mmHg for 15 minutes, again followed by echocardiography and blood sample collection.

Measurements

Blood pressure and heart rate were registered continuously through finger blood pressure measurement by the Finapres device (Ohmeda 2300, Englewood CO, USA). CVP was measured continuously using a pressure transducer (Ohmeda single transducer kit) positioned at heart level, and a monitor (HP 1290A, Hewlett Packard, California, USA). The average of all blood pressure, heart rate and CVP measurements during a one-minute period at the end of equilibration, -20 mmHg and -40 mmHg LBNP, were used for analysis. Left ventricular end-diastolic volume, Stroke volume and cardiac output were assessed in triplicate by echocardiography, using the bi-plane discs method. The volume of the ventricle was calculated from the apical two- and four chamber views using a modification of Simpson's rule[12]. The principle of Simpson's rule is to divide the left ventricle into known slices of thickness. The volume of the ventricle is then equal to the sum of the volume of the slices. Two and four chamber apical views were recorded and stored. The endocardial borders of these views were digitally traced at end diastole and end systole. Each projection was divided in 20 sections along the long axis. Then the volumes were computed. Stroke volume was calculated as the difference between end-diastolic and end-systolic volume. Diastolic left ventricular function was assessed by pulse wave Doppler evaluation of left ventricular filling. The pulse wave Doppler studies were recorded from the apical four chamber view, with the doppler sampler positioned just within the inflow portion of the left ventricle, midway between the annular margins of the mitral valve. Mitral velocity profiles were digitized from the modal velocity of the Doppler tracings. After measuring early (E) and atrial (A) flow over the mitral valve, the E/A ratio was calculated. Total peripheral resistance was calculated from mean arterial pressure and cardiac output. Concentrations of plasma epinephrine (E; normal limit: < 120 pg/ml (< 655 pmol/L) and norepinephrine (NE; normal limits: 100-600 pg/ml (0.59-3.55 nmol/L) were measured by fluorometric detection after high-performance liquid chromatography as described previously [13]. Plasma atrial natriuretic peptide levels (ANP; normal limits: 60-120ng/L) were measured by means of a commercially available radioimmunoassay (Nichols institute, Wijchen, The Netherlands) [14].

Statistics

Hemodynamic data are given as mean ± standard deviation. Stroke volume, cardiac output, and total peripheral resistance are expressed per m^2 body surface area and are mentioned SI, Cardiac index, and total peripheral resistance index respectively . Differences in the baseline data were tested with the unpaired two-tailed Student's t-test. Changes during LBNP were analyzed using Analysis of Variance for repeated measurements, in the case of a significant F-ratio followed by the Student Neuman Keuls test for multiple comparisons.

Plasma concentrations of vasoactive hormones are given as median values and range. Baseline data were tested with Mann-Whitney's non-parametric test. Changes during LBNP were tested with Friedman P-test, when significant, followed by the Dunn test for multiple comparisons.

Of all parameters, changes at –20 and –40 mmHg LBNP are given as percentages of change compared to baseline. However, the changes in CVP are given as absolute values. Correlations were assessed by calculating Pearson's correlation coefficient, in the case of vasoactive hormones after log-transformation. A p-value of less than 0.05 was assumed to indicate statistical significance.

Results

Baseline values

At baseline, CVP tended to be lower in HP patients, but this difference was not significant (Table 2). Baseline SAP was significantly lower in the HP-group than in the HR-group. Heart rate, SI, cardiac index and total peripheral resistance index were all similar in both groups. Diastolic dysfunction (E/A ratio <1.0) was present in 19 out of 22 subjects, with no significant differences between both groups. Median values of NE and E were within normal limits and were not different in the two groups. However, all patients in both groups had elevated ANP-levels. In HR-patients, ANP levels were significantly higher than in HP-patients.

Table 2 Baseline hemodynamic and hormonal data in hypotension-prone (HP) and hypotension-resistant (HR) patients

	HP	HR	p
n =	11	11	
Hemodynamics			
CVP (mmHg)	12 ± 5	16 ± 7	n.s.
SAP (mmHg)	141 ± 26	164 ± 22	<0.05
MAP (mmHg)	95 ± 11	110 ± 15	n.s.
DAP (mmHg)	73 ± 8	85 ± 14	n.s.
HR (bpm)	72 ± 9	70 ± 13	n.s.
SV (ml)	55 ± 11	63 ± 27	n.s.
CO (l/min)	4.0 ± 1.1	4.3 ± 1.6	n.s.
TPR (dyne/sec/cm^{-5})	2055 ± 645	2297 ± 749	n.s.
E/A ratio	0.85 ± 0.30	0.85 ± 0.44	n.s.
E/A ratio > 1	2/11	1/11	
Vasoactive hormones			
NE (pg/ml)	341 (198 - 789)	365 (177 - 675)	n.s.
E (pg/ml)	46 (18 - 339)	58 (21 - 122)	n.s.
ANP (pg/ml)	441 (152 - 1330)	804 (517 - 3560)	<0.05

Note. Hemodynamic data are expressed as mean ± SD, hormonal data expressed as median (range). To Convert to SI units: for norepinephrine, 1pg/mL = 0.00591 nmol/L; for epinephrine, 1 pg/mL= 5.46 pmol/L; for ANP, 1 pg/mL = 1 ng/L. Abbreviation: NS, not significant.

Hemodynamic and hormonal changes during LBNP

In HP-patients, -40 mmHg LBNP induced a decrease in CVP of 6.5 ± 4.0 mmHg. Systolic arterial pressure decreased significantly by 19 ± 21% at -40 mmHg LBNP. Interestingly, heart rate did not change during the investigation. SI decreased by 37 ± 16%, while cardiac index decreased by 34 ± 18% at –40 mmHg LBNP. Total peripheral resistance index increased by 44 ± 47%. Both E and NE levels increased significantly at –40 mmHg LBNP, while ANP did not change.

In HR-patients, CVP decreased by 4.9 ± 4.9 mmHg at –40 mmHg LBNP. Blood pressure and heart rate remained constant, while SI and cardiac index decreased by 27 ± 16% and 24 ± 19% respectively. These changes were accompanied by a 38 ± 25% increase in total

Table 3. Hemodynamic and hormonal changes during LBNP in hypotension-prone (HP) and hypotension-resistant (HR) patients

	HP		HR		
LBNP	-20 mmHg LBNP	-40 mmHg LBNP	-20 mmHg LBNP	-40 mmHg LBNP	
Hemodynamics					
CVP (mmHg)	-4.0 ± 2.4 [c]	-6.5 ± 4.0 [c,e]	-3.8 ± 3.5 [b]	-4.9 ± 4.9 [c]	
SAP (%)	-3 ± 7	-19 ± 21 [b,d]	0 ± 6	-4 ± 14	
MAP (%)	1 ± 9	-10 ± 18	3 ± 7	2 ± 13	n.s.
DAP (%)	3 ± 10	-2 ± 18	5 ± 7	6 ± 14	n.s.
HR (%)	0 ± 7	5 ± 14	-1 ± 6	4 ± 15	n.s.
SV (%)	-20 ± 13 [c]	-37 ± 16 [c,f]	-16 ± 18	-27 ± 16 [b,d]	<0.05
CO (%)	-19 ± 17 [b]	-34 ± 18 [c,e]	-17 ± 17	-24 ± 19 [c,d]	n.s.
TPR (%)	29 ± 29	44 ± 47 [b]	27 ± 21	38 ± 25 [c]	n.s.
Neurohormones					
NE (%)	28 (3-61) [a]	87 (27-182) [c]	21 (0-73)	53 (15-86) [c]	n.s.
E (%)	33 (0-66)	144 (-4-1030) [b]	37 (-17-71)	115 (17-625) [b,d]	n.s.
ANP (%)	28 (3-61)	-4 (-31-29)	1 (-33-132)	-19 (-42-104)	n.s.

Hemodyamic changes are mean ± SD. LBNP, lower body negative pressure; CVP, central venous pressure; SAP, MAP and DAP, systolic, mean and diastolic
arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance.
Hormonal changes are given as median and range NE, norepinephrin; E, epinephrin; ANP, atrial natriuretic peptide; [a] $p<0.05$, [b] $p<0.01$ and [c] $p<0.001$ vs baseline; [d] $p<0.05$, [e] $p<0.01$, [f] $p<0.001$ vs -20 mmHg LBNP

peripheral resistance index. Again E and NE levels increased significantly at –40 mmHg LBNP and ANP-levels remained constant.

The decrease in CVP was comparable in HP and HR-patients. However, this resulted in a decrease in systolic arterial pressure in HP-patients, but not in HR patients. At –40 mmHg LBNP, the decrease in SI was significantly higher in HP than in HR patients (Table 3; $p<0.05$). Changes in cardiac index, total peripheral resistance index, NE-, E- and ANP-levels were not significantly different in both groups. During –40 mmHg of LBNP five patients experienced symptomatic hypotension, four of which were classified as hypotension prone. In order to study the factors responsible for hypotension in these patients we also presented the data in these patients compared to the patients in which hypotension did not occur during

LBNP (Table 4). In the patients in which hypotension occurred during LBNP, the decrease in CVP was not significantly diff
rent from the other patients. There was however a significantly greater reduction in SV and cardiac index. Heart rate remained stable, although it decreased in 4 out of 5 hypotensive subjects. Plasma E levels increased in both groups, but the magnitude of the increase was fourfold higher in the patients that became hypotensive.

Table 4. Hemodynamic and hormonal data in patients who experienced hypotension during -40 mmHg LBNP

Patients	1	2	3	4	5	hypotensive patients (H) (1-5)	all other patients	H versus. all other patients
Group:	HP	HP	HP	HP	HR			P
No. of patients						5	17	
Haemodynamic Changes								
CVP (mmHg)	-12	-10	-4	-4	-2	-6.4 ± 4.3	-5.5 ± 3.2	n.s.
SAP (%)	-47	-27	-57	-33	-41	-40.9 ± 11.7	-2.9 ± 12.1	
MAP (%)	-30	-23	-43	-24	-25	-29.0 ± 8.3	3.4 ± 11.4	
DAP (%)	-13	-15	-32	-20	-21	-20.2 ± 7.3	8.5 ± 7.2	
HR (%)	28	-10	-15	-6	-26	-5.6 ± 20.3	7.5 ± 4.8	n.s.
SI (%)	-50	-25	-48	-49	-40	-42.6 ± 10.8	-23.9 ± 9.9	< 0.05
CI (%)	-36	-32	-56	-52	-56	-46.5 ± 11.4	-28.9 ± 9.4	< 0.05
TPRI (%)	10	14	29	59	68	36.2 ± 26.4	42.4 ± 22.9	n.s.
Hormonal changes								
NE (%)	141	84	91	45	21	84 (21 - 141)	62 (15 - 182)	n.s.
E (%)	415	147	1030	371	625	415 (147 - 1030)	81 (17 - 625)	< 0.05
ANP (%)	3	3	24	-15	-11	3 (-15 - 24)	-15 (-42 - 104)	n.s.
Medication								
beta-blockers	no	no	yes	No	no	1/5	10/17	< 0.05

Hemodyamic changes are mean ± SD. LBNP, lower body negative pressure; CVP, central venous pressure; SAP, MAP and DAP, systolic, mean and diastolic arterial pressure; HR, heart rate; SV, stroke volume index; CO, cardiac index; TPR, total peripheral resistance index. Hormonal changes are given as median and range NE, norepinephrin; E, epinephrin; ANP, atrial natriuretic peptide

Discussion

In the present study we assessed whether the hemodynamic and neurohumoral responses to LBNP in HP and HR hemodialysis patients are different. Our findings showed that a comparable LBNP-induced decrease in CVP is associated with a greater fall in SI and systolic blood pressure in HP than in HR patients, whereas the neurohumoral responses between the two groups of patients did not differ. These findings could imply a greater dependency of SI on cardiac filling pressure in HP resulting from reduced diastolic function, inadequate sympathetic tone or impaired cardiac contractility.

Baseline values of CVP and ANP were elevated in both groups of patients. Compared to HR patients, baseline values of ANP were lower and baseline values of CVP tended to be lower in HP patients. These findings strongly suggest that overhydration was less pronounced in the HP patients. This contention is supported by the finding that interdialytic weight gain (Table 1) was lower in HP than in HR patients.

An explanation why LBNP was associated with a greater decrease in SI in HP than in HR patients is not easy to provide. Echocardiographic examination did not reveal the presence of valvular, pericardial or pulmonary abnormalities that could cause a decrease in cardiac inflow in either HP or HR patients. Left ventricular hypertrophy and uremic myocardial fibrosis are commonly observed in hemodialysis patients[15]. These abnormalities impair ventricular relaxation and diastolic function, resulting in a decrease in SI when cardiac-filling pressure is lowered. Diastolic dysfunction can be diagnosed by considering the ratio of the mitral flow velocities of early ventricular filling to atrial assisted ventricular filling (E/A ratio), as measured by pulse wave Doppler Echocardiography [16]. An E/A ration below 1.0 indicates the presence of diastolic dysfunction. Of the patients participating in the present study almost all (19/22) had diastolic dysfunction. No difference in E/A ratios was observed between the HP and HR. A caveat for using the E/A ratio as a measure for diastolic function is the dependency of this parameter on volume status [17]. Unfortunately E/A ratio's in the present study were only determined before application of LBNP and before hemodialysis. It is therefore possible that a difference in the diastolic properties of the left ventricle between the groups of subjects has been missed.

Differences in blood pressure behavior during LBNP could be due changes in sympathetic tone and/or systolic function. Of the 22 patients studied five (four of the HP and one of the

HR group) developed hypotension during –40 mmHg of LBNP. In all five subjects the hypotension was caused by a decrease in cardiac index. Although the decrease in cardiac index was predominantly due to a fall in SI, heart rate in all but one of the subjects decreased as well.

A reduction in heart rate during episodes of hypotension has been described by Converse *et al*, who ascribed this response to a paradoxical withdrawal of sympathetic activity [18]. This phenomenon, also known as the Bezold-Jarisch reflex, is thought to result from increased activity of left ventricular mechanoreceptors as a consequence of a decrease in stroke volume and increased cardiac contractility. This form of bradycardia-associated hypotension occurs as a result from marked hypovolemia [19].

However, the results concerning the heart rate response have to be interpreted with care, as fluctuations in heart rate normally occur. Mean heart rate remained stable in the HP and a severe bradycardia occurred only in one patient, in the HR group. Therefore heart rate was of minor importance in the pathogenesis of hypotension during LBNP, although no increase in the baroreceptor mediated heart rate response was found. Beta blockade was not likely to be responsible for the impairment in the baroreceptor mediated heart rate response, as these were mainly used in non hypotensive patients. It is known that bradycardia can exist independently of defects in the autonomic nervous system [20]

Although plasma norepinephrine almost doubled, we found no differences in norepinephrine levels between hypotensive and non-hypotensive subjects. In view of the hypotensive response, the increase in plasma norepinephrine concentration in these subjects can be considered inappropriate. This would suggest the presence of sympathetic inhibition.

In patients experiencing hypotension plasma epinephrine concentration was markedly increased. As hypotension is a powerful stimulus of epinephrine secretion by the adrenal gland and epinephrine concentrations were measured several minutes after the hypotensive episode, this could be considered a secondary phenomenon.

SI was decreased in HP despite comparable filling pressures and sympathetic tone. This suggests a reduced sensitivity of β adrenoreceptors.

The seemingly comparable level of sympathetic drive could also suggest an incapability to maintain sympatic tone. The pivotal role of the heart in patients prone to develop hypotension during dialysis can be demonstrated by infusion of dobutamine, a β-adrenergic receptor

agonist. In this group patients, prone to develop hypotension during dialysis, we observed impaired myocardial contractile reserve in response to sympathetic stress [21]. These findings support the hypothesis of impaired myocardial contractile reserve in the pathogenesis of dialysis-induced hypotension. An impaired myocardial contractile reserve could be partly due to the fact that patients were by mean five years older and had spent by mean one year more on dialysis.

We conclude that patients that frequently experience episodes of hypotension during dialysis are also prone to develop hypotension during LBNP. The hypotension during LBNP results from reduced myocardial contractile reserve and/or inadequate sympathetic tone.

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Chapter 9 : Summary and Conclusions

Summary and Conclusions

Chapter 1 is a brief introduction is to the physical principles and the technical procedure of hemodialysis. Factors that can contribute to the occurrence of dialysis related hypotension are discussed. We concluded from the available literature that for most factors it is unknown whether the most detrimental effect on effective blood volume during hemodialysis is due to a decreased plasma refilling or to an inadequate cardiovascular response. Moreover, we hypothesized that both mechanisms can affect each other. We concluded that more knowledge concerning this relationship is essential before blood volume monitoring and modeling, in order to prevent of dialysis related hypotension, can be applied clinically.

In chapter 2, we constructed a mathemathical model of the intercompartmental fluid shifts during combined hemodialysis, diffusive hemodialysis, and isolated ultrafiltration (IU). We analyzed the relative importance of the factors that govern plasma refilling. We concluded that the ultrafiltration rate, the size of sodium gradient between the dialysate and blood side of the dialyzer membrane, and the change in regional blood flow are the most important factors influencing the magnitude of plasma refilling.

In chapter 3, we analyzed the reproducibility of the decrease in relative blood volume during hemodialysis, as it is essential for the application of blood volume modelling that a critical level of reduction in relative blood volume can be determined. However, we observed a considerable intra- and inter-individual variability and no correlation was observed between changes in relative blood volume and either blood pressure or the incidence of hypotension. We concluded that the critical level of reduction in relative blood volume, at which hypotension occurs, depend more on cardiovascular defence mechanisms, such as sympathetic drive.

In chapter 4, we evaluated the effects of diffusive dialysis on the changes in relative blood volume during diffusive dialysis without ultrafilitration. During the first and second hour, relative blood volume was paradoxically increased. Thus, the detrimental effect of diffusive

dialysis may be caused by a decrease in vascular resistance, rather than by reduced plasma volume preservation.

In chapter 5, we have compared the effect of isotonic saline (0.9 %), glucose (5%), hypertonic (3%) saline, mannitol (20%) and glucose (20%) on RBV, as these infusions are most frequently used in order to prevent hemodynamic instability during dialysis. We observed that hypertonic glucose during dialysis results in a greater increase in relative blood volume than equal volumes of other solutions. As mannitol has the same osmolarity, molecule mass and charge, the greater increase in RBV following hypertonic glucose appears to be a specific effect, possibly related to a decline in vascular tone.

In chapter 6, we studied the pathophysiology of hemodialysis related hypotension. In order to distinguish between dialysis related and patient related factors hypotensive dialysis sessions were compared with Lower Body Negative Pressure experiments. We observed that dialysis related hypotension did not result from an inability to maintain blood volume or from decreased cardiac filling. Hypotension appeared to result from the inability to increase arteriolar tone adequately and from a reduction in left ventricular function. Both vascular tone and left ventricular function appeared to be impaired by the dialysis procedure.

In chapter 7, we observed that an increase in total peripheral resistance resulted in a decrease in relative blood volume. This indicates that the improved hemodynamic stability during hemodialysis through vasoconstriction can be accompanied by a decrease in relative blood volume. Part of the variability in blood volume as described in chapter 4 may be due to changes in arterial tone. A diminished vasoconstriction during diffusive dialysis could also explain the observed increase in relative blood volume, as observed in chapter 5. Moreover, it can be concluded that glucose, which increases relative blood volume more than equal amounts of mannitol or sodium, is paradoxically of less benefit in the prevention of dialysis hypotension. Therefore, during sodium profiling, the cardiovascular effect of sodium during on plasma refilling should be taken into account.

In *chapter 8* we observed that patients that frequently experience episodes of hypotension during dialysis are also prone to develop hypotension during Lower Body Negative Pressure, which results from reduced myocardial contractile reserve and/or inadequate sympathetic tone.

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Chapter 10 : Samenvatting en Conclusies

Samenvatting en Conclusies

Hoofdstuk 1 is een beknopte inleiding tot de physische aspecten en de technische uitvoering van hemodialyse. Factoren die kunnen bijdragen aan bloeddrukverlaging (hypotensie) in samenhang tot hemodialyse worden besproken. Uit de beschikbare literatuur konden wij vaststellen dat het voor de meeste factoren onbekend is of deze de bloeddruk tijdens hemodialyse verlagen via een verminderde vulling vanuit de extravasculaire ruimtes (plasma refilling) of door een ontoereikende reactie van het hartvaatstelsel op de door ultrafiltratie ontstane hypovolemie. Wij veronderstellen echter dat beide mechanismen elkaar kunnen beïnvloeden. Wij kwamen tot de conclusie dat meer kennis betreffende deze relatie absoluut noodzakelijk is voordat het kritisch volgen en bewaken van het bloedvolume, ter voorkoming van aan dialyse gerelateerde bloeddrukverlaging, klinisch kan worden toegepast.

In *hoofdstuk* 2 hebben we een rekenkundig model ontworpen van de vloeistofstromen binnen de verschillende compartimenten tijdens gecombineerde hemodialyse, hemodialyse zonder ultrafiltratie en geïsoleerde ultrafiltratie. Hiermee analyseerden we de relatieve waarde van de factoren op de plasma refilling. We kwamen tot de conclusie dat de snelheid van ultrafiltratie, de grootte van het natrium gradiënt over de dialyse membraan en de verandering van de bloedstroom ter plaatse, de belangrijkste factoren zijn die in hoge mate de plasma refilling beïnvloeden.

In *hoofdstuk* 3 is de reproduceerbaarheid bepaald met betrekking tot de verlaging van het relatieve bloedvolume gedurende de hemodialyse sessie. Dit is van wezenlijk belang voor de toepassing van bloedvolume regulering, omdat dan bij een eventueel kritisch niveau van de verlaging van het relatief bloedvolume de hypotensieve episode kan worden voorspeld. We hebben echter aanzienlijke intra-en interindividuele afwijkingen waargenomen. Er is ook geen correlatie gevonden tussen veranderingen in het relatieve bloedvolume en bloeddruk of het ontstaan van hypotensie. We zijn tot de conclusie gekomen dat het kritisch niveau van verlaging in bloedvolume, waarbij hypotensie ontstaat met name afhangt van de reactie van het hartvaatstelsel op de door ultrafiltratie ontstane hypovolemie.

In *hoofdstuk* 4 hebben we de effecten geëvalueerd van hemodialyse zonder ultrafiltratie op de veranderingen in relatief bloedvolume. Tijdens het eerste en tweede uur was het relatieve bloedvolume paradoxaal verhoogd. Dus, het schadelijke effect van diffunderende dialyse zou eerder veroorzaakt worden door een verlaging van de vasculaire bescherming dan door het in stand houden van een gereduceerd plasma volume.

In *hoofdstuk* 5 hebben we het effect vergeleken tussen fysiologische zoutoplossing (0,9%), glucose (5%), hypertone zoutoplossing (3%), mannitol (20%) en glucose (20%) op het relatieve bloedvolume (RBV) omdat deze infusievloeistoffen het meest worden gebruikt om hemodynamische instabiliteit tijdens de dialyse te voorkomen. We hebben waargenomen dat hypertonisch glucose tijdens de dialyse in een grotere toename van het relatieve bloedvolume resulteerde dan een gelijk volume van de andere oplossingen. Alhoewel mannitol dezelfde osmolariteit, molecuul massa en elektrische lading heeft, blijkt de toename van het RBV met hypertone glucose groter te zijn, welke mogelijkerwijs gerelateerd is aan de verminderde capaciteit van glucose om de vaatweerstand te verhogen.

In *hoofdstuk* 6 wordt de pathosfysiologie van hemodialyse gerelateerde hypotensie bestudeerd. Om een onderscheid te maken tussen hemodialyse gerelateerde en patiënt gerelateerde factoren, werden hypotensieve dialyse sessies vergeleken met experimentele situaties waarbij kunstmatig een hypovolemie werd gecreëerd zonder dat dialyse plaatsvond (Lower Body Negative Pressure). Hypotensie bleek met name te worden veroorzaakt door het onvermogen om de arteriële vaatweerstand toereikend te verhogen en door een afname in de linker ventrikel functie.

In *hoofdstuk* 7 hebben we waargenomen dat een verhoging van de totale perifere vaatweerstand resulteerde in een verlaging van het relatieve bloedvolume. Dit geeft aan dat de verbeterde hemodynamische stabiliteit tijdens de hemodialyse, door vasoconstrictie, gepaard kan gaan met een verlaging van het relatieve bloedvolume. Deels kan dus de variatie in bloedvolume, zoals beschreven in *hoofdstuk* 3, veroorzaakt worden door veranderingen in de arteriële vaattonus. Een verminderde vasoconstrictie tijdens dialyse zonder ultrafiltratie zou ook de waargenomen verhoging in relatieve bloedvolume kunnen verklaren, zoals aangegeven

in *hoofdstuk* 5. Bovendien kan worden vastgesteld dat glucose, dat het relatieve bloedvolume meer verhoogd dan gelijke delen mannitol of natrium, paradoxaal minder voordeel laat zien ter voorkoming van dialyse hypotensie. Om deze reden zou, tijdens Natrium-profiling rekening moeten worden gehouden met het cardiovasculair effect van natrium tijdens de plasma refilling.

In *hoofdstuk* 8 hebben we vastgesteld dat patiënten die regelmatig perioden doormaken van hypotensie tijdens de dialyse, tevens neigen naar het ontwikkelen van hypotensie tijdens Lower Body Negative Pressure.

Curriculum Vitae

Robert Willem Nette werd op 7 september 1967 geboren te Vlaardingen.In 1986 behaalde hij het diploma Atheneum-B aan de christelijke scholengemeenschap "Groen van Prinsterer" te Vlaardingen. In hetzelfde jaar begon hij met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. Na een afstudeeronderzoek over onstabiele angina pectoris op de afdelingen Cardiologie en Klinische Besliskunde haalde hij in 1991 zijn doctoraal examen geneeskunde, gevolgd door zijn arts examen in 1993. In november van hetzelfde jaar werd hij opgeroepen voor zijn militaire dienstplicht die hij vervulde als eerste luitenant-arts in de regio Harderwijk-Ermelo als kazerne arts.

Na de militaire diensttijd werd in 1995 begonnen als AGNIO neurologie in het Erasmus MC te Rotterdam. Van 1996 tot 1998 in de funktie van AGNIO Inwendige Geneeskunde in het Leyenburg Ziekenhuis in Den Haag. Vanaf 1998 begon hij als arts-onderzoeker bij de afdeling Inwendige Geneeskunde van het Erasmus MC te Rotterdam o.l.v.Dr.R.Zietse. Sinds 2001 is hij in opleiding tot Internist bij de afdeling Inwendige Geneeskunde van het Erasmus MC(2001-2003) o.l.v. Prof.dr.H.A.P. Pols en bij de Reinier de Graaf Groep,locatie Delft o.l.v. Dr.E.Maartense (vanaf 2003 tot heden).

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