Fluid volume assessment in hemodialysis patients

by

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Abstract

Achievement of normal volume status is crucial in hemodialysis (HD), since both volume overload and volume depletion have been associated with adverse outcome and events. The main objectives of this thesis were to find out the prevalence of volume overload and to identify the best clinical parameter or set of parameters that can predict volume overload in HD patients along with the development of volume management protocol. Another objective was investigating the literature about the use of sodium profiling in alleviating intradialytic side effects. Volume status of 194 HD patients in 2 hemodialysis units was assessed by multi-frequency bio-impedance spectroscopy. Of all patients 48% (n=94) were volume expanded. ECFV depletion was present in 9% of patients (n=17). Interdialytic weight gain (IDWG) was not different between hypovolemic, normovolemic and hypervolemic patients. Only 50% of the volume overloaded patients were hypertensive (>140/90mmHg). Paradoxical hypertension was common (31% of all patients) in our HD population, however, its incidence was not different between patients. Intradialytic hypotension was relatively common and was more frequent amongst hypovolemic patients. Blood pressure was neither sensitive nor specific for volume assessment. Edema was highly specific for detection of volume overload but lacks sensitivity. In sum, the study indicates that volume overload is highly prevalent in HD population and could not be identified using clinical parameters alone. Only 4 clinical parameters (edema, SBP, lower BMI, smoking) were found to be significant predictors for volume overload. None of the 4 parameters was sensitive and specific. We found that bio-impedance was a helpful bedside method to better identify hidden volume overload.

Preface

The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, project name 'Clinical and bio-impedance based fluid volume assessment in hemodialysis', No. Pro00031776, June 2012.

Chapter 2 of this thesis will be submitted for publication. I was responsible for patient recruitment, data collection and analysis as well as writing the manuscript. Ryan Reid contributed to designing the study, applying for ethics approval and assisted in data collection. Dr. Neesh Pannu and Dr. kailash Jindal contributed to revising the manuscript. Dr. Branko Braam was responsible for designing the study, ethics approval, data analysis and writing the manuscript.

I dedicate this thesis to my family whose continuous love and support gave me strength to make this work possible

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List of abbreviations

DW	Dry weight
ANP	Atrial natruiritic peptide
BNP	Brain natruiritic peptide
ECFV	Extracellular fluid volume
BP	Blood pressure
IVC	Inferior vena cava
IVCD	Inferior vena cava diameter
CI	Collapse index
CTNT	Cardiac troponins
TBW	Total body water
BCM	Body composition monitor
CHF	Congestive heart failure
IDWG	Inter-dialytic weight gain
ESRD	End stage renal disease
IH	Intradialytic hypotension
CO	Cardiac output
TPR	Total peripheral resistance

BV	Blood volume
IHD	Ischemic heart disease
SV	Stroke volume
MAP	Mean arterial pressure
UF	Ultrafiltration
BBs	Beta blockers
CCBs	Calcium channel blockers
LVH	Left ventricular hypertrophy
ICFV	Intracellular fluid volume
ADH	Anti-diuretic hormone
MCV	Mean corpuscular volume
PNa	Plasma sodium
DNa	Dialysate sodium
VS	Volume status
VS/ECFV	Volume status/Extracellular fluid volume
AV	Arterio-venous

Chapter 1

1. Introduction

1.1. Importance of volume assessment in HD patients

In healthy subjects, hypervolemia activates renal mechanisms which aim to diminish extracellular fluid volume (ECFV) expansion. However, patients with impaired renal function will not show these mechanisms and ECFV expansion will have drastic outcomes. Therefore it is important to understand how the body (specifically the vasculature and the kidneys) responds to volume expansion. As the ECFV (and therefore the blood volume) expands, rising cardiac output drives tissue perfusion beyond that required for the metabolic needs of the tissue. In response, autoregulatory mechanisms increase total peripheral resistance first by systemic vasoconstriction and, over time, by structural alterations that narrow the lumen of blood vessels (1)**.**. This so-called total body autoregulation will raise arterial pressure which will be corrected by normal kidneys through 'pressure natriuresis' (1).

Small increases in the ECFV will trigger the autoregulatory response and this can lead to hypertension (1). This is of great importance to end stage renal disease patients who do not have kidneys capable of reacting properly to increased ECFV (2); these patients will likely be hypertensive unless body fluid volumes are carefully and accurately maintained as close to normal as possible through ultrafilatration during dialysis (2). Accordingly, it is crucial that volume assessment in the clinical setting accurately determines the hydration status of dialysis patients

1.2. Methods of volume assessment

1.2.1. Clinical methods (the dry weight concept)

The concept of dry weight (DW) is crucial for dialysis therapy. DW refers to the body weight at physiological extracellular fluid volume (3). The term DW was introduced in 1960s as "not merely the absence of edema, but the edge of hypovolemia which should be achieved by the end of the session, to allow the patient to gain some weight up to the next dialysis session without becoming hypertensive" (4). Daugirdas defined DW as "the post dialysis weight at which all or most excess body fluid had been removed, below which the patient more often than not will develop symptoms of hypotension" (5). Both are clearly not accurate definitions but are commonly used. The use of these clinical definitions of DW is mainly due to the lack of accurate objective methods for DW assessment (3).

Numerous methods have been investigated to assess the DW, such as clinical, bedside assessment of volume status, inferior vena cava collapse index using ultrasound, biomarkers for volume overload (atrial natriuretic peptide, ANP; brain natriuretic peptide, BNP), and cardio-thoracic ratio by chest X-ray. Dilution methods used to be the gold standard method for volume assessment; however, it is not a clinically feasible approach (4). Multi-frequency bio-impedance measurement is easy to use and can yield relatively reliable estimates of intra- and extracellular fluid volume. Dilution methods used to be the gold standard method for volume assessment; however, it is not a clinically feasible approach (4). A recent report stated that there is no gold standard with absolute accuracy especially in dialysis patients. They found a proportional error with both bio-impedance and dilution methods as shown by regression analysis (5).

Assessing DW by body weight measurement does not take into account changes in nutritional status (lean and fat body mass). The two most frequently used methods are measurement of blood pressure and body weight. In absence of overt clinical signs of hypervolemia or hypovolemia, normal blood pressure is often considered as a sign for normovolemia, however, it is not usually the case (6). DW then approached by trial and error. This is cumbersome both for the patient and dialysis staff, because (1) BP is affected by other factors other than ECFV expansion, (2) the effect of volume control on BP may be delayed by weeks or even months (lag phenomenon) (3). Available evidence suggests that clinical examination lacks sensitivity and specificity in diagnosis of either volume overload or hypovolemia (7-9). The ability of clinical examination to detect modest degree of volume depletion or volume overload is poor (10).

1.2.2. Measurement of inferior vena cava diameter

Imaging studies of diameter of inferior vena cava (IVC) can be used to assess intravascular volume in HD patients. Measuring IVC diameter has been shown to correlate well with central venous pressure (11) . As ultrasonography is non-invasive and fast, it has been investigated as a method to assess volume status. Ultrasound guidance for the determination of DW has been tested by measuring IVC diameter and its decrease on deep inspiration, better known as the collapse index (CI). Calculation of CI follows the following formula (10):

CI= [(end expiratory IVCD – end inspiratory IVCD) / end expiratory IVCD] x 100

Nonlinear regression analysis found that the CI strongly correlated with mean right atrial pressure, as assessed by cardiac catheterization. Hypervolemia is defined as a decrease in IVC diameter during inspiration less than 25% of the baseline diameter during expiration.

Hypovolemia is defined as a decrease in IVC diameter during inspiration more than 60% of the baseline diameter during expiration (10).

If IVCD measuring is performed before post-dialysis refilling has ceased, it will underestimate fluid volume and also has disadvantages in terms of costs and interoperator error. Its applicability in patients with congestive heart failure and valvular heart disease is also limited (12).

1.2.3. Cardiac biomarkers

Much attention has been given to biochemical markers of changes in extracellular fluid volume. Brain natruiritic peptide (BNP) and N-Terminal–pro BNP (NT-proBNP) are produced by stretched atrial and ventricular cardiomyocytes and seem to be valuable cardiac markers in HD patients with volume overload . However, these markers do not accurately reflect ECFV as cardiac stretch is not well correlated with ECFV .

Cardiac troponin (cTNT) is proposed to be the most reliable biomarker for the diagnosis of acute myocardial infarction . CTNT is exclusively expressed in cardiomyocytes and is released into the circulation after irreversible myocardial damage. In HD patients, cTNT is elevated in a high percentage of patients despite absence of acute myocardial ischemia . Recent studies have documented that cTNT is of cardiac origin and that the presence and magnitude of CTNT is an independent variable with respect to morbidity and mortality in HD patients .

Similar to IVCD measurement, these biomarkers are not useful in patients with congestive heart failure or tricuspid or mitral valve disease. Another important limitation of these markers is their

inability to detect volume depletion, since there is no difference in values between normovolemia and hypovolemia .

1.2.4. Dilution methods

The basic rule for tracer dilution methods is that the tracer mass within the compartment of interest is constant and that ideal mixing in that compartment occurs (13). Deuterium and tritium can measure total body water (TBW), and bromide dilution measures ECFV. These methods are considered the gold standard for evaluating volume status (3). It is important to note that although tracer methods may provide accurate measures of fluid compartments, they cannot assess degree of fluid status. Their usefulness in clinical practice is limited due to their invasive nature, complexity of procedure and high cost (3).

1.2.5. Continuous blood volume monitoring

Continuous measurements of blood volume to assess volume status has been performed in dialysis patients by measuring changes in hematocrit or total protein content in the whole blood via ultrasonically measured blood velocity (14). The rationale is that the red cell mass or protein content should remain constant while ultrafiltration removes fluid from the intravascular space, making the change in blood volume inversely proportional to the change in hematocrit or plasma protein (14). The availability of continuous hematocrit monitors has facilitated the use of this technology in HD patients (14). The relative changes in blood volume determined by this technique have correlated well with those determined by albumin concentration (15).

A previous observational study of 37 HD patients found that patients with intradialytic hypotension had larger changes in blood volume during HD sessions complicated by

hypotension than in uncomplicated sessions (16). In a prospective randomized trial, using blood volume monitoring resulted in a decrease in the incidence of intradialytic hypotension. Intradialytic hypotensive events were reduced by 30% compared to 33.5% during the control period (17). In another study of hypotensive prone patients, only 8 out of 13 patients, a hematocrit threshold could be found. Blood volume monitoring was not useful in the remaining 5 patients (15).

The use of blood volume monitoring has been shown to be a useful tool to prevent hypotensive episodes and identify patients with volume overload (10). While the technique is easy and feasible, several limitations apply: there is no standardization of blood volume (no absolute values exist), it also requires active changes during dialysis to achieve best results, and lastly the expense of this equipment could limit its use in HD.

1.2.6. Multi-frequency bio-impedance spectroscopy

Bio-impedance spectroscopy is a non-invasive, objective and relatively inexpensive method that can be used to detect body fluid compartments in healthy individuals as well as HD patients (18). An example of a modern bio-impedance device is the body composition monitor (BCM), marketed by Fresenius. This device works by alternating current at 50 different frequencies (5-1000 kHz). The way in which the current is retarded or impeded by the body structures allows for determination of the body fluid volume. This measurement is harmless, quick, and reliable and has been applied to many patients worldwide. A patient height, gender, and age are entered, electrodes are applied on one wrist and foot of the same side then, the measurement can be done. It gives information about the patient's nutritional and fluid status by measuring total body

water, ECFV, intracellular fluid volume, lean tissue index, fat tissue index and body cell mass. It is very easy and rapid method for assessing the fluid status of HD patients.

The basic theory behind bio-impedance spectroscopy is that low frequency alternating currents cannot cross the cell membrane and travels only through the extracellular fluid volume allowing for measurement of this compartment, whereas high frequency alternating current can travel through both intracellular and extracellular fluid volumes (19). Recent studies used the BCM to estimate volume overload and DW in HD patients. They proved that using the BCM to assess and adjust DW was very effective to improve IDWG, BP control, and cardiovascular outcome (20, 21). Bio-impedance spectroscopy was also extensively validated against the gold standard dilution methods, and there was a strong agreement between the two methods for volume assessment (22). Comparison between different methods for volume assessment is shown in table 1.3.

1.2.7. Lung ultrasound

Lung ultrasound has been recently introduced as a method for fluid volume assessment in dialysis patients. Lung ultrasound can evaluate extravascular lung water by identifying B-lines, vertical artifacts arising from the pleural line and extending to the edge of the screen that move synchronously with respiratory acts (23). Such artifacts arise from internal reverberation due to increase in fluid in lung lobes and segments. There is a good evidence of correlation between such ultrasound findings and extravascular lung water evaluated by invasive methods (24)

There was a significant reduction in the number of B-lines when lung ultrasound was done before and after dialysis, confirming that these artifacts seen before dialysis are due to fluid overload (23). The finding that post-dialysis B-lines number correlated with excess residual

weight as assessed by bio-impedance spectroscopy, suggests the use of lung ultrasound for determination of volume status. However, lung ultrasound only gives information on volume overload (the minimal number of B lines is zero), so it cannot differentiate between normovolemia and hypovolemia (23). Another limitation of this technique is that it B-lines will be higher and will not accurately reflect volume status in patients with heart failure especially patients with NYHA class III- IV (23)

Table 1.3: Comparison between different volume assessment methods in HD patients:

Method	Advantages	Disadvantages
Clinical assessment	• Easy to perform • Inexpensive	• Lacks sensitivity and specificity. • Indirect method for volume assessment.
Ultrasound of IVC	• Non-invasive • Strong correlation with right sided heart failure	• Costly • Inter-operator error • Limited applicability in patients with CHF and valvular heart disease
Dilution methods	• Accurate • Direct method for volume assessment	• Time consuming • Invasive • Cannot be used in daily clinical practice
Continuous blood volume monitoring	• Easy to use, non-invasive. • Helps to prevent intradialytic hypotension	• There is no standardization of blood volume • Indirect method for volume assessment. • It only measures changes in BV during dialysis not absolute BV
Multi-frequency bio-impedance spectroscopy	• Fast, non-invasive, bedside method. • Accurate. • Can identify both hyper and hypovolemia	Relatively expensive
Lung ultrasound	• Non-invasive	• Cannot differentiate between normovolemia and hypovolemia Limited applicability in patients with CHF

1.3. Management of volume overload in HD patients

Dietary measures

The first mention of the ability to control hypertension in HD patients without the use of drugs was in 1961 (25). The first four patients treated by long term dialysis in Seattle were hypertensive, and their hypertension was controlled by low sodium diet and ultrafiltration (25). Similar observations have been recorded from Tassin, France where low sodium diet was combined with extended hours of dialysis and ultrafiltration (26). More recently salt restriction was neglected (27). Previous interventional studies have examined the effects of reducing sodium in diet (28). Almost all of them showed that a low salt diet is essential for BP control in HD patients.

A recent study evaluated the effect of dietary sodium restriction on fluid volume and blood pressure control (29). They concluded that dietary sodium restriction did not significantly affect inter-dialytic weight gain (IDWG) and blood pressure (29). However, there were many limitations for this study such as the small number of patients and the absence of an accurate method to evaluate the amount of sodium consumed. Moreover, bio-impedance measurements were performed after dialysis sessions, and were not used to adjust the DW (29).

Another factor which may have contributed to the worldwide neglect of salt restriction is the unjustified emphasis on water restriction instead of salt restriction (30). Altogether, in order to achieve DW under the present conditions, with short HD duration, it is essential to reduce IDWG through low salt diet (28) .

1.4. Linking between volume and blood pressure control

Numerous studies indicate that maintenance of dry weight in dialysis patients leads to better blood pressure control. In a small study of ESRD patients, ultrafiltration alone significantly lowered blood pressure in one hypertensive subgroup (31). Other studies also suggest that improved volume control has a beneficial impact on blood pressure. A previous study focusing on ultrafiltration and salt restriction reported a reduction of systolic blood pressure from 173±17 to 118±12 mmHg over a 36-month period (32). Also of interest is the observation that 6 months of nocturnal hemodialysis (5-6 sessions weekly) reduced both left ventricular mass and systolic blood pressure (33). This is consistent with better control over body fluid volumes, as volume expansion is a causal factor in both left ventricular hypertrophy and hypertension (2, 34).

Another study of HD patients from Tassin, France found that three 8 hour dialysis sessions per week results in normotension in 98% of the patients (35). The benefit of achieving normovolemia and normotension was clearly demonstrated by the long-term survival of the Tassin patients relative to other HD patient studies likely due to prevention of cardiovascular disease (35).

Altogether, this suggests that improved blood pressure control can be achieved by maintaining dry weight through improved volume control. Further, normotension is associated with improved survival in dialysis patients. This also indicates the importance of identifying accurate methods for volume assessment.

1.5. Intradialytic hypotension

Intradialytic hypotension (IH) is a common adverse reaction that occurs in about 15-25% of HD patients (36-38). IH is a major clinical problem not only causing discomfort but also it increases the patient mortality. According to recent data, a low post-dialysis blood pressure is associated with significant increase risk of mortality (39, 40).

IH is defined as gradual or acute fall in blood pressure with accompanying clinical symptoms that occurs during the dialysis sessions and is caused by exhaustion or failure of compensatory mechanisms to maintain adequate perfusion of tissues. Blood pressure is the resultant product of cardiac output (CO) and total peripheral resistance (TPR) (41). Therefore, IH is the result of lowered CO and/ or inappropriately low TPR (41). Compensatory mechanisms to prevent IH will work by maintaining CO and/or TPR. The compensatory mechanisms can become activated to a maximum, so that further compensation is not possible. Alternatively, the compensation may fail, due to the pathophysiology of the ESRD patient, or due to medications. Pathophysiology of intradialytic hypotension will be discussed in detail in the next few chapters.

1.6. Sodium profiling

Sodium profiling has been introduced as a method to reduce IH episodes occurring during dialysis sessions (42). Sodium profiling is mainly performed by using a higher dialysate sodium concentration at the beginning of the dialysis session and then decreasing sodium concentration in the dialysate either gradually or abruptly towards the end of dialysis session (43). The highest sodium concentration is used at the beginning of the dialysis session when blood urea

concentration and urea removal is high (44). One tries to avoid the inevitable drop in plasma osmolality due to urea removal. The lower dialysate sodium concentration for the rest of dialysis session then functions to avoid sodium accumulation (44).

In a previous study at the university of Alberta hospital, they divided participating patients into 3 groups; for the 1st group, they used a steady dialysate sodium concentration of 140mEq/L, the 2nd group with linear dialysate sodium ramping from 155mEq/L to 140mEq/L, the 3rd group with stepwise ramping (155mEq/L for 3 hours then 140mEq/L for 1hour) (42). There were fewer IH episodes in the 2 ramping protocols comparing to standard protocol. Thirst and IDWG were increased with the 2 ramping protocols compared to standard dialysis. There was no difference between the 2 ramping protocols (42). However, pre-dialysis blood pressure was the highest with the stepwise ramping protocol (42).

Few side effects have appeared with the use of sodium profiling like increased thirst sensation which will in turn increase fluid intake and IDWG in these patients (45). This would paradoxically lead to some volume expansion. If one optimizes the sodium profiling by using a dialysate sodium concentration not much exceeding the standard dialysate sodium concentration, this would prevent IH episodes and while not leading to increased thirst sensation and IDWG in HD patients.

1.7. Hypotheses

Volume expansion in HD patients leads to hypertension and cardiovascular complications. On the other hand, episodes of intradialytic hypotension (IH) occur in up to 25% of dialysis sessions. Hypotension is a major clinical problem not only because it's frequency but also because it substantially affects the well-being of the dialysis patients. Unfortunately, these episodes of

symptomatic hypotension and muscle cramps during dialysis sessions frequently lead to the misconception that patients are normo or even hypovolemic. Obviously this is not necessarily the case, but leads often to increases in target weight and using techniques to alleviate these symptoms like sodium profiling. Taken together, if volume overload is the major cause for hypertension, hypotensive episodes and cardiovascular complications, it should be adequately controlled. Therefore we were looking for more objective methods for volume assessment. Also important is investigating the use of sodium profiling for prevention of intradialytic hypotension. Our hypotheses are:

1. Clinical parameters are not sufficient to evaluate volume status in hemodialysis patients:

To test this hypothesis, we compared clinical parameters with bio-impedance spectroscopy for volume assessment in a cohort of hemodialysis patients. We were expecting to have a subgroup of patients who are considered volume overloaded by clinical examination and by the BCM, a subgroup of patients who are identified as volume overloaded by the BCM but not by clinical assessment, and finally a subgroup of patients in which the BCM and clinical assessment did not indicate fluid overload. We wanted to compare bio-impedance spectroscopy as a method for volume assessment with clinical parameters.

2. Side effects of sodium profiling outweighs its benefits in HD patients

To test this hypothesis, we investigated the literature for most of the studies that used sodium profiling in HD patients. We wanted to investigate the best sodium profiling protocol, and whether the use of sodium profiling could be recommended for all HD patients or in select cases. Through this literature review we identified different sodium profiling protocols with advantages

and side effects of each. Also we investigated the patho-physiology of sodium profiling and how it ameliorates intradialytic complications.

Chapter 2

2. Hidden fluid overload is prevalent in hemodialysis patients: a bio-impedance study

2.1. Introduction

Accurate assessment of volume status remains one of the greatest challenges in the treatment of hemodialysis (HD) patients (10, 46). Chronic volume overload contributes to hypertension, left ventricular hypertrophy and heart failure in HD patients (47, 48). Therefore, adequate extracellular fluid volume (ECFV) control is crucial for blood pressure regulation (49) and to prevent cardiovascular complications in this population (50, 51). Conversely, hypovolemia could predispose the HD patient to intradialytic hypotension, cramps, arrhythmias, and reduced well-being after treatment (2). As such, ECFV expansion and depletion can negatively impact HD patients.

Clinical assessment of volume overload by assessing blood pressure, edema and central venous pressure has limitations (3, 13, 52, 53). Interdialytic weight gain is not an accurate measure of volume overload since it does not necessarily correlate with actual ECFV expansion (54). The inferior vena cava collapse index (10), ultrasound assisted assessment of pulmonary fluid content (23) and echocardiography (10) can contribute to the assessment of fluid volume status but they do not provide an accurate estimate of fluid expansion or depletion and are difficult to implement in clinical practice. Multifrequency bio-impedance spectroscopy is a convenient bedside method to assess extracellular and intracellular fluid volume compartments (55). This method had been validated against gold standard dilution methods (55, 56), and is generally applicable in the setting of HD.

Given the high risk of mortality associated with ECFV expansion (57) and the knowledge that adequate volume control provides better control of blood pressure (58), more accurate objective methods for volume assessment would be valuable. In the current study, we tested the hypothesis

that volume overload is highly prevalent in HD patients, likely due to the inability to judge volume status from clinical parameters. We used bio-impedance spectroscopy to assess volume status in our HD population and to compare it with clinical volume assessment. Our aims were (1) to assess the prevalence of volume overload and volume depletion in our HD population using bio-impedance spectroscopy measurements, (2) to investigate the association between clinical parameters and volume status as assessed by the BCM, and (3) to search for a set of clinical parameters that best predict volume status in HD patients.

2.2. Materials and Methods

Patients

One hundred and ninety four HD patients were included in the study. Inclusion criteria included all prevalent HD patients who agreed to participate in the study together with HD patients referred from physicians for volume assessment. Patients were not included or excluded based on their blood pressure. Exclusion criteria were: patients with a pacemaker or implanted defibrillator, major amputation, and metallic prosthesis. No other selection criteria were applied. Ethics approval was obtained from the Human Research Ethics Board at the University of Alberta Hospital. All patients included in the study provided written informed consent.

Evaluation of volume status

The Body-Composition-Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany) is a multifrequency bio-impedance device that provides a convenient method to obtain extracellular fluid volume (ECFV) and has been validated previously (58, 59). Measurements were performed on one occasion in triplicate with the device. Measurements were performed before

the start of mid-week HD treatment with the patients in supine position for 10 minutes. Electrodes were applied on the ipsilateral arm and foot of the non- AV- fistula side.

The BCM device measures the impedance of different body compartments at 50 different frequencies between 5 kHz and 1000 kHz. The BCM calculates volume status (VS) which is expressed as volume excess or depletion in liters compared to the estimated ideal ECFV. The accuracy of bio-impedance in ECFV was within -0.4±1.4L when compared to dilution methods (59). To facilitate comparison between patients, the volume status was related to estimated ideal extracellular fluid volume (VS/ECFV). The patient population was divided into hypovolemic, normovolemic and hypervolemic groups. Hypovolemia was considered more than 7% below normal ECFV (equivalent to 1.1L below normal ECFV). Normovolemia was considered any measurement between -7% and 7% relative to normal ECFV. Hypervolemia was considered more than 7% above normal ECFV (equivalent to 1.1L above normal ECFV). The 7% cutoff point was based on 1.1L above normal ECFV (based on optimal daily dietary sodium intake) and corrected for the average ECFV for the study population.

Clinical and biochemical parameters

Clinical parameters collected include pre and post dialysis blood pressure for the same session and 5 previous sessions. Hypertension was considered as the average pre-dialysis BP >140/90mmHg for the 5 previous sessions. Intradialytic hypotension was defined as post dialysis SBP falling below 100mmHg and the difference between pre dialysis SBP to post dialysis SBP >20 mmHg with accompanying clinical symptoms during dialysis that required an intervention or cessation of UF (60). As there is no widely accepted definition of paradoxical hypertension, we considered it as a rise of SBP of >20mmHg during or after dialysis with post dialysis BP

exceeding 140/90mmHg. Patients were considered diabetic if it was mentioned in their charts or if the patient was on anti-diabetic medications. Pedal edema was assessed as present or absent. DW was obtained from the patient charts, however, we are not aware of how recently the DW was assessed by physicians. Interdialytic weight gain (IDWG) for the previous 5 sessions was recorded. IDWG was calculated by subtracting the post-dialysis weight of HD session from the pre-dialysis weight of the subsequent HD session. To determine the correlation between IDWG and volume overload, IDWG more than 7% of ideal ECFV was considered elevated. All biochemical parameters (plasma Na, K^+, serum albumin, WBCs, urea reduction ratio, and cholesterol level) were obtained from the most recent monthly blood work of the patient. Clinical volume assessment routinely assessed by rounding physicians by assessment of regular clinical parameters such as edema, shortness of breath and blood pressure. The rounding physicians according to their judgment of volume status adjusted dry weight.

Statistical analysis

Continuous data are expressed as mean± standard deviation. Categorical variables are expressed as percentage of total. One way ANOVA was used for univariate comparisons. Pearson's test was used for univariate correlations. Multivariate linear regression was performed with volume overload as the target variable, to find predictors for volume overload. Variables selected for the multivariate model based on a significant univariate analysis with a P- value<0.10. All data analysis was done with Graph prism (Graphpad 5, San Diego, CA, USA), and SPSS version 21 (SPSS Inc., Chicago, IL, USA). A P-value <0.05 was considered statistically significant.

2.3. Results

2.3.1. General characteristics of the study population

Characteristics of the study population are shown in table 2.3.1. Of the 194 participants, the percentage of male and female was similar. When judged by pre-dialysis blood pressure, 45% of the patients were classified as hypertensive. On average patients tended to be volume expanded with an average volume status of +7.8% (volume expansion related to ECFV) for the whole study population. Antihypertensive medications were prescribed to 48% of the study population. Most commonly prescribed were beta-blockers (26%), followed by calcium channel blockers (21%), angiotensin converting enzyme inhibitors (12%), and angiotensin receptor blockers (3%). Loop diuretics were prescribed for 14% of patients.

Table 2.3.1: Characteristics of the study population

Characteristics	Total (n=194)	Hypovolemic (n=17)	Normovolemic (n=83)	Hypervolemic (n=94)	P value
VS, L.	1.1 ± 2	-2.1 ± 0.6 [a,b]	0.1 ± 0.7 [a,c]	2.6 ± 1.5 [b,c]	<0.001*
VS/ECFV%	7.8± 12	-12 ± 3.4 [a,b]	0.9 ± 4 [a,c]	17±10 [b,c]	<0.001*
Gender, M/F	115/79	10/7	47/36	58/36	0.702
Age ,yrs	61 ± 15	60 ± 16	60 ± 16	62 ± 15	0.788
Diabetes, %	45% (n=88)	47%(n=8)	3% (n=29) [c]	54% (n=51) [c]	0.035*
Smoking, %	11%(n=23)	0% (n=0)	6% (n=5) [c]	17% (n=16) [c]	0.02*
Edema, %	28% (n=54)	0% (n=0) [b]	9% (n=8) [c]	47% (n=46) [b,c]	<0.001*
Obesity, %	26% (n=51)	47% (n=8) [b]	30% (n=25) [c]	19% (n=18) [b,c]	0.001*
Pre-HD-SBP, mmHg	131 ± 25	128 ± 26	129 ± 26	137 ± 25	0.088
Pre-HD-DBP, mmHg	71 ± 16	70± 15	72± 18	72± 16	0.843
Pre-HD-PP, mmHg	60 ± 22	59 ± 29 [b]	57 ± 19	65 ± 19 [b]	0.025*
Pre-HD-MAP, mmHg	91 ± 17	89 ± 14	91 ± 19	94 ± 17	0.418
HTN, %	45% (n=88)	41% (n= 7)	36% (n=30) [c]	54% (n=51) [c]	0.015*
Intradialytic hypotension	17% (n=33)	35% (n=6)[b]	20% (n=17)	11% (n=10) [b]	0.007*
Paradoxical hypertension	31% (n=60)	35% (n=6)	29% (n=24)	32% (n=36)	0.840
Plasma sodium	136 ± 3	136 ± 2.6	137 ± 3 [c]	135.5 ± 3 [c]	0.002*
Serum potassium	4.7 ± 0.6	4.8 ± 0.6	4.6 ± 0.6	4.8 ± 0.7	0.163
Albumin	36 ± 3.5	36 ± 4	37 ± 3.	36 ± 3.5	0.184

* P<0.05

[a] significant difference between hypovolemic and normovolemic

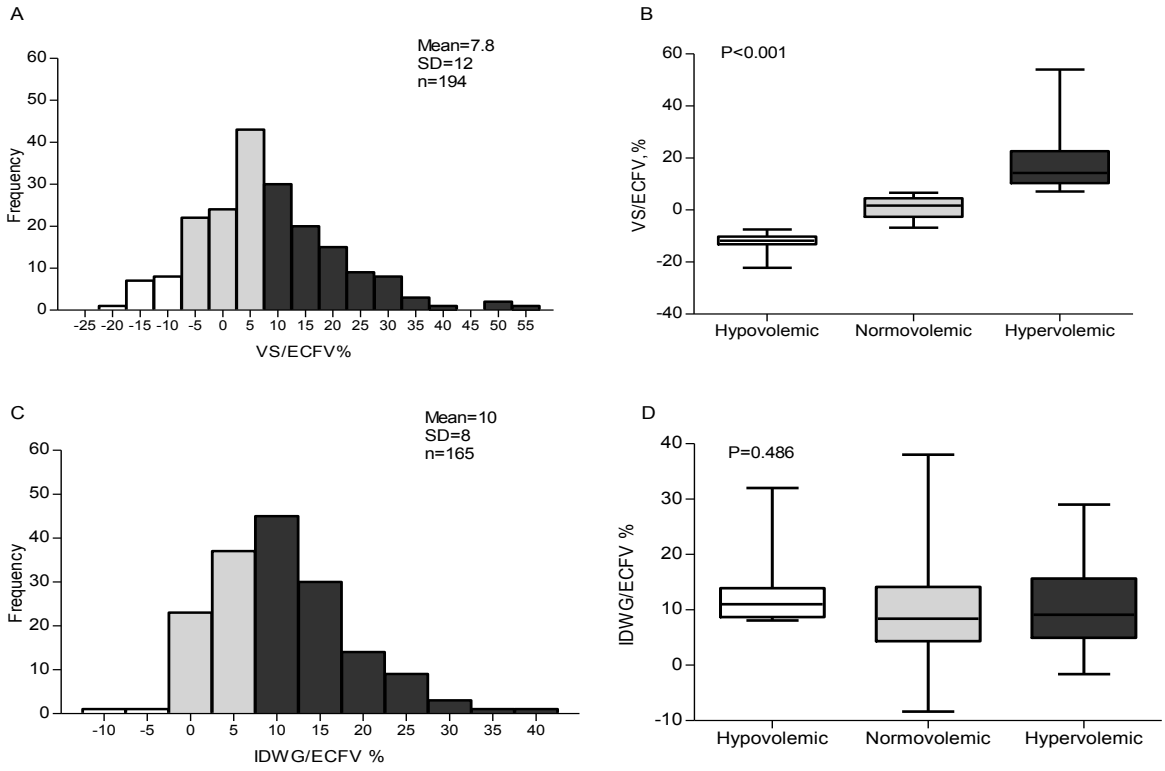
[b] significant difference between hypovolemic and hypervolemic

[c] significant difference between normovolemic and hypervolemic

2.3.2. Prevalence of volume abnormalities

Frequency distribution of volume status and comparison between the 3 groups is shown in figure 2.3.2; 43% of participants had normal volume status, defined as any measurement lying between -7% and 7% of the ideal ECFV; 48% of all patients had volume overload more than 7% of normal extracellular fluid volume. Of these fluid overloaded patients, in 47% (23 % of the whole study group) volume overload exceeded 15% of normal extracellular fluid volume (equivalent to 2.5L when related to an average ideal ECFV). Hypovolemia was observed in 9% of all patients.

Figure 2.3.2: Frequency distribution of volume status and IDWG



A)Frequency distribution of volume status corrected for extracellular fluid volume (VS/ECFV) for the whole study population, **B)** Significant difference in VS/ECFV between the 3 study groups, (P<0.0001). **C)**Frequency distribution of interdialytic weight gain (IDWG) for the whole study population corrected for ECFV, **D)** No significant difference in IDWG between the 3 patient groups as assessed by one way ANOVA, P=0.486

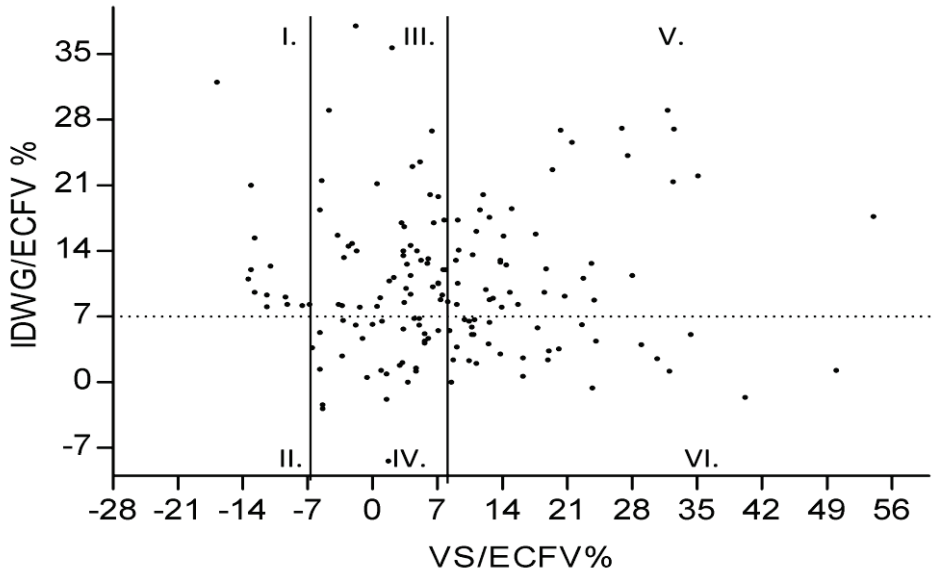
2.3.3. Clinical and biochemical characteristics in hypovolemic, normovolemic and hypervolemic patients

Age was not significantly different between patients. Volume status (VS) and volume status corrected for extracellular fluid volume (VS/ECFV) were significantly different between 3 groups. Hypervolemic patients had diabetes and hypertension more frequently. Pre-HD systolic blood pressure (Pre-HD-SBP) and diastolic blood pressure (Pre-HD-DBP) were not different between groups; pulse pressure, however, was higher in the hypervolemic group.. Plasma sodium levels were slightly but significantly lower in hypervolemic patients compared to normovolemic patients. When the hypervolemic group was divided further into two groups; patients with mild hypervolemia (1.1<VS<2.5L), and severe hypervolemia (VS>2.5L), incidence of edema was higher among patients with severe hypervolemia. Also potassium level was higher (5±0.7mEq/l) among patients with severe hypervolemia compared with patients with mild hypervolemia (4.6±0.6mEq/l). No other clinical parameters were different between these patients.

2.3.4. Relation between interdialytic weight gain and volume overload

On testing whether a relation between IDWG and volume status existed, the data did not reveal a correlation between IDWG and volume status both corrected for ECFV (figure 2.3.4). Moreover, IDWG was not elevated (IDWG<7% of ECFV) in all hypervolemic patients, but was also elevated (IDWG>7% of ECFV) in a subset of the normovolemic and hypovolemic patients. Altogether, IDWG was widely variable between patients regardless of their volume status (figure 2.3.2).

Figure 2.3.4: Correlation between IDWG and volume overload



No significant correlation between volume status and IDWG (both corrected for ECFV), P=0.985. **I.** Hypovolemic & high IDWG, **II.** Hypovolemic & low IDWG, **III.** Normovolemic & high IDWG, **IV.** Normovolemic & low IDWG, **V.** Hypervolemic & high IDWG, **VI.** Hypervolemic & low IDWG.

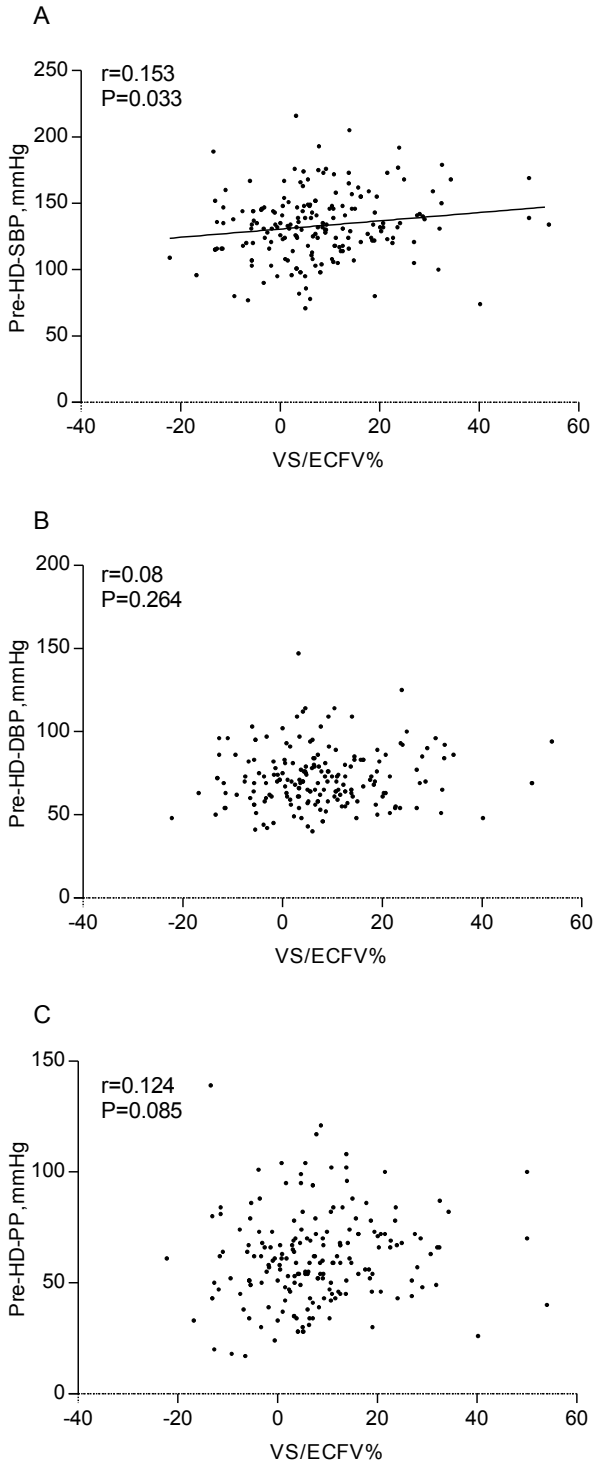
2.3.5. Relation between blood pressure and volume status as assessed by bio-impedance

The largest fraction of the patient population measured (28%) were found to have hypertension and volume overload. Among this group, antihypertensive medications were used more frequently. Of all patients, 23.5% were normotensive and normovolemic and 19.5% had normal blood pressure despite volume overload. The majority of hypovolemic patients had normal blood pressure. Our results show the wide variability in blood pressure regardless of the volume status. Relation between blood pressure and volume is shown in figure 2.3.5.

2.3.6. Incidence of intradialytic hypotension and paradoxical hypertension

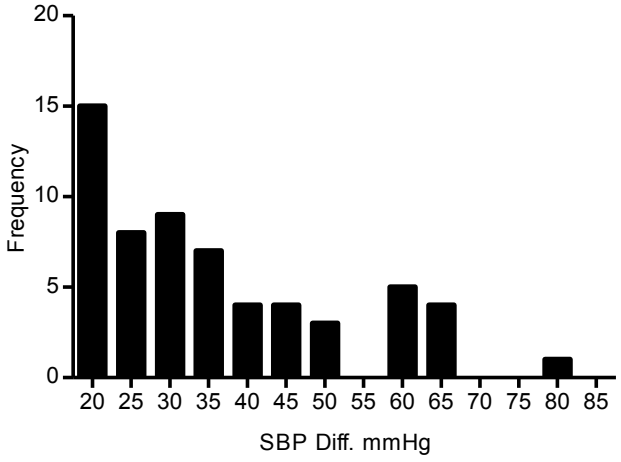
Intradialytic hypotension was found in 17% of the study population. Incidence of intradialytic hypotension was significantly higher among hypovolemic patients ($p=0.007$). . Incidence of paradoxical hypertension was high (31% of all study population). The average rise of blood pressure was 38 ± 15 mmHg for all patients with paradoxical hypertension. Numerically, paradoxical hypertension appeared more frequent in hypervolemic (18% of all study population) and normovolemic patients (14% of all study population) compared to the low frequency in hypovolemic patients (3% of all study population), yet this was not statistically significant. The distribution of severity of paradoxical hypertension is shown in figure 2.3.6.

Figure 2.3.5: Correlation between blood pressure and volume status assessed by bio-impedance



A) Significant correlation between volume status and pre-HD SBP, **B)** No significant correlation between volume status and pre-HD DBP, **C)** No significant correlation between volume status and pre-HD pulse pressure (Pre-HD-PP).

Figure 2.3.6: Frequency distribution of severity of paradoxical hypertension



Frequency distribution of severity of paradoxical hypertension, illustrated as rise in SBP in mmHg (post-dialysis SBP – pre-dialysis SBP), average rise of SBP from pre- to post-dialysis was 38mmHg

2.3.7. Using clinical parameters to identify volume overloaded patients

In an attempt to develop a volume overload score, we performed multiple linear regression to identify independent predictors of volume overload. Based on univariate analysis, 9 variables were selected for the multiple regression model (DM, HTN, edema, BMI, smoking, Pre-HD-PP, Pre-HD-SBP, sodium, and albumin). Edema, lower BMI, higher SBP, and smoking were the only significant predictors for volume overload, with a p-values of <0.0001, <0.0001, 0.001, and 0.037 respectively. Volume overloaded patients were 2.4 times more likely to have edema (relative risk=2.439), 1.6 times more likely to have lower BMI, and1.5 times more likely to have higher SBP (>140mmHg) and to be a smoker. We could not develop a volume overload score due to the presence of very few predictors as revealed by regression analysis. Sensitivity, specificity and positive and negative predictive values for the 4 individual parameters are shown in table 2.3.7.

Table 2.3.7: Sensitivity and specificity of single clinical parameters in predicting volume overload

Criteria	Relative Risk	PPV	NPV	Sensitivity	Specificity
Edema	2.4	85 %	65%	47 %	92 %
Lower BMI	1.6	54 %	67 %	84 %	32 %
Pre-HD-SBP	1.5	60 %	60%	55 %	64 %
Smoking	1.5	73 %	54 %	16 %	94 %

2.4. Discussion

In the current study, we assessed volume status and clinical parameters in a stable hemodialysis population. First, we demonstrate that a large proportion of our HD patients are volume overloaded (48%). Second, we describe discordance between clinical parameters that are routinely used to assess dry weight (DW) and bio-impedance spectroscopy.

Volume overload (more than 15% relative to normal ECFV) is associated with hypertension, dilated cardiomyopathy, heart failure and eventually with high mortality rates (61). Most important finding was despite clinical volume management, about 50% of our patients had volume overload (>7% of ECFV). Severe volume overload (>15% of ECFV) was observed in 23% of the study population. Previous studies using bio-impedance for quantification of volume status reported the similar findings (50, 61, 62). Interestingly, interdialytic weight gain was not significantly correlated to volume status assessed by bio-impedance. Among patients with high IDWG, there are patients of whom dry weight is not set at the level of normovolemia. Others have large intake of sodium and water, and thereby would benefit from salt restriction. This information implies that strategies to improve volume status need to address both components of volume regulation.

Volume depletion was detected in 9% of the study population. A previous study reported a slightly lower fraction of 5% of patients with predialysis volume depletion more than 1.1L pre-dialysis (47). Clinical characteristics of the volume depleted patients were not different from normo- or hypervolemic patients except for the higher incidence of intradialytic hypotension. Incidence of paradoxical hypertension was not different between patients. If one takes into account that the volume status of the patients was assessed pre-dialysis, and several hypovolemic patients had interdialytic weight gains of >25% of estimated optimal ECFV, with excessive UF these patients would be severely hypovolemic post dialysis. Although several patients with volume depletion had very substantial interdialytic weight gain, no correlation could be established between higher interdialytic weight gain and more severe hypovolemia, others have reported that volume depletion indeed may trigger higher IDWG (54). Recent literature suggests that these large swings in extracellular fluid volume, perhaps even more so that volume status per se is associated with cardiac stunning (63) and with cardiac hypertrophy (64). In one study, reducing the interdialytic weight gain without changing the dry weight reduced ventricular hypertrophy. Therefore, a risk might be imposed also in the volume depleted patients.

Extracellular fluid volume expansion is a major cause of hypertension in HD patients (2, 65). One half of the hypervolemic patients in this study were hypertensive (27% of total), the other half had normal blood pressure despite volume overload (22% of total). Twenty percent of all patients had hypertension and were not volume overloaded. This shows that the relationship between blood pressure and volume status is complex. Yet ECFV expansion and systolic blood pressure were correlated, in contrast to ECFV expansion and diastolic and pulse pressure. Using a comparable methodology, Wabel et al. analyzed the relation between blood pressure and volume overload in 500 HD patients and developed a hydration reference plot where volume

overload is plotted against blood pressure (66). Volume dependent hypertension was found in 15% of patients, majority of patients (27%) were normotensive and normovolemic. Only 10% of patients had normal blood pressure despite volume overload. Only 48% of our patients were prescribed antihypertensive medications. Previous studies reported higher percentage up to 70% (65). The reasons for this observation are not clear.

Paradoxical hypertension was a common complication of HD treatment in our study population (31%). Interestingly, the incidence of paradoxical hypertension was not significantly different between the 3 patient groups. To our knowledge, the prevalence of paradoxical hypertension and its relation to volume status has not been assessed in a large HD population. A previous study using similar definition of paradoxical hypertension reported prevalence of 21% among their patients (67). They also reported that UF rate was significantly lower in patients with paradoxical hypertension but all other parameters related to weight gain were similar between patient groups (67). A recent study reported a decline in the incidence of paradoxical hypertension with excessive ultrafiltration concluding that intradialytic hypertension may be a sign of volume overload (68), however, they did not use any method to assess volume. Another study reported that paradoxical hypertension was associated with higher hazard ratio for mortality (69). Intradialytic hypotension occurred in 17 % of all patients. Previous studies reported the incidence of intradialytic hypotension to be between 15-25% of HD sessions (30, 39). Hypovolemia has been shown to be the major cause for intradialytic hypotension, (41, 70) Incidence of intradialytic hypotension was significantly higher in hypovolemic patients. .

Only 50% of hypervolemic patients had edema, the other half did not show any signs of volume overload (hidden volume overload). A previous study reported that pedal edema correlates well with cardiovascular risk factors and left ventricular mass but it did not reflect volume in HD

patients as assessed by cardiac biomarkers and echocardiography (71). Hypertension in the present study was a poor indicator of volume overload with a low sensitivity and specificity. Fifty percent of all patients had hypertension, however only 27% had volume overload as well. This finding is similar to a previous study using bio-impedance for volume assessment (72). A substantial proportion of the patients were hypertensive but normohydrated indicating that hypertension in HD patients is not only due to volume expansion. No correlation was found between blood pressure and volume status assessed by U/S of inferior vena cava diameter in a previous study (73). Using a similar methodology in PD patients, multiple regression analysis revealed that DM, higher SBP, older age, male gender, lower serum albumin, and lower BMI were significant predictors for volume overload (74). We only found 4 significant predictors for volume overload in our study (edema, lower BMI, higher SBP, and smoking) in hemodialysis patients.

Our study has several limitations. First of all, the bio-impedance spectroscopy-based estimate of extracellular fluid volume has some error. In validity studies (59) ECFV had an error of -0.4±1.4L compared to the gold standard dilution methods, however a recent report stated that there is no real gold standard with absolute accuracy especially in dialysis patients (22). They found an error with both bio-impedance and dilution methods reflected by regression analysis. Although there is an error with bio-impedance in measuring the absolute volume of ECFV, it has been shown to be accurate in detecting fluid changes in the same patient. Also bio-impedance is highly reproducible with interobserver and intraobserver errors of less than 2% (75). Second, the measurement was performed once, prior to the 2nd dialysis session of the week. This could result in over/underestimation of the issue. Third, the clinical variables we used as edema are subjective and will depend on the observer. Also, we did not compare bio-impedance with other

methods like echocardiography or lung ultrasound to confirm volume assessment. Lastly, 42% of our study population was referred by physicians for volume assessment, so they might have been a clinical suspicion for volume overload or depletion.

In summary, using bio-impedance spectroscopy, we found that volume overload is highly prevalent in our HD patients and hypovolemia was also not uncommon. Neither fluid overload nor depletion could be reliably identified by clinical parameters. IDWG and BP showed wide variability among the patients regardless of their volume state. This study indicates that bio-impedance technology is a helpful tool beside clinical assessment to better recognize hidden fluid overload in hemodialysis patients.

Chapter 3

3. Sodium profiling in hemodialysis

3.1. Introduction

The relatively short period of hemodialysis (HD) sessions nowadays induces acute changes in fluid volume and sodium concentration. This led to the development of dialysis discomfort in the form of intradialytic hypotension, muscle cramps, nausea, vomiting, and increased thirst sensation. These intradialytic complications are mainly due to rapid changes in sodium concentration and water shifts between the intracellular and extracellular fluid compartments (10).

Intradialytic hypotension (IH) is a common adverse reaction that occurs in about 15-25% of HD sessions (36-38). IH is a major clinical problem not only causing discomfort but also it increases the patient mortality. On the other hand, some reports suggested that a mild fall in blood pressure during HD may be advantageous compared to no changes or a rise in blood pressure during HD (76).

The use of sodium profiling in HD has been introduced as a method to improve intradialytic hypotension, but its use still controversial. The aim of the current review is to address the benefits and drawbacks associated with the use of sodium profiling.

Sodium profiling means the application of a variable dialysate sodium concentration at any point of the HD session then increasing or decreasing either gradually or abruptly sodium concentration for the remaining of the HD session (77). Sodium profiling has shown to be very effective in prevention of IH if it is conducted in the right way. However, many studies reported that using sodium profiling was associated with increased plasma sodium concentration, excessive interdialytic weight gain (IDWG), increased thirst sensation and elevated blood pressure levels (78).

A literature search was undertaken using Pubmed. Since the studies were small in number, small in sample sizes and very heterogeneous, we could not perform a systematic review and/or meta-analysis. We included all clinical trials that used sodium profiling to compare it with conventional hemodialysis or to compare it with other sodium profiling protocols. Search terms were sodium profiling in hemodialysis. Exclusion criteria included abstracts, review articles, case reports and articles published in a language other than English. Twenty four articles were included in our review.

3.2. Sodium balance in HD patients

Sodium balance in dialysis patients is different from healthy subjects. Individuals with normal kidney function excrete sodium and water continuously, while in dialysis patients, sodium and water are removed mainly through dialysis (77). The excess sodium and water accumulated during the interdialytic interval is mainly stored in the extracellular fluid compartment (77). Therefore, plasma sodium concentration and ECFV in dialysis patients are mainly dependent on salt and water ingestion during the interdialytic period. Sodium and water balance can be maintained only when the patient's salt and water intake is equal to the amount removed during dialysis (77). As sodium moves freely across dialysis membranes, dialysate sodium levels influence plasma sodium concentration, and in turn the resulting fluid shift between different body compartments during HD. Therefore dialysate sodium concentration is usually chosen to be close or equal to plasma sodium concentration. Osmotic disequilibrium may occur when there is a large difference between plasma and dialysate sodium concentrations (79). Most of the excess sodium is removed by convection together with excess water (ultrafiltration). Diffusive sodium transport depends on the difference between dialysate to plasma sodium concentrations.

If no significant amount of sodium is gained or lost by diffusion, the dialysis treatment can be called isonatremic. Under current HD practice, more than 80% of sodium removal is convective and only 15-20% is diffusive (80). The aim of sodium profiling is to support plasma refilling in order to prevent intradialytic hypotension.

3.3. Pathophysiology of intradialytic hypotension

Intradialytic hypotension (IH) is still a highly prevalent complication that occurs in up to 25% of HD sessions (36-38). IH is associated with increased morbidity and mortality, but this may be due to the fact that low pre-dialysis blood pressure can be a sign of pre-existing cardiac disease (39, 40).

IH is defined as acute or gradual fall in blood pressure with accompanying clinical symptoms that occurs during the dialysis sessions and is caused by exhaustion or failure of compensatory mechanisms to maintain blood pressure during acute changes in ECFV. Blood pressure is the resultant product of cardiac output (CO) and total peripheral resistance (TPR) (41). Therefore, IH is the result of lowered CO and/ or inappropriately low TPR (41). In turn, compensatory mechanisms to prevent IH will work by maintaining CO and/or TPR. The compensatory mechanisms can become activated to a maximum, so that further compensation is not possible. Alternatively, the compensation may fail, due to the pathophysiology of the ESRD patient, or due to medications. In the next section we will analyze the pathophysiology of IH.

3.3.1. Intradialytic hypotension and cardiac output:

A drop in CO was associated with IH in 6 previous studies, of which two deserve special attention. In the 1st study (81), 13 chronic HD patients were monitored twice during their

midweek session regarding intradialytic variations of blood volume and CO. Before the HD session, BV was determined by Evans blue dilution method. Changes in BV were continuously monitored by means of an optical monitor. Monitoring of CO was carried out every 30 minutes by means of impedance cardiography and by the echocardiography. A weak correlation between variation in BV and intradialytic BP changes was found. The percent change of BV did not predict the onset of IH. Refilling rate increased significantly when BP decreased.

In the 2nd study (82), 48 HD patients were divided into unstable group (n=18) and stable group (n=30) depending on the frequency of IH. Continuous non-invasive cardiac monitoring (Physioflow) was done 30 minutes before, during and 30 minutes after a regular dialysis session. Patients in the unstable group had higher incidence of ischemic heart disease (IHD) and were using more beta blockers and calcium channel blockers than in the stable group. Changes in the filling index, cardiac output, ejection fraction and systemic vascular resistance during dialysis were not significantly different between the two groups. Within the unstable group, 2 subgroups were distinguished: one group with decreased CO (n=11) and higher TPR, the other group with stable CO (n=7) and reduced TPR. This may represent 2 separate groups of patients with different pathophysiologic mechanisms of IH, such as increased vascular resistance associated with a failing or ischemic heart, or vasodilatation due to autonomic dysfunction and inefficient compensatory vasoconstriction.

3.3.2. Intradialytic hypotension and heart rate variability

During UF, CO and SV decrease and MAP is maintained through an increase in heart rate. Increase in heart rate was previously observed in HD (83, 84). The greatest increase in heart rate was observed in hypotension prone patients with impaired baroreflex sensitivity (84). Baroreflex

sensitivity was impaired only in hypotension prone patients in 2 studies (83, 85), while it was impaired in a hypotension prone and hypotension resistant patients in another study (84).

3.3.3. Intradialytic hypotension and refilling rate

Estimation of refilling rate by a means of a feedback regulated UF mechanism was done in 5 unstable chronic HD male patients (86). Refilling rate was 20ml/min during the 1st 15 min of HD which declined to 9ml/min during the 1st hour of HD. In 4 of the 5 patients, refilling reached zero halfway during HD (86). These results agree with another study which measured refilling rate from changes in hematocrit and plasma volume during linear UF. Refilling rate was approximately 23ml/min during the 1st hour of HD. During IH, refilling rate fell to approximately 4ml/min which agrees with the notion that imbalance between UF rate and refill can have an important role in the genesis of IH (87).

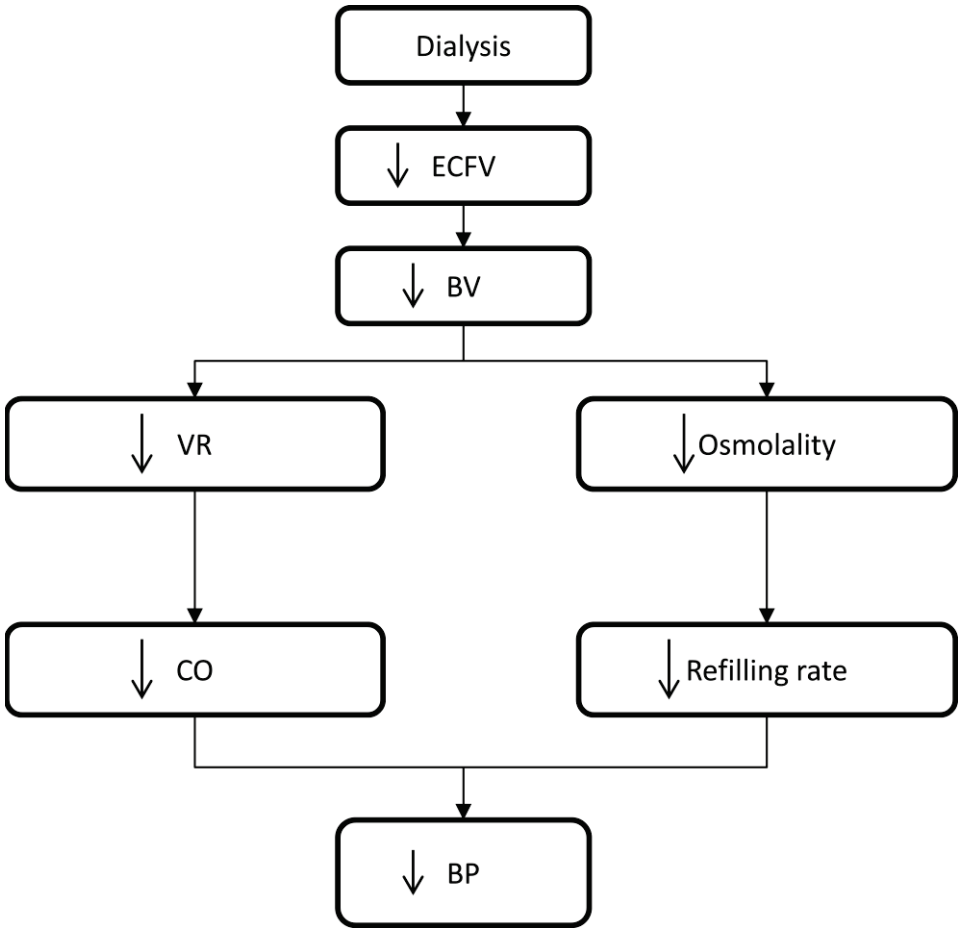
3.3.4. Blood volume changes and IH

Blood volume increases as the ECFV increase in healthy and HD patients. The absolute blood volume at the start of dialysis is extremely variable as it depends on hydration status of the patient (39). Recent studies found that IH episodes occur once a certain decrease in blood volume is exceeded which is specific for each individual patient (88, 89). In this study, the association between relative decline in blood volume and symptomatic hypotension was examined. In 72% of patients the investigators could identify an individual blood volume threshold which varied by less than 4% (90). The majority of hypotensive episodes occurred when this individually defined threshold was exceeded (90). However in 30% of patients a

critical threshold couldn't be identified (90). This blood volume threshold could not be identified in other studies (81).

During HD, the ultra-filtrated volume will be withdrawn from the intravascular compartment. A fluid shift from the overhydrated interstituim towards this compartment forms the only compensatory mechanism to overcome or diminish hypovolemia (91). Previous reports have shown that conventional hemodialysis causes a transcellular fluid shift from the ECFV to the (intracellular fluid volume) ICFV compartment (91). Consequently the refill of the intravascular compartment might be diminished since the amount of the ECFV available for the compensatory process decreases (91). It was demonstrated that the use of dialysate with high sodium concentration could remove fluid from the ECFV as well as from the ICFV compartments by inducing a transcellular fluid shift in the opposite direction (91). A significant correlation between the change in ICFV and the ratio post-dialysis: pre-dialysis serum sodium concentration was found. The greater the latter ratio, the more the observed ICFV decreased (91).

Figure 3.3: Patho-physiology of intradialytic hypotension



UF induced hypovolemia leads to decrease in venous return reducing both filling pressures and CO. In the mean time, UF leads to drop in plasma osmolality which delay the transfer of fluid from the extra-vascular compartment to the vascular compartment and probably producing a shift of fluid in the opposite direction aggravating the decrease in filling pressures.

3.4. Primary and secondary responses to high dialysate sodium concentration

3.4.1. Primary response: change in plasma sodium concentration

High dialysate sodium leads directly to an increase in plasma sodium concentration as measured by conductivity methods in 3 different studies (91-93). High dialysate sodium concentration was also associated with rise in plasma osmolality (93). Rise of plasma sodium levels after

using high dialysate sodium concentration led to contraction in intracellular compartment and was significantly correlated with changes in intracellular fluid volume (91, 92). A previous report stated that, at a given difference between dialysate and plasma sodium concentrations of 5mmol/L, the diffusive sodium transport was about 10gm during 5 hours of dialysis (94). Another study reported that an hourly variation of dialysate sodium concentration between 160-140mmol/L, led to increase in plasma sodium concentration from 140-152mmol/L without UF (79). This is equivalent to ingestion of about 25g of sodium chloride to the patient (79).

3.4.2. Secondary responses to increased plasma sodium concentration:

3.4.2.1. ADH changes during hemodialysis

In hemodialysis patients, vasopressin clearance rate may be lowered which would lead to increased vasopressin levels (95). However, vasopressin levels typically falls during hemodialysis despite volume removal. Autonomic dysfunction which is very common among HD patients and a fall in osmolality are thought to be the cause for the fall in plasma vasopressin level (96-98). Vasopressin secretion is closely related to changes in plasma osmolality (95, 96, 99). In a previous study, infusion of hypertonic saline enhanced vasopressin release in HD patients suggesting the role of vasopressin in intradialytic hypotension (99). Evidence that vasopressin deficiency contributes to intradialytic hypotension is that administration of exogenous vasopressin prevented drop in blood pressure during hemodialysis in patients with autonomic dysfunction (100).

In other studies, there was no change in vasopressin levels in response to pressure/volume stimuli until significant hypotension or hypovolemia occurred (101, 102). Vasopressin also plays a role in salt-sensitive hypertension in animals and in man with volume mediated

hypertension including end stage renal disease patients, the administration of V1a receptor antagonist significantly lowered blood pressure in these patients (103, 104).

Using sodium profiling and other therapies to support blood pressure during hemodialysis were traditionally thought to stabilize blood pressure by affecting plasma refilling rate. There is also an evidence that vasopressin may play a role in their efficacy. As during sodium profiling, the fall in serum osmolality and plasma vasopressin level will be prevented (105). This finding suggests that preventing the fall in vasopressin level during dialysis results in part from changes in osmolality and the blood pressure stabilizing effects of therapies such as sodium profiling (106). There is some evidence that sodium profiling raises plasma osmolality and plasma vasopressin levels which preserves blood pressure during hemodialysis.

3.4.2.2. Thirst sensation

Increased plasma sodium concentration will increase plasma osmolality, and vasopressin levels, which in turn will increase thirst sensation (107). Increased thirst sensation was associated with higher IDWG (108). Sodium profiling was compared to standard HD in 4 studies, two of them (109, 110) found higher IDWG and increased thirst sensation with sodium profiling compared to standard HD, while the other 2 studies found no difference in IDWG and thirst between 2 treatment modalities (111, 112). Data in subjects with normal renal function show that the relationship between thirst and plasma osmolality (sodium setpoint) varies from person to person but quite constant in the same individual (113).

3.4.2.3. Effect of sodium load on vascular endothelium

High plasma sodium concentration was associated with endothelial cell stiffness in the presence of aldosterone. Absence of aldosterone in culture medium (unphysiological conditions) or treatment with sodium channel blocker (amiloride) prevented this effect (114). High plasma sodium concentration was also associated with down regulation of nitric oxide release. In the absence of aldosterone, cells were insensitive to changes in plasma sodium concentration (114). Acute increase in plasma sodium concentration within narrow range (135-145mmol/L) can alter the mechanical properties of the vascular endothelium (115). In cultured human endothelial cells, cell stiffness increased by 20% in a few minutes of raising plasma sodium concentration from 135 to 145mmol/L. This was associated with reduction in nitric oxide and endothelial nitric oxide synthase activity, suggesting a functional link between nitric oxide metabolism and plasma sodium concentration (114).

3.5. Effect of plasma sodium concentration on blood pressure

Sodium balance is the cornerstone of good interdialytic blood pressure control (45). Although sodium balance in dialysis patients is determined by several factors, changes in dialysate sodium concentration have an immediate and major effect on plasma sodium (116). Numerous studies have demonstrated that lower sodium dialysate (117, 118), particularly in combination with a low dietary sodium intake (119, 120)**,** reduces interdialytic weight gain, improves blood pressure control, decreases the severity of interdialytic symptoms and decreases cardiac volume loading**.** Furthermore, gradual decrease of dialysate sodium concentration doesn't increase the frequency of substantive hypotension, headache, nausea, and vomiting or dialysis morbidity (121)**.** The mechanisms whereby plasma sodium directly affects blood pressure are not fully understood.

There is compelling evidence demonstrating that dietary salt intake has major effect on blood pressure regulation. Clinical trials on hypertensive and normotensive individuals has shown that an increase or decrease in salt intake causes parallel changes in plasma sodium, and the change in plasma sodium was weakly but significantly correlated with changes in systolic blood pressure (122). Several epidemiological studies in the general population have shown a positive association between plasma sodium and blood pressure on the individuals' usual diet (123, 124). It has been shown that a meal containing salt has immediate and significant effect on plasma sodium levels (122). To further study the relationship between plasma sodium and blood pressure, a retrospective audit was carried out (122). Univariate analysis of their data showed significant relation between plasma sodium and both systolic and diastolic blood pressure. An increase of 1 mmol of plasma sodium was associated with an increase of 0.53 mmHg in systolic and 0.30 mmHg in diastolic blood pressure (122).

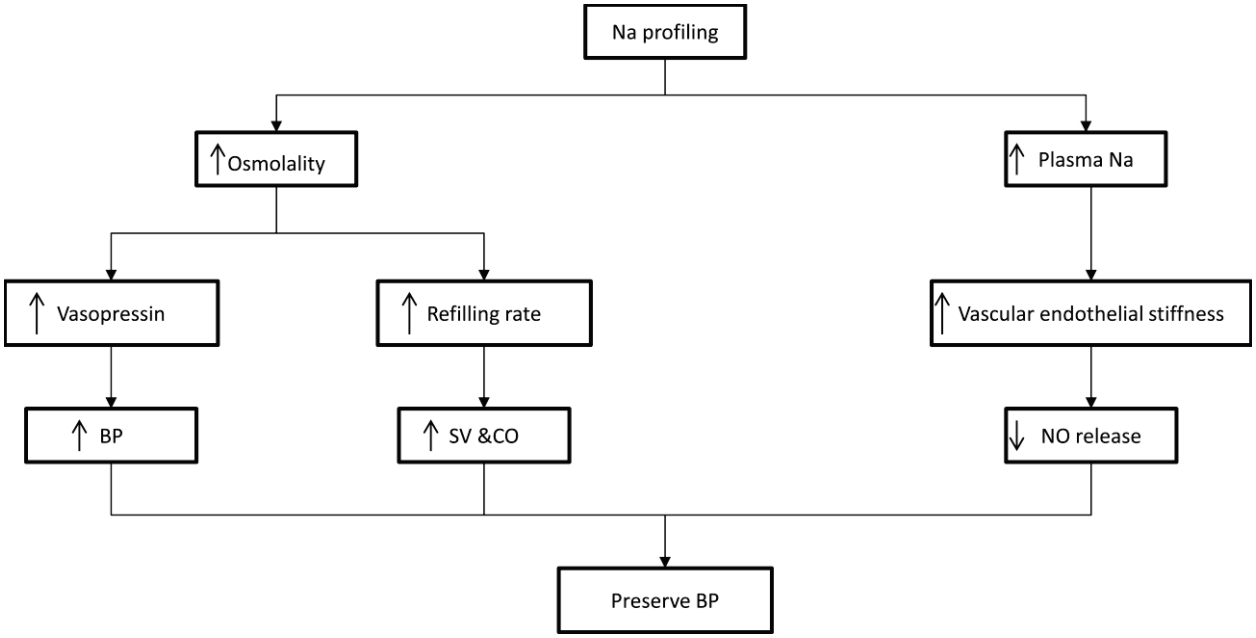
3.6. Effect of sodium profiling on compensatory mechanisms

The effect of sodium profiling on hemodynamic parameters has been studied previously. CO and SV as measured by Echocardiogram in 8 HD patients for 10 sessions duration for each protocol were more stable during sodium profiling than during standard HD (125). Intradialytic cardiovascular stability improved during profiled HD as compared to constant HD as measured by Echo before, during and after one HD session for each protocol in 20 HD patients with frequent IH episodes (126). Another study also reported that CO and SV improved during profiled HD compared to constant HD with quicker post dialysis return to basal conditions as measured by Echo in 12 unstable HD patients (127).

Using dialysate sodium concentration higher than plasma sodium concentration reduces the osmolar water shift leading to increased refilling rate as compared to conventional HD (86). In a previous study, the effect of cool dialysate and sodium profiling on refilling rate was compared in 6 stable HD patients. Sodium profiling but not cool dialysate increased refilling rate significantly from baseline (86). Another study evaluated the effect of 3 different profiles on 15 stable HD patients. The 1st profile had constant UF rate with constant dialysate sodium concentration, the 2nd with dialysate sodium profiling with constant UF rate, the 3rd profile with combined UF and dialysate sodium profiling. Total UF volume was the same for all treatments. Better preservation of BV was reported with the high sodium treatment which could be explained by improved refilling during sodium profiling treatments (91).

Changes in erythrocyte volume are mainly due to changes in water content of the cell leading to changes in MCV. In a previous study, changes in erythrocyte volume during HD were tested through measuring packed cell volume in 5 patients dialyzing with high, low and normal dialysate sodium concentrations for 2 hours each (128). Erythrocyte water content decreased with high and increased with low dialysate sodium concentration (128). Erythrocyte volume calculated from MCHC decreased with high and increased with low dialysate sodium concentration (128). Erythrocyte volume correlated with changes in plasma sodium concentrations (128).

Figure 3.6: Mechanism of action of sodium profiling



Sodium profiling maintain BP by 2 main mechanisms: 1st by increasing plasma osmolality which will enhance refilling rate increasing CO & SV, higher osmolality will also increase vasopressin levels which will prevent drop in BP, 2nd by increasing plasma sodium levels which increases vascular endothelial stiffness with reduced nitric oxide (NO) release

3.7. Sodium profiling

Sodium profiling is applying variable dialysate sodium concentrations through the dialysis session instead of using a constant dialysate sodium concentration (129). A higher dialysate sodium concentration is used at any point of the dialysis session then decreasing or increasing sodium concentration either gradually or abruptly for the remaining of the session. Using the high dialysate sodium concentration tends to prevent the inevitable drop in plasma osmolality due to urea removal. Lowering the dialysate sodium concentration for the rest of the session is to prevent sodium accumulation. Dialysate sodium level can be decreasing, increasing or alternating. Sodium profiling protocols can be linear, stepwise, or exponential. Regarding diffusive sodium transport, sodium profiling can be classified into: positive sodium balance,

negative sodium balance and isonatremic sodium balance. Isonatremic (neutral) sodium balance is the ideal form of sodium profiling. There is a wide variety of sodium profiles with a very wide range in the dialysate sodium level used extending from 190mEq/L to 130mEq/L (77).

Decreasing sodium profiles were the most commonly employed, it takes the advantage of high dialysate sodium concentration at the beginning of dialysis when ultrafiltration is best tolerated. This method has been shown to improve IDWG, thirst, hypotension and disequilibrium syndrome (44). Alternating sodium profiles improves disequilibrium syndrome by preserving the plasma volume through induction of alternating fluid shift across the cellular membrane to improve the transport of uremic toxins (44). Increasing sodium profiles are less commonly used, they are used to preserve the plasma volume during the last period of dialysis allowing a lower incidence of cramps compared to constant or decreasing profiles, probably because of reduced sodium removal (44). Combining UF profiling with sodium profiling may enhance the effect of sodium profiling.

3.7.1. Sodium positive profiling

The results from 24 previous studies are cited in table 2. A wide variety of sodium profiles have been used. Decreasing sodium profiles were mostly employed. The effects of linear, stepwise and exponential profiles had been also compared in some studies. Early intradialytic hypotension and post-dialysis hypotension were best reduced by decreasing stepwise profiles (111). Muscle cramps and late intradialytic hypotension were best reduced by decreasing linear sodium profiles (111). Sodium profiling was found to be beneficial in young adults (111) and geriatric patients (37).

Independent of the sodium profiling protocol used, 16 of these studies showed a reduced incidence of intradialytic hypotension with sodium profiling. Another 2 studies showed a reduced incidence of muscle cramps but not hypotension during dialysis (111, 130). Better cardiovascular stability through more stable blood volume was shown in 5 studies (37, 86, 125, 131, 132).

Regarding the possibility of sodium accumulation with the use of sodium profiling, it is worth noting that there was no follow up for pre or post-dialysis plasma sodium levels in 9 studies. Clinical or laboratory signs of sodium accumulation were found in 8 studies but not in another 7 studies. Some studies found that sodium profiling is beneficial for the majority of their patients (37, 111), while others found it to be beneficial for a small group of their patients (109). Some of these studies were very brief being only one session to test for each sodium profiling protocol. Accordingly most of them only focus on short term effects except in few studies where the duration was longer. One of the long term studies lasted for one year (78) , they found that sodium profiling was useful to alleviate intradialytic symptoms but was associated with increased thirst sensation, IDWG, and increased plasma sodium concentration. The only weakness of this study (78) is there small sample size (20 patients), and only 9 patients in the treatment group (profiled HD). Another study by Flanigan et al. (133) compared standard HD to exponential decreasing sodium profiling (3.5 months for each treatment protocol). Incidence of hypotension did not decrease with sodium profiling, also IDWG did not increase.

Regarding sodium balance neutral sodium profiling, a study by Song et al. (134) compared 8 different sodium profiling protocols. They found that sodium neutral balance sodium profiling plus UF profiling decreased incidence of intradialytic hypotension and was not associated with increase in IDWG or sodium accumulation. In another study (135), they concluded that using

sodium balance neutral sodium profiling failed to decrease intradialytic symptoms even when combined with UF profiling.

Table 3.7: Clinical results of sodium profiling

Reference	N	Duration	Sodium protocols	IH	Muscle cramps	IDWG	Thirst	BP	Plasma Na	BV	Refilling rate
1-(43) Prospective study	14	10 sessions each	**1-**Constant (139mmol/L)+constant UF rate **2-**Linear profile (147 to 131 mmol/L)+UF profile **3-**Linear profile (147 to 131 mmol/L) + constant UF rate	↓	↓	Not↑	N/A	↑	N/A	N/A	N/A
2(136) Randomized crossover study	22	12 sessions each	**1-** Standard HD (139 mmol/L). **2-** Profiling HD (from 147 to138 mmol/L) either stepwise or linear.	↓	↓with linear profile	Not↑	N/A	↓with linear profile	N/A	N/A	N/A
3-(86)	6	1 session each	**1-** Exponential profile (150 to 140mmol/L) **2-** Cool dialysate 1˚C below core body temperature.	N/A	N/A	N/A	N/A	↑	N/A	More stable	↑
4-(78) Randomized controlled trail	20	One year	**1-** Standard HD (140mmol/L) **2-** Linear decreasing profile (144 to 140mmol/L)	Not↓	N/A	↑	↑	↑	↑	N/A	N/A
5-(38)	14	12 sessions	**1-**Standard HD (139mmol/L). **2-**Linear profile (147mmol/L to 139mmol/L).	Not↓	↓	↓	N/A	↑	N/A	N/A	N/A
6-(42) Non randomized cross over study	13	4 weeks each	**1-** Standard HD (135-140mmol/L) **2-** Linear profile (150 to 140mmol/L).	↓	↓	↑	N/A	↑	Not↑	N/A	N/A

Reference	N	Duration	Sodium protocols	IH	Muscle cramps	IDWG	Thirst	BP	Plasma Na	BV	Refilling rate
7-(125) Randomized cross over controlled trial	8	10 sessions each	**1-** Standard HD (138mmol/L) + constant UF **2-** Linear profile (148 to 131mol/L) + constant UF **3-** Linear UF profile + constant dialysate sodium (138mmol/L) **4**-Sodium + UF profiling	↓with Na+UF profile	N/A	↑with Na+UF profile	N/A	N/A	Not↑	More stable (Na+ UF profile	N/A
8-(134) Prospective study	11	33 sessions each	**1-** Conventional HD **2-**Sodium balance positive step down profiling (PS) **3-**Sodium down neutral step down profiling (NS) **4-**Sodium balance neutral alternating profiling (NA) **5-** UF profiling only (UFP) **6-** PS+UFP **7-** NS+UFP **8-** NA+UFP	↓	N/A	↑with PS, PS+UFP	N/A	↑	↑	N/A	N/A
9- (137) Prospective study	40	6 weeks	**1-** Profiled HD (146 to 138mmol/L) + UF profiling.	↓	↓	Not↑	N/A	Not↑	N/A	N/A	N/A
10- (138) Single blind cross over study	27	9 sessions each	**1-** Standard HD (138mmol/L) **2-**Individualized dialysate sodium concentration according to the mean pre-HD plasma sodium multiplied by the Donnan coefficient (0.95).	N/A	N/A	↓	↓	N/A	N/A	N/A	N/A
11-(129) Cross over non-randomized trial	11		**1-** Standard HD (138mmol/L). **2-** Profiled HD (145 to 135mmol/L, with TAC140). **3-** Profiled HD, (158 to 130, with TAC147). Depending on the TAC, they designed the final Na to be the lowest during the highest TAC and highest during lower TAC.	↓	N/A	↑	N/A	↑	↑	N/A	N/A

Reference	N	duration	Sodium protocols	IH	Muscle cramps	IDWG	Thirst	BP	Plasma Na	BV	Refilling rate
12-(135) Randomized cross over study	9	3 months	**1-** Linear profile (145 to 133mmol/L) with linear UF profiling. **2-** Stepwise UF profile with/without stepwise sodium profile (145 to 133mmol/L)	↑	Not↓	Not↑	N/A	N/A	N/A	No change	N/A
13(139) Randomized controlled cross over study	32	4 weeks	**1-** Standard HD (142mmol/L), constant UF **2-**Exponential profile (152 to 142mmol/L) + exponential UF profile.	↓	↓	↑	Not↑	N/A	↑	More stable	N/A
14-(131) Non-randomized controlled cross over study	11	2 HD sessions	**1-** standard HD (138-144mmol/L) **2-** Profiled HD (they used a mathematical model to determine the profile for each patient according to plasma sodium concentration and desired sodium balance)	↓	N/A	Not↑	Not↑	Not↑	Not↑	More stable	N/A
15-(109) Randomized cross over controlled trial	23	2 weeks each	**1-** Standard HD (140mmol/L) **2-** Linear profile (155 to 140mmol/L) **3-** Stepwise profile (155 to 140mmol/L)	↓	↓	↑	↑	↑	↑	N/A	N/A
16-(133) Randomized cross over trial	18	7 months	**1-** Standard HD (140mmol/L) **2-**Exponential profile (155 to 135mmol/L)	Not↓	N/A	Not↑	N/A	N/A	N/A	N/A	N/A
17-(132)	10	3 HD sessions	**1-** Standard HD (141mmol/L) **2-**Decreasing profile (160 to 133mmol/L) **3-**Increasing profile (133 to 160mmol/L)	N/A	N/A	Not↑	Not↑	Not↑	Not↑	More stable (decreasing profile)	N/A
18-(44)	16	4 months	**1-**Standard HD **2-**Biofeedback technique to individualized dialysate sodium concentration according to the patients plasma sodium	↓	↓	Not↑	Not↑	Not↑	Not↑	N/A	N/A

Reference	N	Duration	Sodium protocols	IH	Muscle cramps	IDWG	Thirst	BP	Plasma Na	BV	Refilling rate
19-(37) Randomized crossover	10	1 session each	**1-**Linear profile (160 to 140mmol/L) **2-**Stepwise profile(160 to 140mmol//L) **3-** Standard HD (150mmol/L) + constant UF **4-** Standard HD (140mmol/L) + constant UF	↓	N/A	N/A	N/A	N/A	N/A	More stable	N/A
20-(130) Randomized cross over double blinded	16	3 weeks	**1-** Standard HD (140mmol/L) **2-** Stepwise profile (155-160 to 140mmol/L for the last hour of HD)	Not↓	↓	Not↑	↑	N/A	↑	N/A	N/A
21-(140) Double blind cross over trial	22	7 sessions each	**1-**Standard HD (137mmol/L) + constant UF **2-** Linear profile (from137 to 128mmol/L) + UF profiling	↓	N/A	Not↑	↓	N/A	↓	N/A	N/A
22-(111) Randomized cross over trial	16	8 weeks	**1-** Standard HD (138mmol/L) **2-** Linear (148-138mmol/L) **3-** Stepwise (148-138mmol/L) **4-** Exponential (148-138mmol/L)	N/A	↓with linear, stepwise profiles	N/A	↑	N/A	N/A	N/A	N/A
23-(141)	39	9 weeks	**1-** Standard HD (140mmol/L) **2-** Stepwise profile (starting from 149mmol/L) **3-** Linear profile (starting from 149mmol/L) **4-**Exponential profile(starting from 149mmol/L)	↓	↓	Not↑	Not↑	Not↑	↑	N/A	N/A
24- (142) Non-randomized cross over trial	15	1 session each	**1-** Standard HD (140mmol/L) **2-**Stepwise profile (140 to 148mmol/L)+ constant UF rate **3-** Stepwise profiling as above + UF profiling	↓	↓	N/A	N/A	N/A	↑	N/A	N/A

3.7.2. Sodium neutral profiling and sodium setpoint

Pre-dialysis plasma sodium concentration (PNa) can be regarded as the sodium setpoint. By the end of dialysis PNa approaches the prescribed dialysate sodium concentration (DNa), therefore the difference between DNa and PNa can be considered as the sodium gradient (143). As a consequence of positive or negative sodium gradient, patients either experience sodium loss or gain (144). Most recent data demonstrate that HD patients have a fixed osmolar setpoint above which thirst sensation will develop (145-147). Higher sodium gradient was associated with greater interdialytic weigh gain (IDWG) (143). However, individualized DNa levels have been recommended (144, 147, 148) , there is no available data about its long term effects.

Plasma water sodium concentration is 7% greater than total plasma sodium concentration because of the volume occupied by plasma proteins (77). Roughly cancelling this is the negatively charged proteins mainly albumin which cause a small electrical potential difference across the membrane that retards the movement of positively charged sodium ions (Donnan effect) (149).

There are a few studies regarding sodium neutral balance sodium profiling. One of these studies evaluated the relationship between IDWG and 3 different dialysate sodium concentrations, including standard dialysate sodium concentration of 138mmol/L, dialysate sodium equal to the mean pre-dialysis plasma sodium concentrations, and individualized dialysate sodium concentration (0.95 X mean pre-dialysis plasma sodium to account for Gibbs-Donnan effect) (138). They observed similar pre-dialysis plasma sodium concentrations during the 3 treatments, and a decrease in IDWG and thirst sensation with individualized dialysate sodium compared to standard dialysate sodium concentration. Song et al. used 8 different sodium profiling protocols

for 6 weeks each and they found that sodium neutral profiling with UF profiling was very useful for their patients without reporting increased thirst or any other interdialytic side effects (134). Other studies could not demonstrate the same beneficial effects of sodium neutral balance sodium profiling (135).

3.7.3. Sodium and ultrafiltration profiling

Frequently, sodium profiles combine a variable dialysate sodium concentration during a dialysis session with a variable UF rate. High dialysate sodium concentration is recommended in combination with high UF rates (and vice versa), an approach that optimizes plasma refilling when UF induced plasma volume reductions are the highest (139). Ultrafiltration profiling has been shown to be successful in alleviating intradialytic hypotension without carrying the risk of high post-dialysis plasma sodium concentration. Evidence of blood pressure stabilizing effect of ultrafiltration profiling alone and in combination with sodium profiling has already been shown (150, 151), but long term benefits of profiled dialysis have yet to be identified. Two studies compared UF profiling with constant UF rate, one of them (152) found no effect on thirst or IDWG between 2 treatments, the other study (112) reported increased thirst with constant UF.

Combined ultrafiltration and sodium profiling may be a further step toward an optimal, individualized dialysis therapy, especially for hypotension prone patients. Both profiles have to be chosen for the individual patient according to patient's plasma sodium concentration. Both intradialytic and interdialytic symptoms must be taken into account. Combined sodium and ultrafiltration profiling should be used as a method to reduce intradialytic morbidity while avoiding sodium accumulation in HD patients. The introduction of an online continuous blood

volume monitoring has offered the opportunity of changing both the UF rate and dialysate sodium concentration in order to maintain a constant blood volume reduction rate (153, 154).

3.8. Conclusion

Studies of sodium profiling published to date have some weak points. First, most studies had small number of patients with short duration with no long term follow up. Second, most of the studies used high sodium profiles which added sodium by diffusion. Thus they increase plasma sodium concentration which may explain the reported short term benefits (91, 141). Also plasma sodium concentrations were not assessed in many studies. Third, most of the studies included unstable HD patients with more frequent hypotensive episodes; however, a special attention should be given to these patients. Hypotensive episodes could occur in hypervolemic patients due to high UF targets that could not be compensated by refilling, and also can occur in hypovolemic patients due to excessive UF leading to volume depletion. Assessing volume status of these patients before applying sodium profiling would be more helpful. Dietary sodium restriction would be a better intervention in hypervolemic patients to decrease their IDWG and as a result UF target. Correcting hypovolemia by accurate adjustment of DW would be better than giving excess sodium to the patients.

In summary, sodium profiling has been shown to be effective in preventing intradialytic hypotension, however, sodium accumulation could account for the observed short term benefits. More studies with a large sample size and long term follow-up are needed. Evaluation of volume status before applying sodium profiling could be better approach to alleviate intradialytic symptoms. Using mathematical models and biofeedback techniques to individualize dialysate sodium are very promising techniques but they need more evidence.

Chapter 4

4. Overall discussion

4.1. Prevalence of volume overload and volume depletion in HD

Volume overload is highly prevalent in HD patients. Our results indicate that about 50% of patients had volume overload pre-dialysis, and 27% of patients had severe volume overload (>15% related to normal ECFV) which is associated with higher mortality rates (61). Our results also indicated that clinical parameters lack sensitivity and could not detect volume overload in half of the hypervolemic patients (hidden volume overload). Volume depletion was found in 9% of our study population, however, they could not be differentiated clinically from normovolemic patients.

4.2. Wide variability of BP and IDWG

There was a wide variability of BP level regardless of volume status. Only half of the hypervolemic patients had hypertension (27% of all study population). Most of volume depleted patients had normal blood pressure. Twenty percent of patients were hypertensive despite normal volume status. This shows that relation between volume and blood pressure is complex. Our results are in agreement with a recent study by Wabel et al. who analyzed the relation between blood pressure and volume. Volume overload and hypertension (probable volume dependant hypertension) was found in 15% of patients (it was found in 27% of patients in our study population).

Interdialytic weight gain (IDWG) was not significantly correlated with volume status assessed by bio-impedance. IDWG was not elevated in all hypervolemic patients and was highly elevated in some of hypovolemic patients. A recent study reported that volume depletion may trigger higher IDWG (54).

4.3. Incidence of intradialytic hypotension and paradoxical hypertension

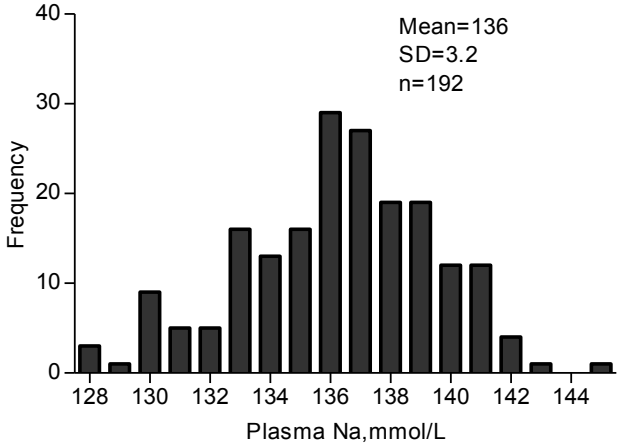
However intradialytic hypotension is a common intradialytic complication that occur in about 15-25% of dialysis sessions (36-38), incidence of intradialytic hypotension was 17% in our study population.

There is no widely accepted definition for paradoxical hypertension. In fact there is not even a widely acceptable level of blood pressure which is required to meet the definition of paradoxical hypertension (155). Few definitions had emerged from clinical studies, and include the following: any increase in mean arterial pressure (MAP) of 15mmHg or more during or immediately after HD (156). An increase in blood pressure during dialysis that is resistant to ultrafiltration (157). An increase in SBP of more than 10mmHg during or immediately after HD (67). It has been shown that every 10mmHg increase in SBP after dialysis is associated with a 6% increased hazard of death (69). Due to lack of a common definition, the prevalence of paradoxical hypertension is widely variable in the literature. Incidence of paradoxical hypertension was 31% in our study population. The incidence was not different among the hypo/normo/hypervolemic patients. A previous study reported a slightly lower incidence of 21% (67), however, they followed up with patients for a longer duration, while in our study, we only assessed patients during one dialysis session.

4.4. Sodium profiling

We assessed volume status using bio-impedance spectroscopy in 200 HD patients. Pre-dialysis plasma sodium levels obtained from the most recently blood work varied widely between patients in our cohort (figure 4.4). Mean plasma sodium concentration was 136mmol/L. Dialysate sodium concentration was set to 137mmol/L for most of the patients. Using the same constant dialysate sodium concentration for most of the patients without considering their pre-dialysis plasma sodium level will lead to sodium gain in some patients and sodium loss in others. Even with the use of the same sodium profiling protocol without considering plasma sodium concentration, this will lead to either sodium gain or loss. As mentioned previously individualized dialysate sodium profiling is the best way to alleviate intradialytic complications without increasing interdialytic side effects. Assessment of volume status before using sodium profiling will prevent undesirable side effects of sodium profiling. Using sodium profiling in volume overloaded patients may lead to sodium gain. Also using sodium profiling in volume depleted patients is like treating intradialytic hypotension by saline infusion, instead of decreasing UF target.

Figure 4.4: Plasma sodium level for the study population



Frequency distribution of plasma sodium levels for 192 HD patients, obtained from their monthly blood work. Mean plasma sodium level was 136mmol/L

4.5. Multifactorial intervention to improve volume and blood pressure control in HD patients

In an attempt to provide a multifactorial approach (DW adjustment, dietary sodium restriction, sodium profiling and cold dialysate) to control volume overload in our patients using bio-impedance for volume assessment. We realized that blinding will not be possible as after assessing the volume status, both the patient and the treating physician are curious to know the results and start correcting volume status immediately mainly through adjusting dry weight according to the measurement. Our plan was to include all volume overloaded patients as assessed by bio-impedance. We would have a control period for 6 weeks without any intervention and then an intervention period (dietary sodium restriction, DW adjustment, sodium profiling, and cool dialysate). We found that providing patients and physicians with the volume status information is an intervention per se. We could not have a control period as physicians

started correcting patients immediately mainly by adjusting their DW according to the BCM measurements. Physicians even requested repeating the measurements for some patients when clinically indicated or just for follow up. Our aims were to provide better volume control and assess the effect of volume control on blood pressure and cardiovascular outcome. We were not able to continue the study due to the above mentioned reasons, however, we are interested to re-evaluate these patients after a period of time to evaluate effectiveness of volume assessment using bio-impedance.

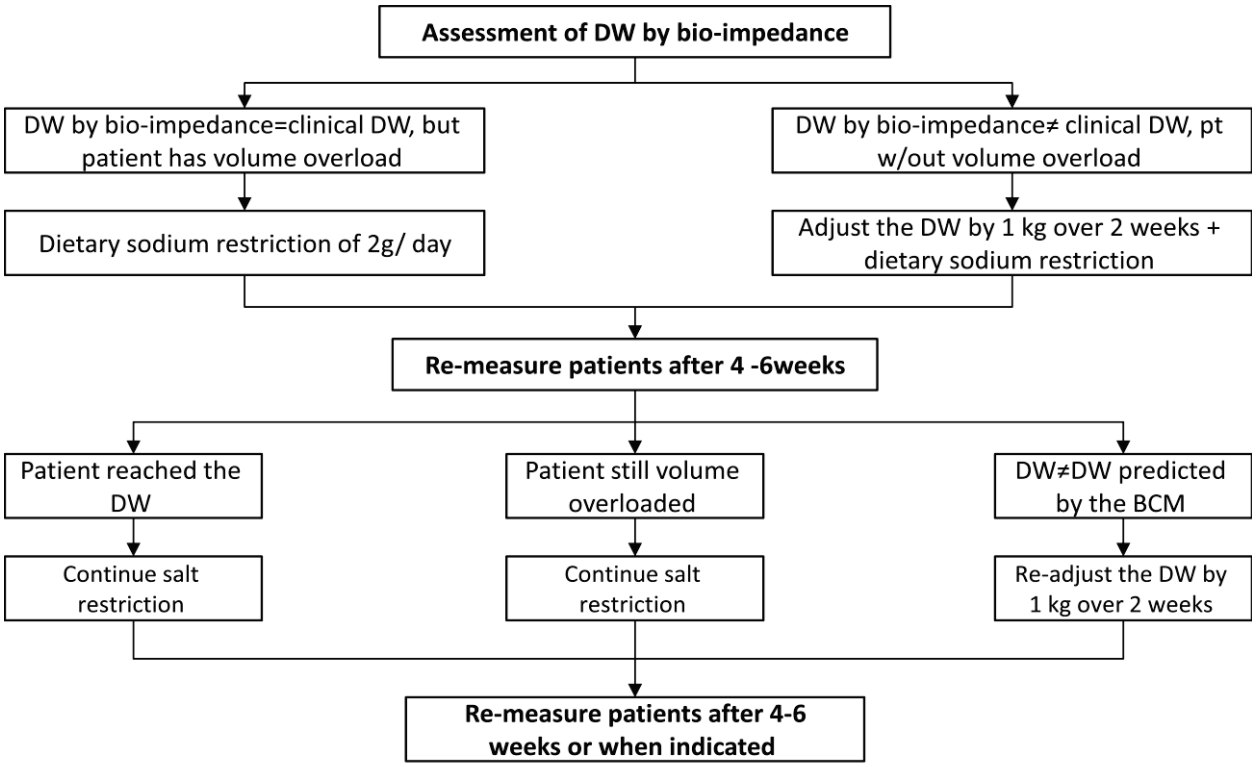
Chapter 5

5. Future directions

5.1. Volume management protocol

Towards volume control protocol, we developed a multifactorial intervention for volume control. This intervention failed as a study as we could not have a control period followed by an intervention period to compare with; however, it would be useful as a volume management protocol for volume overloaded patients. Our protocol includes dry weight assessment and adjustment through regular bio-impedance measurements every 4-6 weeks, and dietary sodium restriction of 2g/day. Gradual adjustment of DW will be done according to bio-impedance assessment (figure 5.1). Dietary sodium restriction will be done through educational tools about sodium intake and food labels, feedback about sodium intake will be given to the patients through their interdialytic weight gains. For patients with frequent IH, sodium profiling and /or cold dialysate will be used. We will use a linear sodium profiling starting with 4mmol/L above the average of pre-dialysis plasma sodium concentration for 4 previous HD sessions and ending by 4mmol/L below this average. Patients will be followed up by bio-impedance measurements for continuous volume assessment. Blood pressure will be assessed for each dialysis session to determine the effect of volume control on blood pressure.

Figure 5.1: Adjustment of dry weight (DW) using bio-impedance spectroscopy



5.2. Effect of volume overload on survival

There is strong evidence in the literature regarding the association between volume overload and higher mortality rates. Given the information obtained from our cohort, volume overload was present in about 50% of patients. We would like to follow up with a subgroup of volume overloaded patients to determine mortality rates, and if correction of volume overload would reduce mortality rate among this group or not. There is also a conflicting data regarding mortality rates among volume depleted HD patients. We would be interested to follow up with a subgroup of volume depleted patients as well to determine mortality rates.

5.3. Volume depletion and myocardial stunning

It is widely known that cardiovascular disease is the major cause of death in HD patients (158). It has long been suspected that myocardial ischemia may be precipitated by HD. HD treatments exert significant hemodynamic effects and are even complicated by episodes of intradialytic hypotension (159). Repeated episodes of myocardial ischemia are associated with irreversible loss of contractile function (160). A previous study reported that myocardial stunning was detected in 64% of their patients, and that myocardial stunning was associated with increased relative mortality after 12 months follow up (161). There is evidence that subclinical ischemia is precipitated by HD. Episodes of ischemia may have a potential role in the development of heart failure, and as a trigger for arrhythmias (162). Therefore reducing the impact of dialysis on the cardiovascular system would be a desirable therapeutic target (162). More understanding of myocardial stunning would provide methods to reduce cardiovascular mortality in HD patients (161). We would like to determine the prevalence of myocardial stunning in a subgroup of HD patients. We would also like to combine it with volume assessment to determine the effect of volume status on myocardial blood flow.

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