Thesis

HEMODYNAMICS STUDIES IN ISOLATED ULTRAFILTRATION AND HEMODIALYSIS

submitted by

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Graz, 11th June 2026

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Zusammenfassung

EINLEITUNG: Die intradialytische Hypotonie ist eine häufige und klinisch relevante Komplikation der Hämodialyse und geht mit einer erhöhten Mortalität einher. Die Pathophysiologie der Entstehung von intradialytische Hypotonie-Episoden ist komplex und wird von zahlreichen Faktoren beeinflusst. Die isolierte Ultrafiltration als Bestandteil der sequenziellen Dialyse (isolierte Ultrafiltration gefolgt von Hämodialyse) wurde als effektive präventive Behandlungsstrategie zur Verbesserung der hämodynamischen Stabilität empfohlen. Die Evidenz für dieses Therapieform ist jedoch begrenzt und basiert größtenteils auf älteren Studien. Die ISO-UF-Studie wurde konzipiert, um hämodynamische Reaktionen während der sequenziellen Dialyse mit jenen während der Hämodialyse zu vergleichen. Ziel dieser Arbeit ist die Erfassung von hämodynamischen Parametern, um ein verbessertes Verständnis und Management der intradialytischen Hypotonie während der Hämodialyse zu ermöglichen.

METHODEN: Die ISO-UF-Studie ist eine monozentrische, randomisiert, kontrollierte, Crossover-Studie mit zwei Behandlungsarmen und zwei Studienperioden. Die Patienten:innen erhielten standardisierte Behandlungsprotokolle während der Dialysesitzung zur mid-weed Hämodialyse, mit einem Crossover nach insgesamt vier Wochen. In Protokoll 1 erhielten die Patienten:innen in der ersten Hälfte der Sitzung eine isolierte Ultrafiltration, gefolgt von Hämodialyse, während in Protokoll 2 während der gesamten Sitzung eine Hämodialyse durchgeführt wurde. Hämodynamische Parameter einschließlich totalem peripheren Widerstandsindex, Herzleistungsindex, mittlerem arteriellem Blutdruck und systolischem Blutdruck wurden mittels nichtinvasiver Bioimpedanz-Kardiographie (NICaS Medical, Israel) vor, während und nach der Dialysebehandlung in 20-minütigen Intervallen erfasst.

ERGEBNISSE: In dieser Diplomarbeit werden präliminäre Ergebnisse der ISO-UF Studie besprochen. Insgesamt wurden acht Patientinnen und Patienten in die vorläufige statistische Analyse eingeschlossen, mit einer gleichmäßigen Verteilung

von Männern und Frauen. Die Randomisierung erfolgte gleichmäßig auf beide Sequenzen. Sieben Patientinnen und Patienten absolvierten jeweils vier Behandlungssitzungen pro Protokoll, während eine Person eine verlängerte Studienphase mit acht Sitzungen pro Protokoll durchlief. Für jede Person wurden behandlungsspezifische Mittelwerte berechnet und die Ergebnisse deskriptiv ausgewertet. Zwischen den beiden Behandlungsmodalitäten zeigten sich nur minimale Unterschiede im systolischen Blutdruck (relative Änderung: 1,3 %), im mittleren arteriellen Blutdruck (relative Änderung: 1,4 %), im totalen peripheren Widerstandsindex (relative Änderung: 5,6 %) sowie im Herzleistungsindex (relative Änderung: 5,4 %). Die Inzidenz der intradialytischen Hypotonie war in beiden Behandlungsmodalitäten vergleichbar und trat in 23,6 % der konventionellen Dialysesitzungen sowie in 29,2 % der sequenziellen Dialysesitzungen auf.

DISKUSSION: In dieser vorläufigen Analyse zeigte die sequenzielle Dialyse keine überlegene hämodynamische Stabilität bezüglich des totalen peripheren Widerstandes im Vergleich zur Hämodialyse. Somit ergibt sich aus den bisherigen Ergebnissen kein Hinweis auf eine Überlegenheit der sequenziellen Dialyse hinsichtlich der Hämodynamik insgesamt. Einschränkungen bestehen in der vorläufigen Natur der Daten, da bislang lediglich eine deskriptive Analyse vorliegt. Dennoch sollten diese vielversprechenden ersten Ergebnisse in Studien mit größerer Stichprobe und inferenzstatistischer Auswertung weiter untersucht werden, um mögliche Unterschiede zu identifizieren und deren Bedeutung für die klinische Praxis zu bewerten.

Abstract

INTRODUCTION: Intradialytic hypotension is a frequent and clinically relevant complication in hemodialysis and is associated with increased mortality. The pathophysiology behind the development of intradialytic hypotension episodes is complex and is influenced by multiple factors. Isolated ultrafiltration as part of sequential dialysis (isolated ultrafiltration followed by hemodialysis) has been proposed as an effective preventive treatment modality to improve hemodynamic stability, however, evidence supporting this approach remains limited and is largely based on older studies. The ISO-UF study is designed to compare hemodynamic responses during sequential dialysis with those observed during hemodialysis. This thesis aims to provide accurate assessment of key hemodynamic parameters, thus facilitating improved understanding and management of intradialytic hypotension during dialysis.

METHODS: The ISO-UF study is a randomized, controlled, crossover, two treatments, two period single center study. Patients underwent standardized treatment protocols during the mid-week dialysis session with crossover after four weeks. In protocol 1, patients receivied isolated ultrafiltration for the first half of the session followed by hemodialysis, whereas in protocol 2, hemodialysis was performed for the entire session. Hemodynamic parameters including total peripheral resistance index, cardiac power index, mean arterial blood pressure and systolic blood pressure were monitored by using non-invasive bioimpednace cardiography (NICaS Medical, Israel) before, after and during dialysis treatment at 20-minutes intervals.

RESULTS: A total of eight patients were included in the final statical analyses, with an equal distribution of male and female participants. Patients were randomized evenly in both sequences. Seven patients underwent four treatment sessions per protocol, while one patient completed an extended study period with eight sessions per protocol. Treatment-specific mean values were calculated for each patient, and results were analyzed descriptively. Minimal differences were observed in systolic blood pressure (relative change: 1,3%), mean arterial blood pressure (relative

change: 1,4%, total peripheral resistance index (relative change: 5,6%) and cardiac power index (relative change: 5,4%) between the two treatment modalities. The incidence of intradialytic hypotension was comparable between both treatment modalities, occurring in 23.6% of hemodialysis and 29.2% of sequential dialysis sessions.

DISCUSSION: In this preliminary analysis, sequential dialysis did not demonstrate superior hemodynamic stability regarding total peripheral resistance compared with hemodialysis. Thus, with these preliminary results, there seems to be no superiority of sequential dialysis in the incidence of intradialytic hypotension or hemodynamics overall. Limitations include the preliminary nature of the data with so far only descriptive analysis available. Nevertheless, this promising first descriptive analysis should be further investigated with an increase in sample size and statistical analysis to potentially identify a possible difference and evaluate implications for everyday patients.

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List of abbreviations

ADH	antidiuretic hormone
AFO	absolute fluid overload
AKI	acute kidney injury
AVP	arginin vasopressin
CKD	chronic kidney disease
CO	cardiac output
COP	colloid osmotic pressure
CP	cardia power
CPI	cardiac power index
CVP	central venous pressure
dCa	dialysate calcium concertation
dNa	dialysate sodium concentration
ECG	electrocardiography
eGFR	estimated glomerular filtration rate
ESRD	end stage renal disease
HD	hemodialysis
HDF	hemodiafiltration
HF	hemofiltration
HF	hemofiltration
IDH	intradialytic hypotension
ISO-UF	isolated ultrafiltration
KDIGO	Kidney Disease: Improving Global Outcomes
KT	kidney transplantation
MAP	mean arterial pressure
PD	peritoneal dialysis
PRR	plasma refilling rate
RC	relative change
RRT	renal replacement therapy
SBP	systolic blood pressure
SV	stroke volume

SVR	systemic vascular resistance
TBW	total body water
TPR	total peripheral resistance
TPRI	total peripheral resistance index
UFR	ultrafiltration rate

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1 Introduction

1.1 Chronic kidney disease

Chronic Kidney Disease (CKD) is a frequent medical condition characterized by the progressive and irreversible loss of the kidney function associated with structural changes of the nephrons. The incidence and prevalence differ across regions and are mainly influenced by ethnicity and social determinates of health. However, after taking these differences into account the prevalence is estimated to be around 11% in economically developed countries. CKD has heterogeneous causes, the most common one is diabetic kidney disease. Other causes leading to CKD include the different subtypes of glomerulonephritis, underlying genetic diseases, anatomic pathologies and others (1).

Early diagnosis is essential to stop the progression and preserve remaining kidney function. CKD is defined by a decrease of the estimated glomerular filtration rate (eGFR) below 60 mL/min per 1,73m^2 or the presence of markers for kidney damage for at least 3 months, most commonly defined by the presence of albuminuria. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines therefore created a five-stage classification based on eGFR and the degree of albumin in the urine. This classification, shown in Figure 1 primarily serves to assess the risk for cardiovascular diseases (2).

Since the kidneys have multiple exocrine and endocrine functions, the gradual loss of function is accompanied by several comorbidities like hypertension, anemia and mineral bone disorder (2,3).

KDIGO: Prognosis of CKD by GFR and albuminuria categories				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

Figure 1: Stages of albuminuria based on Albumin-creatinine ratio and stages of CKD based on eGFR
adopted from KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (4)

1.2 End-stage renal disease

The progression of CKD could lead to a terminal condition called end stage renal disease (ESRD). This occurs when the GFR reaches a level lower than 15 ml/min per 1,73m2. In this stage, the kidneys suffered severe irreversible damage which leads to a further increase in cardiovascular mortality and other complications due to alterations in fluid and electrolyte balance, acid-base system and clearance of toxins. Due to these changes, patients frequently need renal replacement therapy to help balance those systems and ensure survival (1,5).

1.3 Uremic toxins

Patients suffering from CKD with decreasing renal function are not capable to efficiently remove solutes which than progressively accumulate in the body and are contributing to the development of CKD and are responsible for cardiovascular

morbidity (6). These solutes are summarized as uremic toxins. At the moment according to the European Uremic Toxin Work Group there have been approximately 100 uremic toxins identified. Basically, uremic toxins can be classified in three categories, these are: free water-soluble low-molecular-weight solutes with molecular weight less than 500 Da, protein-bound solutes, and middle molecules with molecular weight more than 500 Da (7).

Protein-bound uremic toxins i.e. indoxyl sulfate and p-cresyl sulfate are the most challenging ones to remove from the circulation, since the clearance through hemodialysis (HD) is limited due their binding to the plasma proteins. They make up approximately 25% of the identified uremic toxins. In contrast to forementioned category free water-soluble low-molecular-weight solutes such as urea, ammonia and uric acid could be removed easily with conventional HD strategies. Middle molecules including especially cytokines and β2-microglubline require advanced HD techniques like the application of high-flux membranes. Furthermore, there can distinguished between endogenous and exogenous uremic toxins. Endogenous uremic toxins are the product of the metabolism, while exogenous uremic toxins are mainly derived from the chronic inflammation and gut-dysbiosis which are accompanying symptoms of CKD (7,8).

1.4 Fluid overload

Fluid overload is a common complication among patients with CKD, as declining renal function leads to progressive fluid accumulation within the tissues, thereby contributing to an increased risk of cardiovascular morbidity and mortality. Accurate assessment of fluid status is essential for optimizing the ultrafiltration volume during HD treatment. However, the classification of fluid overload is not standardized and varies between studies. Siriopol et al. proposed a three-stage classification based on absolute fluid overload (AFO). Patients were categorized as normovolemic with an AFO between −1.1 and +1.1 L, fluid depleted with an AFO < −1.1 L, moderately fluid overloaded with an AFO > +1.1 but < +2.5 L, and severely fluid overloaded with an AFO > +2.5 L (9).

1.5 Renal replacement therapy

When the residual kidney function is insufficient to ensure survival, renal replacement therapy (RRT) must be initiated. Based on the clinical situation and the

patients adherence, different kind of RRTs are available for ESRD patients. There are intra- and extracorporeal techniques. Additionally, extracorporeal techniques can be divided further into intermittently or continuously. Kidney transplantation (KT) is considered as unique and optimal treatment alternative to replace the renal function with a higher quality of life compared to the intra- and extracorporeal techniques (10).

1.5.1 Extracorporeal RRT

Extracorporeal RRT, i.e. HD include a variety of different approaches suitable both for acute kidney injury (AKI) and for ESRD caused by CKD. In all cases the selection of the most suitable technique is based on a clinical decision. For AKI particularly in clinically unstable patients with severe hypervolemia a continuous therapy is preferred, where the patient is treated continuously commonly for a period of several days to a few weeks. For ERSD on the other hand, there is a possibility to use these therapies discontinuously, e.g. three or four times a week. The treatment frequency is mainly depending on the degree of the residual kidney function. Currently HD, hemofiltration (HF), hemodiafiltration (HDF) are commonly available in both continuous and discontinuous modalities (11).

1.5.2 Peritoneal dialysis

Peritoneal dialysis (PD) is a modality of intracorporeal renal replacement therapy. It is based on the infusion of a sterile hyperosmolar solution through a specific catheter, which drains into the peritoneal cavity, thus allowing the removal of fluid by osmosis and solutes by diffusion, while the capillaries of the peritoneum serve as the semipermeable exchange membrane. The infusion and removal of the solution can be performed automatically or manually. PD is an excellent alternative therapeutic modality based on shared-decision making, however it requires engagement and cognitive fitness of the patients as well as the implementation of effectively structured dialysis programs (12,13).

1.5.3 Kidney transplantation

KT represents the ideal long-term therapeutic strategy for patients suffering from ESRD. It is associated with longer survival and better quality of life for the patients,

while at the same time reducing costs for the health system. However, to avoid acute graft rejection, maintenance immunosuppressive therapy is necessary (14,15).

1.6 Physical background of HD

The aim of extracorporeal renal-replacement therapy is to reestablish the homoeostasis of the body by removing solutes primarily electrolytes and toxins by diffusion or convection and balance the volume status by removing fluid through ultrafiltration (11,16).

1.6.1 Diffusion

Diffusion is a physical process which is characterized by the movement of molecules across a semipermeable membrane driven by a concentration gradient generated between two compartments with different concentrations. This results in solute movement from the more concentrated compartment to a less concentrated compartment. In a physical context it can be described by the Law of Fick, which suggest that the diffusive flux is higher for small molecules. Therefore, diffusion is mostly responsible for the clearance of electrolytes and small toxins like urea (11).

1.6.2 Ultrafiltration

Ultrafiltration occurs when plasma water without solutes and colloids is transported through a semipermeable membrane by applying a pressure gradient. During dialysis the transmembrane pressure is generated between blood and dialysate compartment. The rate of ultrafiltration is mainly influenced by the intrinsic properties of the dialysis membrane, which acts as a semipermeable membrane, and by the magnitude of the pressure gradient along the filter (11,16).

1.6.3 Convection

Convection is also relying on the application of pressure across a semipermeable membrane, however in addition to fluid it allows solutes to cross the membrane which is knows a solvent drag. The concentration gradient of the solutes is negligible, since convection exclusively depends on the transmembrane pressure and the pore size of the filter. Convection allows the removal of solutes of higher molecular weight compared to diffusion (11,16).

1.7 Modalities of extracorporeal renal-replacement therapy

Combining the aforementioned physical phenomena results in different modalities of extracorporeal renal-replacement therapies all with the common objective to efficiently imitate kidney function by considering the respective clinical situation.

1.7.1 Isolated ultrafiltration

During isolated ultrafiltration (ISO-UF) the target of the treatment is to remove excessive fluid without clearance of solutes. It is achieved by exclusively applying convection, however without the necessity of administering replacement fluid. As mentioned above the rate of ultrafiltration is directly influenced by the transmembrane pressure gradient and the intrinsic properties of the filter. In this case a filter with high water permeability is preferred, expressed as a high ultrafiltration coefficient. A key feature of ISO-UF is the fact that without solute clearance the serum osmolarity remains constant. The possible benefits of ISO-UF will be discussed in detail throughout (17).

1.7.2 HF

HF functions in a manner similar to ISO-UF, since it is also based on an exclusively convective transport along a filter with high ultrafiltration coefficient, however the transmembrane pressure is much higher than in ISO-UF. This results in more fluid removal accompanied by the removal of mostly larger solutes, which makes the administration of sterile replacement fluid necessary. Two modalities exist to administer replacement fluid, either at the filter inlet (pre-filter) or at the filter outlet (post-filter) (11,18).

1.7.3 HD

The principle of HD, the most widely use technique, is based on diffusion along the semipermeable membrane as well as fluid removal via convection. During HD, the dialysate flows in the dialyzer in a countercurrent direction relative to the blood flow within separate extracorporeal circuits. Solute clearance results from the concentration gradient originating from the concentration difference between dialysate and blood. The diffusion rate is influenced by the rate of blood and dialysate flow as well as the surface area and pore size of the filter. Based on the pore size one can differentiate between low-flux, high-flux and medium cut off

membranes. Low-flux filters have a low molecular weight retention cut-off, making them suitable for the removal of small solutes like urea or creatinine but limited in clearance of middle molecules. In contrast high-flux filters enable the removal of larger molecules such β_2-microglobulin. Medium cut off membranes are the most advanced membranes and enable a higher clearance of large middle molecules. Which membrane to use for an individual patient depends on clinical characteristics as well as socioeconomic factors. In general, however, high-flux membranes are usually more beneficial, as Oshvandi et al. have suggested an association with improved quality of life in HD patients. (11,16,19,20).

1.7.4 HDF

Hemodiafiltration is a combination HD and HF, therefore the solute clearance relies on both diffusion and convection. High-flux membranes are considered a prerequisite with the aim to control solute levels across a wide range of molecular weights, as well as fluid balance. Since the volume of ultrafiltrate largely exceeds the amount of fluid that should be eliminated from the patient, the admission of sterile, non-pyrogenic replacement fluid is the crucial point of the treatment. In analogy to HF discussed above the admission of the replacement fluid can occur either at the filter inlet (pre-filter) or at the filter outlet (post-filter). Both modalities have their own pros and cons, however, post-filter replacement is currently preferred (11,16,20).

1.8 Hemodynamic regulation during HD

Each of the formerly described modalities of extracorporeal renal-replacement therapy are associated with acute changes in the fluid and electrolyte balance of the body, which has significant sequelae for hemodynamics like blood pressure or cardiac output (CO). Effective circulating arterial blood volume, i.e. adequate organ perfusion is paramount to survival, does a number of mechanisms aim to maintain hemodynamic stability.

1.8.1 Short term blood pressure regulation

Stable blood pressure must be maintained to ensure proper organ perfusion. The regulation can be divided into short- and long-term regulatory mechanism. However, considering the situation for patients with ESRD the long-term regulatory

mechanism serves a limited role, since due to the restricted kidney function many patients cannot regulate the blood pressure through active fluid retention and excretion sufficiently (21). Therefore the role of the baroreceptor reflex on the arterial side and role of the venous capacitance on the venous side are of greater importance (22).

Most commonly the term mean arterial pressure (MAP) is used estimate the time weighted average blood pressure, which is determined by the CO, the systemic vascular resistance (SVR) and central venous pressure (CVP). The relationship of these determinants can be expressed in the following equation 1:

$$MAP = (CO \times SVR) + CVP \quad (23)$$

Equation 1: Equation for calculation of MAP derived from systemic circulation relationship
MAP: mean arterial pressure, CO: cardiac output, SVR: systemic vascular resistance, CVP: central venous pressure

This equation indicates that fall in the MAP can be either compensated by increasing CO or by increasing SVR by inducing vasoconstriction on the arterial vessels.

It should be noted that that the compensatory short-term mechanisms observed during intradialytic hemodynamic instability are quite similar to those observed during an acute hemorrhage (24).

1.8.2 Arterial baroreceptor reflex

The key player responsible for a stable arterial blood pressure is the arterial baroreceptor reflex, which is a negative feedback loop and consists of an afferent and efferent branch. Part of the afferent branch are the specialized pressure receptors localized in the carotid sinuses in the aortic arc and at the bifurcation of the internal and external carotid arteries. When the registered MAP decreases below a defined threshold, the efferent branch induces several compensatory mechanisms such as directly increasing sympathetic activity. The activation of the sympathetic nervous system increases heart rate and the myocardial contractility leading to a rise in CO. Furthermore, the sympathetic effect on small arterial vessels and arterioles results in vasoconstriction which elevates the SVR (23).

1.8.3 Venous capacitance vessels

Approximately 70-80% of the blood volume is stored in the venous system in so-called capacitance vessels. Blood in capacitance vessel is referred as an

unstressed volume mostly localized in the skin and gastrointestinal system. Mobilizing this volume back to the circulation can significantly increase the venous return to the heart. According to the mechanism of Frank-Starling the increase in venous return positively influences the CO. During the activation of the sympathetic nervous system caused by a hypotensive episode there is evidence that contraction of the venous vessels increases the re-mobilization of unstressed volume (25,26).
A significantly more important effect is the De-Jager-Krogh phenomenon which describe the relationship between arterial conductance and the mobilization of unstressed venous volume. A high arteriolar conductance allows the arterial pressure to be transmitted to the veins through the capillaries, resulting in a venous distension and enlarging venous capacity. The arteriolar vasoconstriction as part of the arterial baroreceptor reflex reduces arteriolar conductance consequently reducing venous capacity and promote the centralization of unstressed volume, which is beneficial during hypotensive episodes (27).

1.8.4 Hormonal regulation

Arginine vasopressin (AVP) also called antidiuretic hormone (ADH) is a nonapeptide produced in the magnocellular neurons of both paraventricular nucleus and the supraventricular nucleus of the hypothalamus. AVP has a fundamental function both in the osmo- a blood pressure regulation. Secretion can occur as a consequence of both osmotic and non-osmotic stimuli. The osmoregulation is achieved through the V2R receptors, which facilitates the insertion of aquaporins in the distal tubules of the nephrons and mainly the collector tubules when a high osmolality is detected by the osmoreceptors in the hypothalamus. The inserted aquaporins allow the reabsorption of water from the tubules, a then consequently decreasing the osmolality (28).
The non-osmotic stimuli for AVP secretion are hypovolemia and hypotension which are sensed through specialized baroreceptors in the supraoptic and paraventricular nuclei of the hypothalamus (29). The secretion of AVP under these circumstances is likely to occur through the activation of the arterial baroreceptor reflex. The interaction with the V1aR receptors on the vascular smooth muscle cells leads to arterial vasoconstriction (30).

Another significant point is the fact, that effect through V2R receptor in ESRD patients is not relevant due to the underlying restriction of the renal function (31).

1.9 Plasma osmolality

Osmolality can be defined as the number of osmoles of solute per kilogram of solvent. The main component of the blood plasma which determine the plasma osmolality are sodium, urea and glucose. The plasma osmolality can be approximated using the equation 2:

$$Calculated\ plasma\ osmolality\left(\frac{mOsm}{kg}\right) = 2 \times Plasma\ Sodium\left(\frac{mmol}{L}\right) + \frac{Plasma\ Urea\ Nitrogen\ \left(\frac{mg}{dL}\right)}{2.8} + \frac{Plasma\ Glucose\ \left(\frac{mg}{dL}\right)}{18} \quad (28)$$

Equation 2: Equation for the calculation of the plasma osmolality

The total body water is allocated either to the extracellular or the intracellular space, therefore changes in the plasma osmolality can induce the shift of water between the extracellular and intracellular spaces through osmotic forces (33).

1.10 Intradialytic hypotension

Intradialytic hypotension (IDH) is the most common complication during extracorporeal renal-replacement therapy and is a significant factor for the increased mortality among ESRD patients (34). The incidence of IDH varies across the literature but is typically estimated between 10% and 30% mainly depending on used definition of IDH (34–36).

For this reason, the main aspect of this thesis is to discuss factors and challenges leading to intradialytic hypotension and to identify possible countermeasures to lower its incidence and the associated co-morbidities (35).

1.10.1 Definitions

Currently there is no consensus definition for IDH, since different guidelines and authors use different parameters for defining the presence of an intradialytic hypotensive episode. Either a decrease in systolic blood pressure (SBP) or in MAP, defined by different cut-offs, is used. Additionally, the presence of specific symptoms or the requirement for intervention may be included in the definitions. A selection of the most common definitions is summarized below in Table 1 (37).

Definitions for IDH	Decrease in SBP (mmHg)	Nadir in SBP (mmHg)	Decrease in MAP (mmHg)	Need for symptoms or intervention	Year of publication
KDOQI Clinical Practice Guidelines (38)	≥ 20	-	≥ 10	Symptoms	2005
UK Renal Association Guidelines (39)	Any	-	Any	Immediate intervention	2011
European Best Practice Guidelines (40)	≥ 20	-	≥ 10	Symptoms and intervention	2007
Japanese Society of Dialysis Therapy Guidelines (41)	≥ 30	-	≥ 10	Symptoms	2012
Chou et al., USA (42)	-	< 90	-	-	2018
Sands et al., USA (43)	≥ 30 to a level of < 90 mmHg	< 90	-	-	2014

Table 1: Definitions for intradialytic hypotension

1.10.2 Mortality and co-morbidities

There is a strong association between IDH and cardiovascular mortality and morbidity (42). During the hypotensive episode, there is transient hypoperfusion of vital organs such as the myocardium, brain, gastrointestinal system or the retina. The most notable instance is the myocardial stunning with a significant contribution to cardiovascular mortality. This phenomenon leads to transient regional wall motion abnormalities of the myocardium promoting the development of persistent systolic dysfunction. Furthermore, the intradialytic cerebral ischemia caused by the hypotensive episode in long term could be responsible for the increased 5 years risk of new-onset dementia (44,45).

1.11 Pathogenesis of intradialytic hypotension

The pathogenesis of IDH is multifactorial and not completely understood. The focus is on the impaired compensatory reaction of the cardiovascular system during the hypotensive episode (27).

1.11.1 Ultrafiltration rate and plasma refilling rate

One of the primary aims of dialysis is to remove excess fluid that accumulated due to the impaired renal function in different compartments of the body. A strict fluid restriction regimen is crucial in the interval between dialysis sessions. If the interdialytic weight gain is lower, less ultrafiltration volume is needed to keep a preferably euvolemic state. High ultrafiltration volumes are associated with a high incidence of IDH, because once the ultrafiltration rate (UFR) exceeds the plasma refilling rate (PRR) it is causing relative hypovolemia similar to acute hemorrhage (46,47). This leads to reduced cardiac preload and, consequently, decreased CO which promotes hemodynamic instability. This phenomenon occurs more likely in the latter phase of the treatment session, when most of the excess fluid is already removed and the patient is near the estimated target weight. In this phase the PRR is significantly decreased (48–52).

PRR is also influenced by plasma oncotic pressure, which is primarily determined by blood albumin concentration. Consequently, low albumin levels constitute a risk factor for the development of IDH. However, clinical studies have shown that administration of albumin, as compared with saline, does not offer superior efficacy in the treatment of IDH (50).

Several strategies exist for reducing the ultrafiltration rate, such as increasing dialysis time or dialysis frequency along with minimizing interdialytic weight gain by a more stringent fluid and salt restriction (45).

1.11.2 Transient osmotic gradients

Although the PRR tends to be higher at the beginning of the dialysis session due to the hyperhydration, the rapid clearance of osmotically active solutes driven by the high concentration gradient between blood and dialysate promotes the development of transient osmotic gradients between the intracellular and extracellular compartments. The transient osmotic gradient shifts fluid from the extracellular space into intracellular space and thereby reduces the effective circulating volume. The relatively high PRR thus will be reduced through this phenomenon (50,53).

Increasing the dialysate sodium concentration (dNa) could be beneficial since it enhances the shift in the opposite direction. Further a higher dNa would consequently increase the plasma osmolality, which would stimulate the secretion

of AVP, a potent vasoconstriction, contributing to a better hemodynamic stability. Some authors concluded that a higher dNa would significantly reduce the secretion of nitric oxide, a potent vasodilatation and would increase the activity of the sympathetic nervous system. However, a high dNa is clearly associated with higher interdialytic weight gain, which on the other hand increases the amount of ultrafiltration volume needed (44,45,54,55).

1.11.3 Autonomic dysfunction

Autonomous dysfunction is highly prevalent in IDH prone patients (56,57). Uremic toxins result in impairment of both the sympathetic and parasympathetic nervous system which causes an impairment of mechanisms that aim to compensate for the fluid shift during dialysis. The main manifestations of the autonomic dysfunction are the reduced heart rate variability, the lack of compensatory arteriolar vasoconstriction and the impaired release of AVP (31,58).

The lack of compensatory arteriolar vasoconstriction will increase venous pooling and reduce cardiac preload through the DeJager-Krogh phenomenon. Due to these changes, many patients with AD suffer from IDH repeatedly (59).

1.11.4 Food intake during dialysis

Oral food intake during dialysis can activate parasympathetic signalling and blood also shifts to the splanchnic regions, causing the redistribution of the effective blood volume (60).

1.11.5 Calcium dynamics

An increased calcium concentration during dialysis has been shown to be beneficial in hemodynamic stability and preservation of cardiac contractility and CO. Hence, dialysate calcium concentration (dCa) appears to influence the development of IDH. In order to prevent dialysis induced hypercalcemia most commonly a standard dCa of 1,25mmol/L is prescribed. (61,62)

An important aspect of dialysis is the correction of the acid-base status, mostly from an acidotic state toward the normal pH-range. A rapid correction, by applying high bicarbonate in the dialysate could potentially enhance the binding of calcium to albumin a thus lower the free ionized calcium concentration. This could potentially reduce myocardial contractility and thereby predispose to IDH (63,64).

1.12 Management of IDH

Goal of the therapy is to restore adequate blood pressure and to mitigate symptoms like cramps, dizziness and fatigue. (65)

1.12.1 Basic treatment measures

During an IDH episode, ultrafiltration should first be stopped and the patient placed in the Trendelenburg position (65,66).

1.12.2 Administration of plasma volume expander

Assuming the previously mentioned measures prove unsuccessful, the administration of intravenous fluid should be taken into account. Hypertonic saline solute could generate a transient osmotic gradient, which allows fluid to be mobilized from the extravascular space. In a comparable way albumin or mannitol increase the PRR. Albumin mostly acts through the elevation of colloid oncotic pressure, while mannitol is intervening similar to hypertonic saline through osmotic forces. However, authors concluded that albumin administration is not superior to hypertonic saline in treating IDH (37,66).

1.12.3 General preventive interventions

Since high ultrafiltration volumes and rates are mainly considered a risk factor for the development if IDH, the most elementary strategy is the reduction of the required amount of ultrafiltration volume, and particularly the UFR. This can be achieved through increasing the duration of an individual session or increasing dialysis frequency in general. These two strategies are mainly influencing the UFR, while salt and fluid restriction are preventing interdialytic weight gain and thus reducing the ultrafiltration volume needed (65).

Restricting food ingestion during treatment could be a protective measure, although it accounts for only a small fraction of IDH cases (37).

1.12.4 Implementation of ultrafiltration and sodium profiles

The relationship of UFR and PRR was discussed above. In routine clinical practice a constant ultrafiltration rate is prescribed during the whole treatment, however the initially high PRR at the beginning and a gradually lower PRR toward the end of the dialysis treatment session may render ultrafiltration-profiling advantageous.

Specifically, analogous to the physiological course of PRR, a higher UFR can be implemented at the beginning of the treatment at the time of maximal tissue hydration and reduced gradually or in a stepwise manner during the dialysis session as interstitial oedema lessens (53,67–70).

1.12.5 Cool dialysate temperature

During standard-temperature (36,5°C-37°C) dialysis, body temperature rises even though there is a net loss of energy to the extracorporeal system (71). This has a potential negative influence on cardiovascular response promoted through inferior vasoconstriction and therefore a greater need for a compensatory increase in CO. This necessary increase in CO often cannot be achieved due to preexisting cardiac disease. The results in IDH. It has been previously shown that by cooling the dialysate temperature (35,5°C) peripheral vasoconstriction improves, which stabilizes blood pressure and can prevent IDH from happening (72). Despite the discussed benefits, patients sometimes report discomfort due to the cold. Moreover, it has been reported that during cool dialysis the clearance of urea can be impaired, since cold can reduce the muscle perfusion, where urea is present in high concentrations. However, this theory was rejected, since in studies a post-dialysis urea rebound was not observed after cooled dialysis (73). Despite the promising physiological rationale and previously reported improvements in hemodynamic stability, evidence regarding the clinical benefit of cooler dialysate remains inconsistent. In the MyTemp trial evaluating individualized dialysate cooling based on pre-dialysis body temperature, no reduction in major adverse cardiovascular events, intradialytic hypotension, or intradialytic SBP decline was observed compared with standard-temperature dialysis. Furthermore, patients receiving cooler dialysate more frequently reported discomfort related to feeling cold during treatment. Interestingly, no significant benefit was observed even in patient subgroups considered at increased risk for IDH. These findings suggest that although cooler dialysate may exert favourable physiological effects, these do not necessarily translate into improved clinical outcomes (74).

1.12.6 ISO-UF and sequential dialysis

ISO-UF is a strategy for prevention of IDH, which is the subject of this thesis. The concept behind ISO-UF is to solely perform ultrafiltration without applying dialysate

(as is the case in HD) flow or substituting volume (as is the case in HF). Thereby purely a removal of excessive fluid will occur, without changing the electrolytes concentration or the osmolality. The rationale why this approach may confer more hemodynamic stability during treatment relies on several postulated benefits (75,76).

Sequential dialysis is recommended according to a KDIGO Controversies Conference as an alternative probably advantageous technique for fluid overloaded patients to improve hemodynamic stability during the HD treatment (77). It is the combination of ISO-UF with HD in the cases in a 1:1 ratio with respect to the treatment duration. The principle is to use ISO-UF in the first half of the treatment session with the aim of solely removing fluid without diffusive solute clearance, thereby minimizing changes in serum osmolality. In the second part of the treatment session HD is prescribed to correct electrolyte and acid-base balance and to remove uremic toxins (75).

1.12.7 Preventing the formation of transient osmotic gradients

In severely fluid overladed patients with interstitial oedema the application of relatively high ultrafiltration rates are inevitable to correct for the excess in total body water (TBW). As outlined earlier, due to the relatively high PRR, high UFRs are mostly well tolerated. However, rapid solute clearance leads to transient osmotic gradients, predominantly due to extracellular hypoosmolality, causing fluid shifts into the intracellular space that contribute to the development of IDH. ISO-UF during dialysis sessions would allow to overcome phases of high UFR without influencing the serum osmolality and thus preventing the formation of transient osmotic gradient, while at the same time taking advantage of the high PRR to rapidly remove volume (32,78).

1.12.8 AVP secretion

Several studies discuss a potential role of AVP in the development of IDH. As mentioned above the main stimuli for secretion of vasopressin are hyperosmolality, hypovolemia and hypotonus. During ISO-UF plasma water and solutes are removed proportionally resulting in a stable osmolality. Consequently, the lack of decrease in serum osmolality prevents a drop in AVP allowing vascular tone to remain stable.

Eventually, the role of AVP remains unclear since the determination of AVP levels is hampered by several factors such as, instability due to low half-life, a potential elimination during dialysis or the inconsistent assessment of its prohormone, copeptin (30,79–81).

1.12.9 Promoting negative thermal balance

In contrast to HD, during ISO-UF a significantly more negative value of energy transfer from the extracorporeal system to the patient was described. This implies a greater decrease in the body temperature during ISO-UF, which could potentially further contribute to the hypothesized higher hemodynamic stability, which is mainly achieved via vasocontraction of the peripheral blood vessels. (82).

1.13 Disadvantages of isolated ultrafiltration

1.13.1 Hemoconcentration

During ISO-UF diffusive removal does not occur, therefore only fluid and small non-protein-bound solutes can be removed through convective forces. Resulting from the loss of plasma water, however the plasma concentration of the uncleared solutes could slightly increase (83).

1.13.2 Ineffective delivery of the dialysis does

When ISO-UF is performed, one must consider that the effective correction of the electrolyte and acid-base status as well as the removal of uremic toxins through diffusion has to be achieved in less time than during HD. This is associated with a more rapid change of electrolytes concentrations. In particular, accelerated potassium removal may occur due to the use of lower dialysate potassium concentrations and the consequently higher serum-to-dialysate potassium gradient. This abrupt potassium shift could lead to the cardiac electrophysiological instability, promoting the occurrence of arrhythmias. (32,84).

2 Material und methods

2.1 Ethical statement

The study has been approved by the Ethics Committee of the Medical University of Graz (approval number 34-305 ex 21/22). This study has also been approved by the Austrian Federal Office for Safety in Health Care (BASG) according to EU regulation (EU) 2017/745, Article 74 (1).

2.2 Data management

After obtaining the written informed consent of each participant, patients are randomly assigned using the web-based system "Randomizer" (www.randomizer.at), developed by the Institute for Medical Informatics, Statistics, and Documentation at the Medical University of Graz. An unique ID was assigned to each participant in order to protect sensitive patient data.

2.3 Literature research

The literature research for this diploma thesis was performed during January 2025 to August 2025 using PubMed, ResearchGate and Google Scholar databases. In these databases the following keywords were used: IDH, sequential dialysis, ISO-UF, vasopressin-secretion during HD and cool dialysis. Additional literatures were identified through the reference lists of the cited papers. For further bibliographic research the database of the Library of the Medical University of Graz was used.

2.4 Study design

The data described and discussed in this thesis is part of the ISO-UF study, which is an ongoing randomized, controlled, two treatments, two period single center study in crossover design conducted by the Dialysis Department of the Division of Nephrology at the LKH-Univ. Klinikum Graz. Currently, ISO-UF is often used due to the assumption of better hemodynamic stability, but without good quality of evidence. For this reason, this study primarily aims to determine the hemodynamic response to ISO-UF followed by HD compared to HD alone in terms of the change of the total peripheral resistance. Secondary aims include to elucidate differences in incidence of IDH as well as characteristics of the intradialytic episodes in terms

of symptoms and dependence of co-medication with vasoactive substances. Consequently, additional cardiovascular parameters such as SBP and MAP and cardiac power index will also be determined. After a sample size calculation the enclosure of 32 patients is necessary to reach a power of 80% with a α of 5%. A Crossover design allows to compare each patient with themselves.

2.5 Study structure

The study was initiated in August 2023 and is currently divided in three major phases.

In the first phase, which took place from August 2023 to September 2023 a so-called pilot phase was initiated, with the aim to acquire expertise in bioimpedance cardiography measurements on discontinuous HD patients using the NiCAS device. After recruiting two patients, who fulfilled the inclusion criteria and were giving written consent, randomly chosen dialysis sessions were selected to perform the measurements. Both patients received their habitually arranged dialysis modality and dialysis prescription.

For the second phase, one patient was recruited to evaluate the approved study protocol, which will be described later, for feasibility. This phase occurred from October 2023 to December 2023.

After the second phase a revision of the study protocol was necessary, which included the reduction of sessions and the introduction of intradialytic temperature measurements.

In the third phase the adapted study protocol was applied on nine more patients. Four patients were enrolled to the study from May 2024 to July 2024 and the rest from October 2024 to January 2025.

2.6 Patient population

Participants for the ISO-UF study were recruited by the clinicians of the Division of Nephrology at the LKH Univ. Klinikum Graz. They screened among all patients on maintenance HD in the division by applying the inclusion and exclusions criteria listed below in Table 2.

Inclusion criteria	Exclusion criteria
Written informed consent obtained	No informed consent obtained
At least 18 years of age	Patients with a pacemaker or implanted medical device preventing compliance with study regulations
End-stage kidney disease patient undergoing HD	Patients with recurrent severe hyperkalemia after the short interdialytic interval (K+ > 6.0 mmol/L, requiring > 2 hours of dialysis)
Dry weight stable for a minimum of one month	Women of childbearing age not using contraception
Interdialytic weight gain > 2 kg and < 4 kg in the short interdialytic interval	

Table 2: Inclusion and exclusion criteria

2.7 Study protocol and procedure

After obtaining informed consent and randomization during a run-in phase takes place during which the individual dry weight will be further reduced if tolerated during a maximum period of 3 weeks. Additionally, there will be bioimpedance spectroscopy measurements, using the BCM device (Fresenius Medical Care, Bad Homburg vor der Höhe, Germany). If the patient was already at their optimal dry weight and no more ultrafiltration was tolerated, this present weight was set as dry weight.

As mentioned above after the randomization the patients will be assigned to one of the two sequences.

Sequence A: protocol 1 followed by protocol 2

Sequence B: protocol 2 followed by protocol 1

During treatment protocol 1 patients will be treated after a short interdialytic interval (once a week) with 2 hours of ISO-UF, followed by HD for the remaining two hours of this dialysis session (sequential dialysis). This protocol will be followed for a total of four weeks.

During treatment protocol 2 patients will be treated with 4 hours of HD for a total of four weeks.

In case the duration of dialysis either exceeds or falls short of four hours, ISO-UF will be performed for half of the treatment time. The study was executed in cross over design after four weeks. Figure 2 summarizes the study protocol.

For the study dialysis sessions, the dialysis machine Fresenius 6008CAREsystem (Fresenius medical care, Bad Homburg vor der Höhe Germany) is used with the high flux membrane CorDiax 800. This device provides a variety of settings including standard HD but also the possibility to use ISO-UF.

During these sessions a standardized treatment will take place for all patients which includes a dialysis composition that is standardized to a dCa of 1.25 mmol/L, a dialysate bicarbonate of 30 mmol/L and a variable potassium concentration, depending on the patients' plasma potassium concentration. dNA will be 2 mmol/l higher than predialysis to achieve isonatraemic dialysis.
For this reason, prior to the start of the dialysis treatment full blood sodium and potassium were measured by point of care blood gas measurements via direct potentiometry.
In case of necessity dialysate potassium was adjusted during the treatment based on repeated arterial blood gas analysis.
The peripheral body temperature was assessed by auricular thermometers, and the dialysate temperature was set 1.0°C below. The measurement of the body temperature occurred before, at the middle and right after the dialysis treatment. In case of Protocol 1 it was crucial to set the dialysis temperature on the basis of measurement right before the switch to HD.
As stated in the inclusion criteria a minimum of 2 liter of ultrafiltration volume needed to be fulfilled. In case of sequential dialysis, the ultrafiltration volume was equally distributed.
The patients were at every study visit evaluated on potentially fulfilling any of the drop out criteria which are listed below in Table 3.

Drop-out criteria
The proband' withdrawal of his/her consent
violation of the study protocol
patients with changes of blood pressure medication which can affect the vascular tone within the study period (betablocker, calcium channel blockers or vasoactive substance such as minoxidil)

Table 3: Drop-out criteria

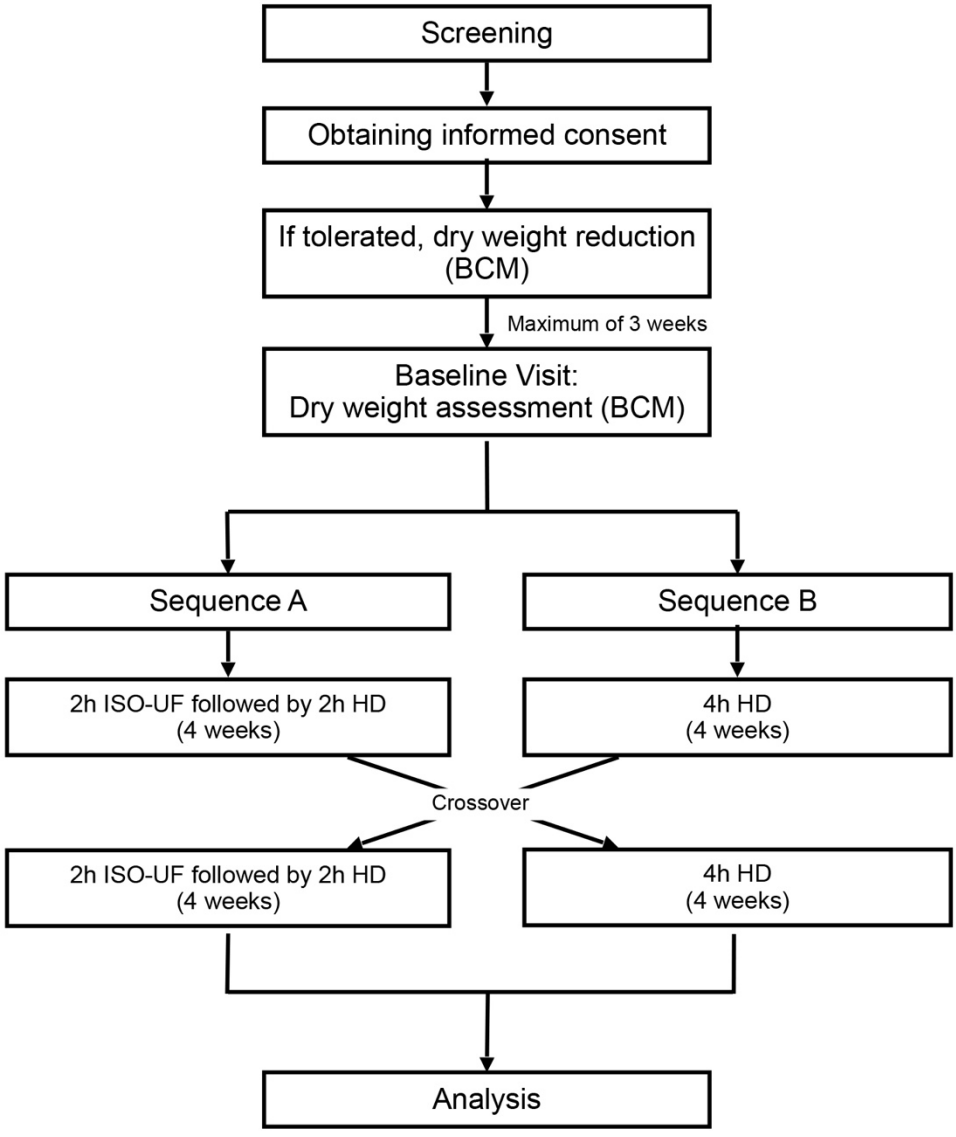

Figure 2: Overview of the study protocol
BCM: body composition monitoring, HD: hemodialysis, ISO-UF: isolated ultrafiltration

2.8 Cardiovascular monitoring

The NiCAS (NI-Medical, Israel), bioimpedance device was utilized to assess the hemodynamic response during the dialysis session. The measurements took place twice a week during the second phase and once a week during the third phase of the study. Basic anthropometric data of the patients must be input before each session manually. Bioimpedance/Resistance is captured by two electrodes that are connected to the patients at designated positions: Two electrode positionings are possible, either a wrist-contralateral ankle or a wrist-wrist positioning. For the most accurate measurements a wrist ankle positioning shown in Figures 3 and 4 is preferred. In case of an arteriovenous fistula the contralateral wrist should be used. The electrodes shown in Figures 5 and 6 were connected via cables to the device, which remained connected during the whole treatment in order to achieve a sufficient signal quality.

Figure 3.: Position of the wrist electrode

Figure 4.: Position of the ankle electrode

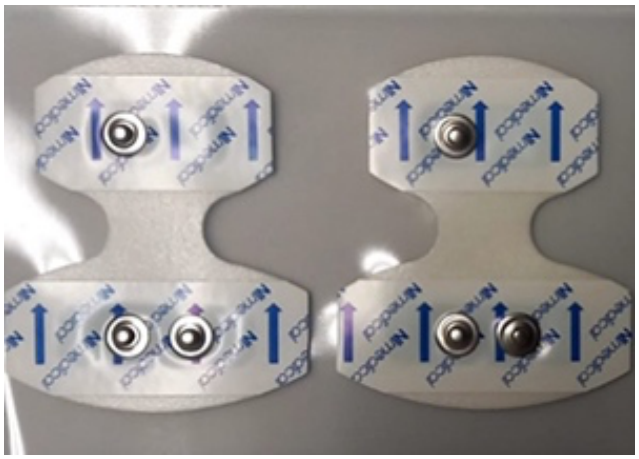

Figure 5.: Connection side of the electrodes

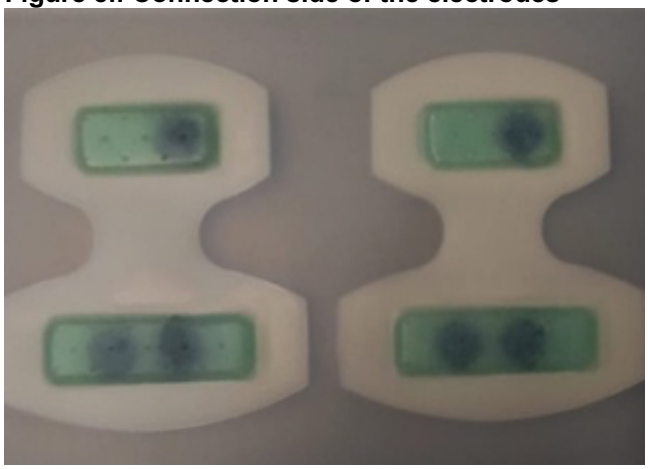

Figure 6.: Skin-contact side of the electrodes

NiCAS allowed to measure parameters directly and also to calculate parameters by using entered anthropometric additional data like the blood pressure and current ultrafiltration volume. Measured, entered and calculated parameters are shown in Table 4. Before each measurement the blood pressure was measured by using the oscillometric method and the ultrafiltration volume was obtained from the dialysis machine.

Hemodynamic measures were conducted via the NiCaS (NI Medical, Israel). Hereby, the stroke volume (SV) is measured by applying an alternating electrical current through the patient's body via sensors, one placed on the. The low electrical current is approximately 1,4mA with frequency of 30kHz. The relationship of voltage, resistance and electric current is described in Ohm's law (59).

$$Voltage\ (V) = Electric\ current\ (A) \times\ Resistance\ (Ohm)$$(85)

Equation 3: Ohm's law

Since the electric current is constant, any changes of the voltage must be due to the changes in the resistance. The pulsatile voltage waveform synchronized with the heartbeat is measured by the sensors and the corresponding resistance is calculated by using Ohm's law. SV is then calculated by Frinerman's formula, using the calculated beat-to-beat resistance changes (59).

$$SV = \left(\frac{dR}{R}\right) \times \rho \times \left(\frac{L^2}{Ri}\right) \times \frac{\alpha + \beta}{\beta} \times KW \times HF$$(59)

Equation 4: Frinerman's formula

dR: impedance change, R: basal resistance, ρ: blood electrical resistance, L: patient's height, Ri: basal resistance corrected for gender and age, KW: correction of weight according to ideal values, HF: hydratation factor, α+β: R-R wave interval, β: diastolic time interval

The SV is automatically calculated every 20s and is the average of three measurements obtained consecutively during 60 s of monitoring. Heart rate is assessed by a one channel electrocardiography. Systolic and diastolic blood pressure measurements are measured by the dialysis machine thus calculating MAP.

$$MAP = 2 \times \frac{SBP + DBP}{3}$$(74)

Equation 5: Formula for the calculation of MAP estimated from SBP and DBP

MAP: mean arterial pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure

Using these calculated parameters, CO, cardia power (CP) and the total peripheral resistance (TRP) can be estimated as well.

$$CO = SV \times HF$$(59,85,86)

Equation 6: Formula for the calculation of CO

CO: cardiac output, SV: stroke volume, HF: heart frequency

$$CP = CO \times MAP$$(59,85,86)

Equation 7: Formula for the calculation of CPI

CP: cardiac power, CO: cardiac output, MAP: mean arterial pressure

$$TPR = MAP/CO$$(59,85,86)

Equation 8: Formula for the calculation of TRP

TPR: total peripheral resistance, MAP: mean arterial pressure, CO: cardiac output

Ultimately the indices for CO, CP and TPR were estimated by dividing through the body surface area.

Entered parameters	Unit
SBP	mmHg
DBP	mmHg
Height	m
Pre-dialytic weight	kg
Ultrafiltration volume	L
Measured parameters	
HR	1/min
SV	mL
Calculated parameters	
TRP	dyn*s*cm^{-5}
UFR index	mL/hour/kg
MAP	mmHg
Cardiac index	L/min/m^2
CPI	W/m^2
TRPI	dyn*s*cm^{-5}* m^{-2}

Table 4: Parameters of the cardiovascular monitoring

For the measurement of cardiovascular responses, a strict protocol was applied including measurements before, after and during the dialysis treatment with an interval of 20 minutes. Each measurement required approximately two minutes, as recommended by the manufacturer. A stable one-channel EKG and pulse curve were indispensable for accurate measurement according to the NiCAS manual.

2.9 Documentation

A standardized dialysis protocol was used for every session as prescribed earlier. The individual measurements were saved via de NiCAS bioimpedance cardiograph. Incidences of IDH and associated clinical signs, therapeutic actions if needed, body temperature, ultrafiltration volume as well as session duration was documented on the dialysis protocol itself. Additionally, a standardized session form and a check list

for inclusion and exclusion criteria as well as for the correct machine settings was used to record every session individually. All documents were stored in individual folders for each patient. After the treatment a copy of the dialysis protocol was also placed in the patient study folder.

2.10 Laboratory analyses

Additionally, to the non-invasive measurement of the cardiovascular responses a laboratory analysis was executed before, in the middle and after the dialysis treatment. The collection of the blood samples were performed by the dialysis nursing staff using Lithium Heparin tubes (BD Vacutainer® Brand Tubes with Lithium-Heparin). The samples were sent immediately to the central lab of the LKH Univ. Klinikum Graz for analysis. Determined were Osmolality (mOsm/kg), Osmolar gap and Kt/V.

2.11 Statistical analysis

The statistical analysis includes exclusively descriptive statistics of the investigated parameters, which are TPRI, CPI, SBP and MAP. These data are presented as mean values with the corresponding standard deviation (SD) for normally distributed variables. All data were tested for normal distribution using the Shapiro-Wilk test. Due to the low number of included participants, it was decided to forgo inferential statistics. The descriptive statistical analysis and the figure illustration of the time course of the investigated parameters were performed by using Microsoft Excel.

3 Results

3.1 Participant flow

As for the analysis that is subject of this thesis, twelve patients were recruited as part of the ISO-UF study and were randomized in the two treatment arms. Of the 14 patients eight finished all study treatments. One patient was excluded due to his retraction of the written informed consent. Two patients had to be excluded due to repeated insufficient ultrafiltration volume after the run-in period and one patient had to be excluded due to frequent hyperkalemia. This patient was assigned to the sequential dialysis protocol and due the reduced time of diffusive clearance, the remove of excess potassium within only half of the usual dialysis time was deemed insufficient. The remaining 8 patients successfully completed all study sessions and were included in this analysis as shown in Figure 7.

The fulfilment of the minimum 2L ultrafiltration volume as stated in the inclusion criteria was a pivotal point for many of the study participants. The planned bioimpedance measurements were only performed when the inclusion criteria were met before an individual session. In a scenario where the inclusion criteria were not fulfilled the scheduled measurement was postponed and the study period for the affected study participant was extended.

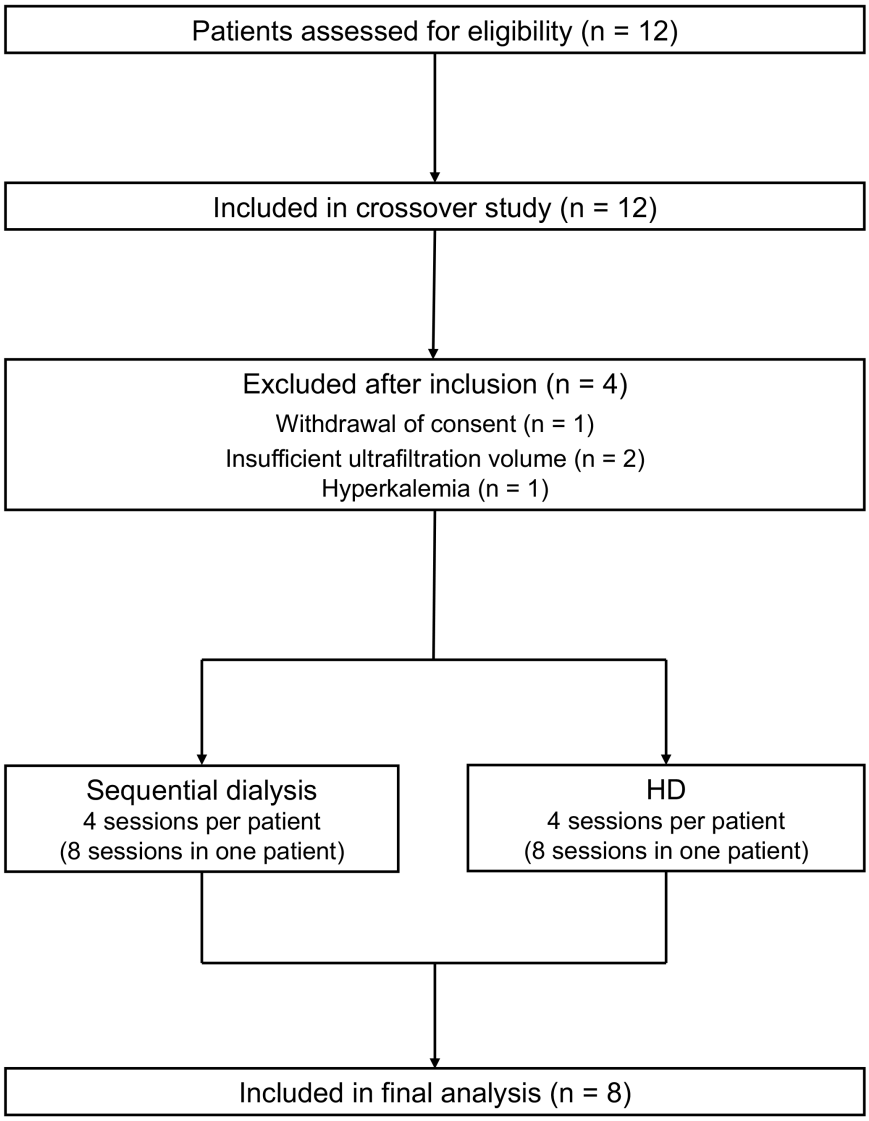

Figure 7: Flowchart of the participant flow

3.2 Baseline characteristics

After completion of multiple recruitment phases, and the above-mentioned drop-out of four patients, a total of eight patients were included in the analysis that is subject of the present thesis. The study population had a mean age of 68±8 years and 50% of the patients were male and 50% female. All patients were on maintenance HD before inclusion in the study with a mean dialysis vintage of 36±21 months. The types of vascular access used for the dialysis treatment were well balanced within

the study population. Fifty percent of the patients were dialyzed via a central venous catheter, while the remaining 50% were treated using an arteriovenous shunt. The underlying cause and renal disease leading to the initiation of dialysis were quite heterogenous across the included patients. The most common etiology was diabetic nephropathy which accounted for ESRD in two patients. Other etiologies included analgesic nephropathy, hepatorenal syndrome and polycystic kidney disease as well as not further classifiable cause of kidney failure. Clinically relevant comorbidities were present across all patients and included arterial hypertension in 88% of the patients, diabetes mellitus in 25% of the patients and heart failure as well as coronary artery disease in 38% of the patients. The antihypertensive medication of each study participant was also assessed, since this is likely to influence the hemodynamic responses. All patients, who were diagnosed with arterial hypertension already received an antihypertensive medication which predominantly included beta-blocker and diuretics in 88% of the patients and calcium channel blockers in 63% of the patients. For the performance of the bioimpedance measurements, additional electrodes were required, the positioning of them was distributed evenly. 50% of the patients carried the electrodes on their left wrist and right ankle, while 50% carried it in the opposite manner. All baseline characteristics can be found in Table 5.

Patient Characteristic (n=8)	*Value*
Mean age, years, (SD)	68 (8)
Male, n (%)	4 (50)
Female, n (%)	4 (50)
Mean dialysis vintage, months, (SD)	36 (21)
Vascular access n (%)	
Central venous catheter	4 (50)
Arteriovenous fistula	4 (50)
Electrode position n (%)	
Left wrist and right ankle	4 (50)
Right wrist and left ankle	4 (50)
Cause of ESRD n (%)	
Diabetic nephropathy	2 (25)
Analgesic nephropathy	1 (13)
Polycystic kidney disease	1 (13)
Unknown Etiology	2 (25)
Obstructive Uropathy	1 (13)
Postoperative AKI	1 (13)
Comorbidities n (%)	
Arterial Hypertension	7 (88)
Diabetes mellitus	2 (25)
Peripheral vascular disease	2 (25)
Heart failure	1 (13)
Coronary artery disease	3 (38)
Aortic stenosis	1 (13)
Antihypertensive medication n (%)	
Angiotensin-converting-enzyme inhibitors	1 (13)
Beta-blocker	7 (88)
Diuretics	7 (88)
Calcium channel blockers	5 (63)

Table 5: Baseline characteristics

3.3 Hemodynamics

Of the eight included patients, seven patients underwent 4 treatment session in each protocol. Their hemodynamic responses were assessed four times during sequential dialysis and four times during HD. One patient completed an extended study period with eight sessions per treatment. This patient was the first to be included in the study during the second phase described above. In this phase. the study was conducted according to the original study protocol which included measurements on both mid-week dialysis days. Based on the results and findings

acquired from this patient, the study protocol was adapted, whereby the number of study visits was reduced while maintaining the required statistical power as well as additional temperature measurements after half of the allotted treatment time were introduced. Given the current small sample size the results are presented descriptively. For each patient, session-specific mean values were calculated for all hemodynamic parameters. These parameters are MAP, SBP, TPRI and CPI. These calculated values were then averaged across the four treatment sessions per protocol or in one case eight treatment sessions per protocol to obtain treatment-specific mean values for each patient. Group-level results are presented as the mean and standard deviation of these patient-level treatment-specific values, these are shown in Table 6.

MAP during sequential dialysis was 91 ± 10 mmHg, compared with 92 ± 9 mmHg during HD. This corresponded to a relative change of 1,4% between treatment modalities.

SBP during sequential dialysis was 134 ± 18 mmHg, compared with 135 ± 15 mmHg during HD. This corresponded to a relative change of 1,3% between treatment modalities.

CPI during sequential dialysis was 0,44 ± 0,11 W/m², compared with 0,42 ± 0,08 W/m² during HD. This corresponded to a relative change of 5,4% between treatment modalities.

TPRI during sequential dialysis was 3556 ± 522 dyn·s·cm^{-5}·m^{-2}, compared with 3757 ± 497 dyn·s·cm^{-5}·m^{-2} during HD. This corresponded to a relative change of 5,6% between treatment modalities.

PARAMETER	SEQUENTIAL DIALYSIS	HD	RC (%)
MAP (mmHg)	91 ± 10	92 ± 9	+1.4
SBP (mmHg)	134 ± 18	135 ± 15	+1.3
CPI (W/m²)	0.44 ± 0.11	0.42 ± 0.08	−5.4
TPRI (dyn·s·cm^{-5}·m^{-2})	3556 ± 522	3757 ± 497	+5.6

Table 6: Hemodynamic parameters

3.4 Time course of mean TPRI during a treatment session

Since TPRI was defined as the primary endpoint of the ISO-UF study, in order to illustrate the temporal course of TPRI during treatment, four representative patients were selected exemplarily for visualization in Figure 8. For each treatment time point, four individual TPRI measurements were included, and the corresponding mean values were calculated for sequential dialysis and HD. In both treatment modalities, mean TPRI increased progressively over the course of treatment, reaching a plateau after approximately 140–180 minutes, followed by a decline at 240 minutes. The increase appeared slightly steeper during the early phase of HD, whereas sequential dialysis demonstrated a more gradual rise in TPRI. However, substantial overlap of the error bars indicated considerable interindividual variability and suggested no clear difference between the two treatment modalities. In the four evaluated patients, the mean TPRI during ISO-UF in sequential dialysis was 3135 ± 672 dyn·s·cm^{-5}·m^{-2}, which was lower than during HD, where the mean TPRI was 3840 ± 815 dyn·s·cm^{-5}·m^{-2}. The average relative difference was 22.5%.

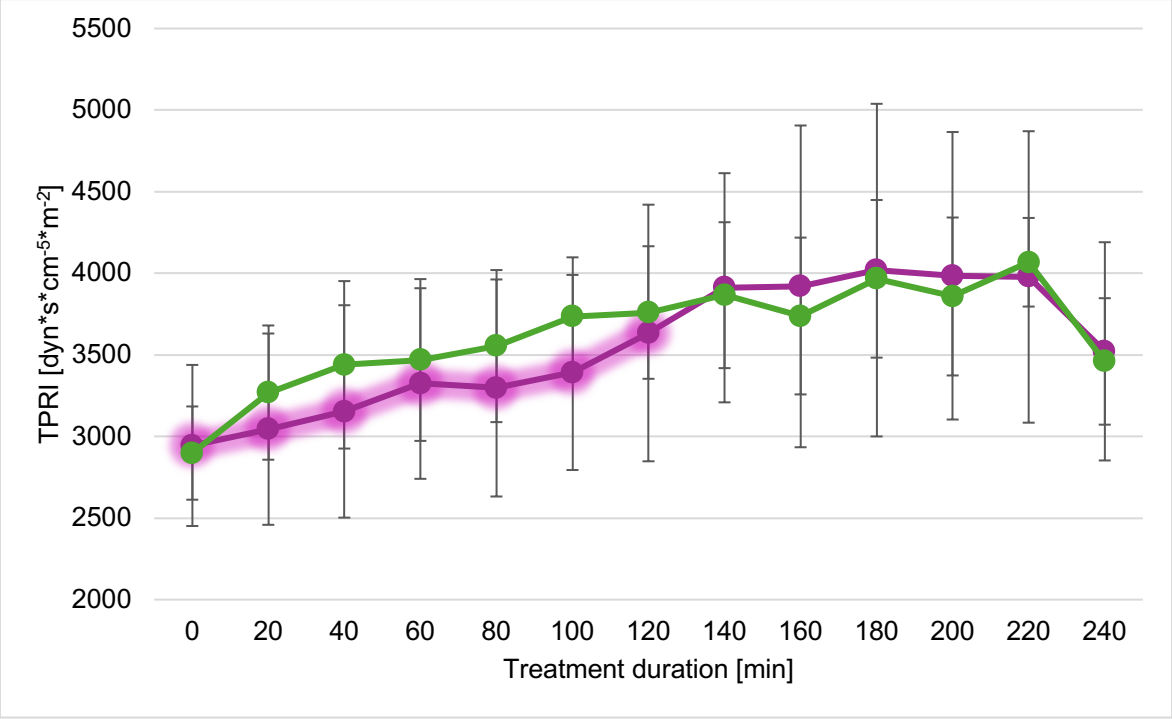

Figure 8.: Time course of mean TPRI during a treatment session
green curve represents the mean TPRI over the treatment of four patients during HD
purple curve represents the mean TPRI over the treatment of four patients during sequential dialysis

3.5 Intraindividual comparison across study visits

Intraindividual comparisons demonstrated largely consistent hemodynamic responses across both treatment modalities, with no systematic increase or decrease observed within individual patients. Across repeated study visits, individual trajectories of SBP, MAP, TPRI, CPI remained relatively stable.

Within-patient variability of the investigated parameters across study visits was modest and did not reveal consistent trends favoring either sequential dialysis or HD. Although minor fluctuations were observed between individual sessions, these changes did not follow a uniform directional pattern and appeared to reflect physiological variability rather than modality-specific effects. Individual courses of SBP, MAP, TPRI, and CPI across study visits are shown in Figures 9–11.

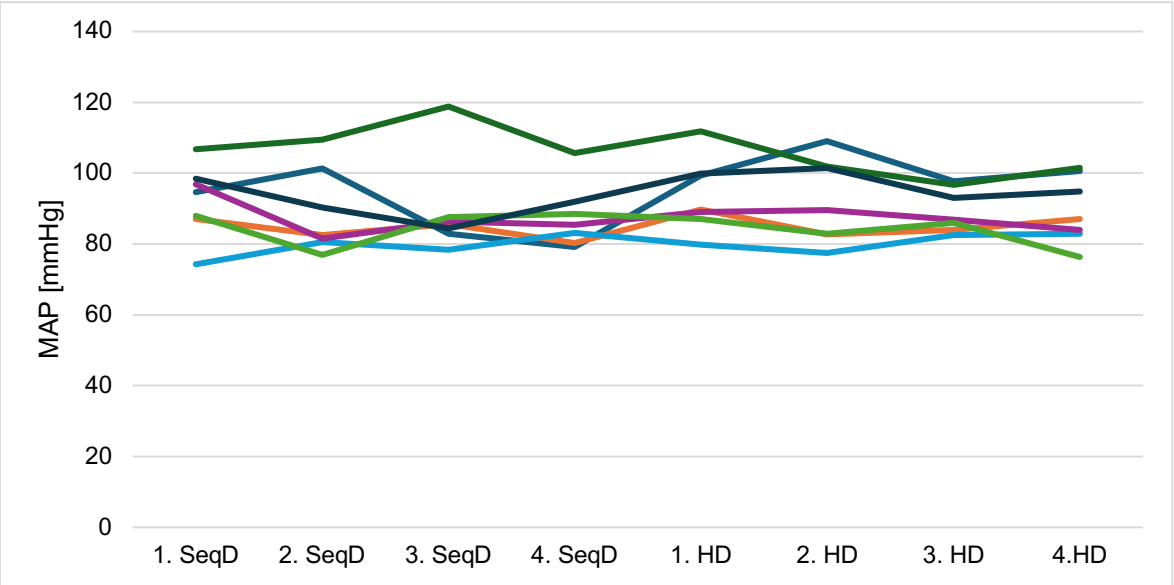

Figure 9: Time course of MAP across study visits
Each colored curve represents the mean value for MAP of one patient during the study period, 1.,2.,3.,4. SeqD: first, second, third and fourth visits using protocol 1 (sequential dialysis), 1.,2.,3.,4. HD: first, second, third and fourth visits using protocol 2 (hemodialysis)

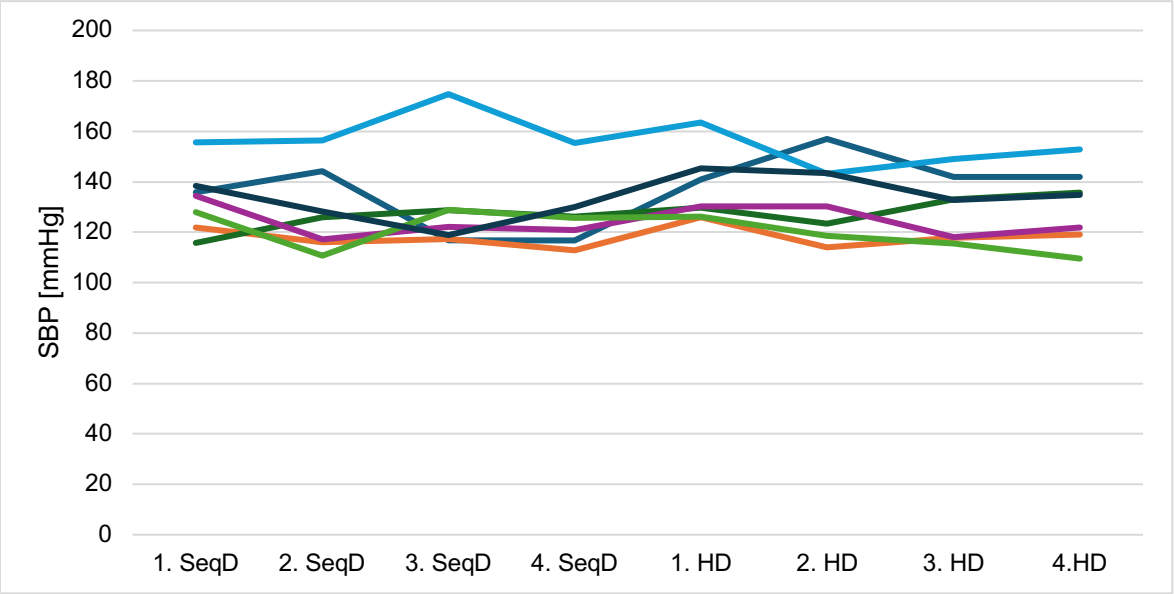

Figure 10: Time course of SBP across study visits
Each colored curve represents the mean value for SBP of one patient during the study period, 1.,2.,3.,4. SeqD: first, second, third and fourth visits using protocol 1 (sequential dialysis), 1.,2.,3.,4. HD: first, second, third and fourth visits using protocol 2 (hemodialysis)

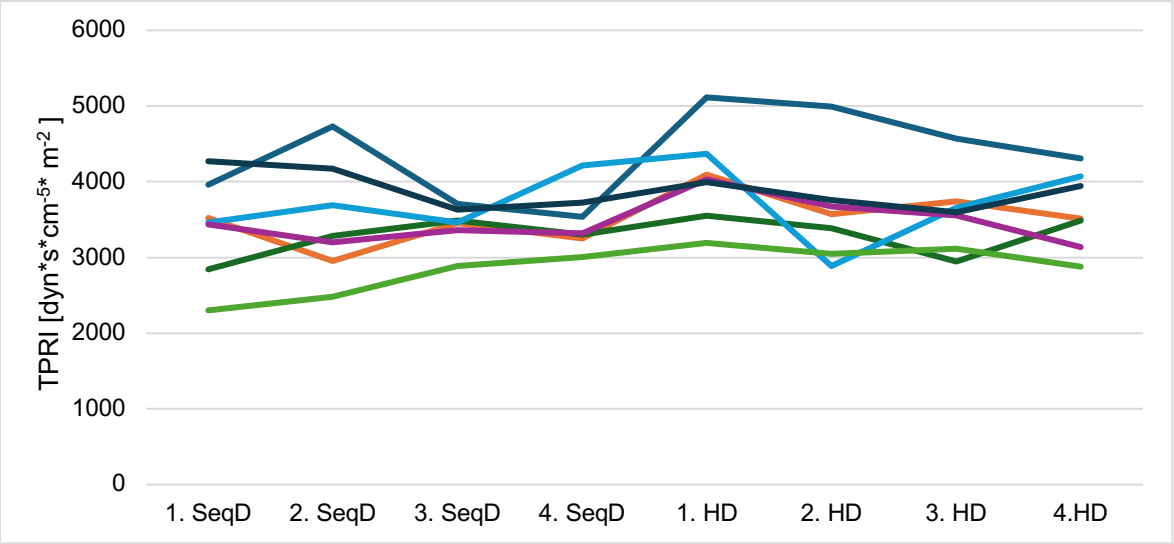

Figure 11: Time course of TPRI pressure across study visits
Each colored curve represents the mean value for TPRI of one patient during the study period, 1.,2.,3.,4. SeqD: first, second, third and fourth visits using protocol 1 (sequential dialysis), 1.,2.,3.,4. HD: first, second, third and fourth visits using protocol 2 (hemodialysis)

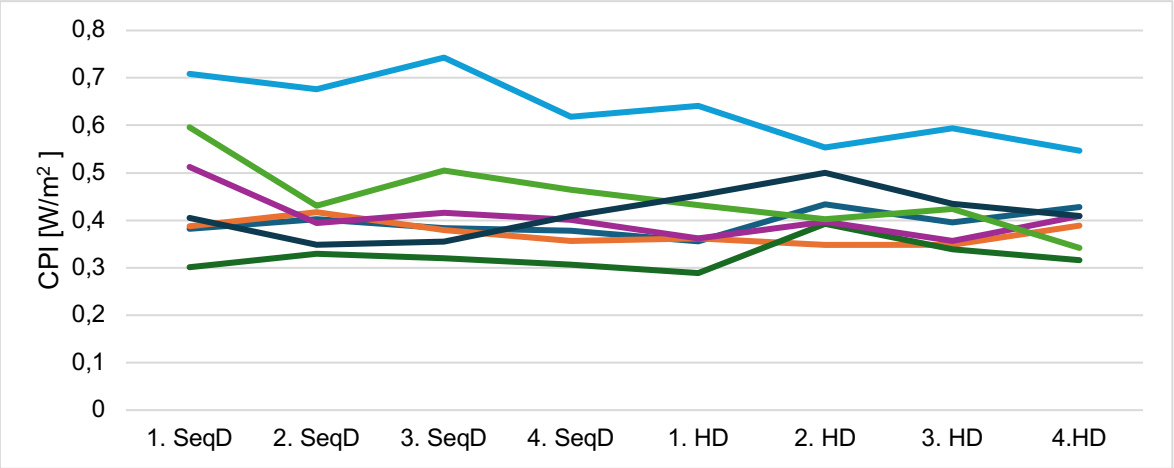

Figure 12: Time course of CPI across study visits
Each colored curve represents the mean value for CPI of one patient during the study period, 1.,2.,3.,4. SeqD: first, second, third and fourth visits using protocol 1 (sequential dialysis), 1.,2.,3.,4. HD: first, second, third and fourth visits using protocol 2 (hemodialysis)

3.6 Intradialytic adverse events

IDH occurred with similar frequency during both treatment modalities, with 17 episodes (23.6% of sessions) during HD and 21 episodes (29.2% of sessions) during ISO-UF across all analyzed sessions. Although IDH occurred in all included patients, it was almost always asymptomatic. There was one study participant, who were prone to IDH. For this patient in 37,5% of the study visit a symptomatic IDH was diagnosed, however without the necessity of fluid administration or pharmacologic intervention. In every case the stop of the ultrafiltration and the positioning in Trendelenburg was sufficient.

3.7 Serious adverse events

Apart from intradialytic hypotensive episodes, no relevant adverse events were observed during the study period

4 Discussion

Maintenance dialysis is associated with numerous complications and significant strain on the cardiovascular system. IDH is an individual risk factor for mortality and is one of the most frequent and most challenging complication during dialysis, with an incidence of 10-30% depending on the literature (34,35,87). Thus, exploration of possible unidentified pathophysiological causes and preventive measures is of utmost significance to reduce incidence rates. IDH is considered a multifactorial complication, and some etiological aspects are still subject of recent research. High ultrafiltration rates exceeding the plasma refilling rate, development of transient osmotic gradients as well as impaired autonomous cardiovascular responses through various mechanism like decreased vasopressin secretion or decreased baroreflex sensitivity are considered likely influencing factors (27,36,46). General preventive strategies include reducing interdialytic weight gain and increasing dialysis time and frequency. However, these approaches are commonly insufficient, this IDH incidence remains high (45). In some cases, it may be attempted to cool the dialysate temperature or apply sodium and ultrafiltration profiles (72). As stated in the KDIGO controversies conference, ISO-UF as part of sequential dialysis treatment could promote hemodynamic stability by preventing the formation of transient osmotic gradients and therefore improving peripheral resistance in patients and thus maintaining hemodynamic stability and avoiding the occurrence of IDH (32,77). However, besides the fact that this assumed improvement in hemodynamic stability has not been convincingly demonstrated in a prospective clinical study, it cannot be excluded that this hypothesized improvement is solely attributable to the negative thermal balance during ISO-UF, which may increase the vascular resistance through vasoconstriction (44,71,82). To further investigate the assumption that ISO-UF improves overall hemodynamic stability in patients via the increase in peripheral resistance, the ISO-UF study was designed. When designing the study, great attention was paid to reducing potentially confounding factors, the most important of which being the effect on temperature. By adjusting the dialysate temperature during HD to mitigate any thermal balance differences between ISO-UF and HD, the study allows a more specific assessment of the actual hemodynamic effects of ISO-UF could be studied. When discussing the results of

the data presented in this thesis, it is paramount to underscore that the results are incomplete and preliminary. Additionally, a formal statistical analysis has not been performed, thus it is not feasible to draw any definite conclusions from

Contrary to the hypothesis underlying the ISO-UF study, the preliminary data available suggest sequential dialysis including ISO-UF to not be associated with superior hemodynamic stability compared with HD. Across the investigated hemodynamic parameters, thus far no relevant differences were observed between the two treatment modalities, suggesting that ISO-UF per se may not confer an additional stabilizing effect under the studied conditions. These findings challenge the assumption derived from earlier literature that the prevention of transient osmotic gradients alone is sufficient to improve intradialytic hemodynamic stability (88). Instead, the present results support the notion that the hemodynamic effects attributed to ISO-UF may, at least in part, be mediated by a negative thermal balance rather than by osmolality-related mechanisms alone. However, given the exploratory nature of this analysis and the limited sample size, these observations should be interpreted with caution.

4.1 Implications of the findings for clinical practice

The application of ISO-UF as part of sequential dialysis is very likely to lead to lower dialysis quality, as less time is available to correct acid–base and electrolyte imbalances and to clear uremic toxins (89,90). In light of the our preliminary findings, which do not demonstrate superior hemodynamic stability, the use of ISO-UF may compromise dialysis adequacy without providing clear clinical benefits and could therefore be considered disadvantageous. Consequently, the risk–benefit balance should be carefully evaluated for each individual clinical decision.

4.2 Challenges during non-invasive cardiovascular monitoring

A relevant challenge during non-invasive cardiovascular monitoring was variable and often poor signal quality. This was mostly caused by patient movement, but even more commonly by poor attachment of the electrodes to the skin. In such cases, the system automatically generated an error message indicating that the measurement could not be performed due to increased skin resistance.

As a solution, manual pressure was applied, the electrodes were secured with adhesive strips and a shunt band, and, in exceptional cases, ultrasound gel was used when all other measures had failed. These difficulties caused delays in measurement timing, which was particularly critical when multiple patients were monitored simultaneously. In some cases, it took so long to reduce skin resistance that the blood pressure measurement had to be repeated and re-entered into the system to ensure accurate calculations.

We also observed that these issues occurred more frequently at the beginning of the session, when patients were overhydrated, and less frequently toward the end. Whether hydration status influences signal quality during measurements remains unclear and may represent a limitation of the device in patients with severe fluid overload.

Moreover, paroxysmal atrial fibrillation, known prior to study inclusion, was observed in several patients and affected the quality of hemodynamic measurements, as the system could not reliably record heart rate due to irregular R–R intervals. Data affected by the above-mentioned factors were manually excluded and did not influence the final analysis.

4.3 Strengths of the study

The benefits of the application of ISO-UF as part of a sequential dialysis treatment modality are mainly based on older studies. Therefore, ISO-UF is often only used due to the assumption of better hemodynamic stability, but without good quality of evidence. To the best of our knowledge there is no such study currently being conducted with the aim of comparing the measured hemodynamic parameters during ISO-UF and HD. This randomized, crossover study may give further evidence, whether use of ISO-UF as part of sequential dialysis treatment is warranted in clinical practice. Furthermore, the crossover design allows to compare each patient with themselves, and the study design enables to monitorize the hemodynamic changes almost continuously, since the measurement intervals were chosen to be quite short.

4.4 Limitations

The primary limitation of this study is the relatively small sample size which limits the statistical power and the generalizability of the recent findings. One important cofounding factor to consider is the antihypertensive medication of study population, which was not standardized and varied between patients, potentially influencing hemodynamic responses. However, since every patient served as their own control and moreover the antihypertensive medication was not changed during the study period, this influencing factor is likely negligible. Furthermore, ISO-UF as part of sequential dialysis in the routine clinical practice is suggested and used for patients with severe fluid overload. In this study also patients with mild and moderate fluid overload were recruited.

4.5 Future perspectives

The descriptive data and findings discussed in this thesis are preliminary and are part of an ongoing study with active patient recruitment. The finding suggest that sequential dialysis is not superior to HD with respect to the hemodynamic stability, which contradicts the expectations previously described in older literature. If the preliminary results can be confirmed after including all intended patients, the possible application of ISO-UF as part of a sequential dialysis treatment with the intention to provide a better hemodynamic stability during dialysis should be reevaluated.

Since the role of impaired secretion of vasopressin is hypothesized as a major contributor to the development of IDH the study could be supplemented by the determination of vasopressin or copeptin levels before, during and after each treatment modality. These levels of vasopressin or copeptin could be analyzed and interpreted in conjunction with the measured osmolality values.

It should be noted that none of the eight study participant, who were included in the finals analysis suffered from severe hypervolemia and they were in a good general clinical condition. For this reason, after completing this study an additional patient group with severe fluid overload could be recruited.

4.6 Conclusion

IDH remains a leading risk factor for morbidity and mortality among maintenance dialysis patients. A better understanding of the pathogenesis of IDH as well as the development and application of adequate preventive strategies are crucial. Whether ISO-UF as part of sequential dialysis treatment promotes higher hemodynamic stability compared to HD is still inconclusive. The preliminary data of the ISO-UF study indicates a similar hemodynamic response during both treatment modalities, however based on the available data no definite conclusion can be reached. Hence it remains to be determined whether the hypothesized superior hemodynamic stability during ISO-UF can genuinely be explained by the maintained osmolality and consequently higher peripheral resistance or if it can be elucidated solely by a negative thermal balance.

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