Thesis

Troponin I Kinetics in Patients Treated with Ambulatory Hemodialysis

submitted by

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 20.04.2024 *Benedikt Krietemeyer m.p.*

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Zusammenfassung

Einleitung: Während kardiale Troponine in den aktuellen Leitlinien für die Diagnose des Myokardinfarkts (MI) eine essenzielle Rolle spielen, ist ihre Bewertung bei Patient*innen während der Hämodialyse (HD) Behandlung mit Unsicherheiten behaftet. Neben den allgemein erhöhten Ausgangswerten der beiden klinisch relevanten Subtypen, Troponin I und Troponin T in dieser Patient*innenpopulation führen verschiedene Dialysemembranen und Dialyseverfahren ebenfalls zu Veränderungen der Troponinwerte. Inwieweit diese Veränderungen eine klinische Rolle spielen, ist jedoch nicht abschließend geklärt. Durch die neuen Medium-Cut-Off-Membranen (MCO), die eine höhere Durchlässigkeit für mittelgroße Moleküle, ähnlich Troponin, aufweisen, ist die Bewertung weiter erschwert worden. All diese Faktoren führen zu einer Unsicherheit bei der Bewertung von intradialytisch gemessenen Troponinwerten bei HD-Patient*innen mit Anzeichen eines akuten Koronarsyndroms.

Methode: In dieser kontrollierten, randomisierten Studie wurden die Ausgangswerte des hochsensitivem kardialen Troponin I (hs-cTnI) und die Auswirkungen von vier verschiedenen Dialysemodalitäten (High-flux HD, Low-flux HD, MCO HD und Hämodiafiltration) auf die hs-cTnI-Werte in einem Cross-over-Studiendesign untersucht. Dabei wurden Blutproben für die hs-cTnI-Bestimmung zu Beginn, eine Stunde nach Dialysebeginn und am Ende jeder Behandlung entnommen und die Ausgangswerte des hs-cTnI sowie die Veränderung des hs-cTnI im Laufe der Dialysebehandlung analysiert.

Ergebnis: Insgesamt wurden 19 Patient*innen in die statistische Analyse einbezogen (10 [52,6 %] männlich; medianes Alter 66 (31-81) Jahre). Die hs-cTnI-Konzentration zu Beginn der HD-Behandlung war in 58,3 % aller Fälle über den Grenzwert für die Diagnose eines MI erhöht (Median 34,25 ng/l; IQR 15,25-121,96). Patient*innen mit kardiovaskulären Erkrankungen wiesen zudem höhere hs-cTnI-Werte auf als Patient*innen ohne kardiovaskuläre Erkrankungen ($p<.001$). Die HD mit High-Flux- und MCO-Membranen sowie die Hämodiafiltration hatten keinen Einfluss auf die hs-cTnI-Werte in der ersten Stunde sowie über eine gesamte Behandlungsdauer ($p>.05$). Im Gegensatz dazu führte die HD mit Low-flux Membran zu einem Anstieg der hs-cTnI-Werte während einer Sitzung ($Z=2,12$; $r =.499$; $p=.034$), jedoch nicht während der ersten Stunde ($p=.227$). Nach der Korrektur der hs-cTnI-Werte für die Hämokonzentration, war auch diese Veränderung nicht mehr nachweisbar ($p=.134$).

Implikationen: Dialysesitzungen mit Low-Flux-Membranen können zu einem Anstieg des hs-cTnI führen und infolgedessen die Interpretation der hs-cTnI-Werte bei HD-Patienten mit akutem Koronarsyndrom (ACS) erschweren. Da bei allen Membranen Dynamiken in beide Richtungen auftreten, ist die Interpretation des hs-cTnI-Wertes bei Patient*innen, die sich einer HD unterziehen, mit einem hohen Risiko von Fehlinterpretationen behaftet. Da bei der Mehrzahl der HD-Patient*innen der hs-cTnI-Wert bereits vor dem Behandlungsbeginn über dem Cut-off-Wert für einen MI liegt, sollte die Interpretation der hs-cTnI-Werte in dieser Patientengruppe immer mit besonderer Vorsicht erfolgen.

Abstract

INTRODUCTION: Whereas cardiac troponins play a fundamental role in the latest guidelines for the diagnosis of myocardial infarction (MI), their evaluation in patients requiring hemodialysis (HD) is afflicted with several challenges. Beside the commonly elevated baseline levels of both clinically relevant subtypes, troponin I and troponin T, in this population, a further uncertainty exists in relation to troponin dynamics during HD and whether effects vary between different membranes and HD modalities. The new generation of medium cut-off membranes, that show higher permeability for middle sized molecules, add an additional layer of complexity to this topic. Due to this lack of clarity, physicians are confronted with ambiguity regarding the evaluation of troponin levels in HD patients presenting with signs of acute coronary syndrome (ACS).

METHODS: In this controlled, randomized single-center trial, the baseline values of high-sensitive troponin I (hs-cTnI) and the effect of four different dialysis modalities (high-flux HD, low-flux HD, medium cut-off HD and hemodiafiltration) on hs-cTnI levels were investigated in a cross-over study design. Therefore, blood samples for hs-cTnI measurement were taken at baseline, one hour after dialysis start and at the end of every session. Baseline levels of hs-cTnI as well as dynamics in hs-cTnI over time were analyzed.

RESULTS: Nineteen patients were included in the statistical analysis (10 [52.6 %] male; age 31–81, median 66). The baseline hs-cTnI was elevated above the cut-off value for MI in 58.3 % (median 34.25 ng/l; IQR 15.25–121.96) of all cases. Patients with cardiovascular disease presented higher hs-cTnI levels compared to those without ($p<.001$). There was no effect of dialysis with high-flux, medium cut-off membranes or HDF on hs-cTnI levels ($p>.05$). In contrast, low-flux HD led to an increase of hs-cTnI levels during one session ($Z=2.12$; $r=.499$; $p=.034$), but not during the first hour ($p=.227$). This observation could not be shown after correction for hemoconcentration.

CONCLUSION: Dialysis sessions conducted with low-flux membranes may lead to an increase in hs-cTnI levels and therefore complicate interpretation of hs-cTnI levels in HD patients presenting with ACS. Other HD modalities also lead to inconclusive effects in relation of hs-cTnI dynamics since we observed interpersonal variations in hs-cTnI dynamics in both directions. Thus, the interpretation of hs-cTnI in patients undergoing HD is afflicted with a high risk of misinterpretation. Since the majority of HD patients present with baseline hs-cTnI levels above the cut-off value for MI, the interpretation of single hs-cTnI values in this population should be done with particular caution.

Angaben von bereits erfolgen Veröffentlichungen

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Table of Contents

List of Abbreviations

ACS	acute coronary syndrome
BP	blood pressure
CAD	coronary artery disease
CKD	chronic kidney disease
CRS	cardiorenal syndrome
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CVD	cardiovascular disease
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESRD	end stage renal disease
FDA	U.S. Food and Drug Administration
GFR	glomerular filtration rate
HD	hemodialysis
HDF	hemodiafiltration
HF	high-flux
HFIL	hemofiltration
hs-cTn	high-sensitivity cardiac troponin
hs-cTnI	high-sensitive cardiac troponin I
hs-cTnT	high-sensitivity cardiac troponin T
IDH	intradialytic hypotension
K/DOQI	Kidney Disease Outcomes Quality Initiative
K_0A	mass transfer area coefficient
kDa	kilodaltons
KDIGO	kidney disease: Improving Global Outcomes [non-profit Organization]
KT	kidney transplantation
K_{UF}	ultrafiltration coefficient
LF	low-flux
LVH	left ventricular hypertrophy
MCO	medium cut-off
MI	myocardial infarction
NSTEMI	Non-ST elevation myocardial infarction
PD	peritoneal dialysis

RRT	renal replacement therapy
SC	sieving coefficient
STEMI	ST-elevation myocardial infarction

Table of Figures

List of Tables

1 Introduction

1.1 Chronic Kidney Disease

Chronic kidney disease (CKD) is a common disorder with a prevalence between 11.0 to 13.4 % in the global population and is responsible for up to 1.5 % of deaths worldwide per year (1,2). The progressive and irreversible loss of functionating nephrons can result from heterogenous causes. The most common causes, especially in high-income countries, are diabetes mellitus and arterial hypertension (1,3). Other causes include glomerulonephritis, infections or autosomal dominant polycystic kidney disease (4,5). According to the Kidney-Disease – Improving Global Outcome (KDIGO) Guideline from 2024, the "CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health"(6). A reduction in the estimated glomerular filtration rate (eGFR), which is calculated using the CKD-EPI formula, is used as the most common index of kidney function (6). Nevertheless, a reduction in GFR below the threshold value is not necessarily present in every case of CKD. Thus, an eGFR >90 ml/min/1.73 m^2 and a severe albuminuria ≥300 mg/24 h is also classified as CKD (3).

The 2024 KDIGO guidelines propose a risk stratification for cardiovascular mortality, that distinguishes six categories for the GFR (G1-G5) and 3 categories for albuminuria (A1-A3) (6). This classification is meant to reflect the escalating cardiovascular mortality resulting linked with elevated albuminuria and reduced GFR (3). In general, the CKD presents a major risk for secondary diseases such as cardiovascular disease and significantly increases the risk of morbidity and mortality (7).

1.1.1 End-stage Renal Disease

End stage renal disease (ESRD) is the terminal and irreversible stage of CKD with progressive loss of the endocrine and exocrine renal functions (8). The severe reduction or complete loss of secretory and endocrine renal function leads to multiple alterations in the homeostasis, such as retention of substances that physiologically are excreted with the urine, fluid overload, anemia as well as changes in mineral and bone metabolism (7,9). These changes come along with the development of secondary disease such as cardiovascular alterations and renal osteopathy. While there is no general definition of ESRD (10), a GFR <15 ml/min/1.73m^2 is commonly used for the definition. Furthermore, some authors define

the necessity of long-term dialysis therapy regardless of the eGFR as ESRD (9). It is important to note, that while ESRD presents the endpoint of CKD, a sizable proportion of patients with CKD die before progressing to this stage of the disease (11). Nevertheless, the prevalence of ESRD is increasing due to better healthcare and the global rise in life expectancy (12).

1.2 Renal Replacement Therapy

Since the renal function of patients with ESRD is insufficient for long-time survival, renal replacement therapy (RRT) is the only way to prolong the survival of these patients. The purpose of these therapies is the elimination of uremic toxins, maintenance of the acid-base and electrolyte balance and the elimination of excess fluids (7). A number of different forms of RTT, such as extracorporeal dialysis, peritoneal dialysis (PD) and kidney transplantations (KT) can be distinguished (4). According to the annual report for 2021 of the Austrian Dialysis and Transplantation Register (13), 9885 people received RRT in 2021, approximately half of whom received extracorporeal dialysis (n=4947). The mean age for patients receiving HD in Austria was 67.9 years in 2021 (14). While RRT technology improved in the last decades, the life-expectancy of patients undergoing RRT in the European union is significantly lower (-70 % in dialysis and -40 % in transplant) compared to the general population. The mean, unadjusted 5-year survival-probability for patients beginning HD in the European union was 42.6 % (42.5–42.7; CI 0.95) in 2018 (15).

1.2.1 Indications for Chronic Dialysis

The optimal start for dialysis treatment in ESRD is not clearly defined, but guidelines advocate dialysis if the eGFR decreases below 15 ml/min/1.73m^2 and signs or symptoms of uremia, malnutrition or hypervolemia occur (8). Depending on the risk and comorbidities of the individual patient, dialysis might be indicated prior, thus evaluation of the need should already begin in earlier stages of CKD (16). The selection of the specific therapy modality is individual and depends on various factors such as medical and logistical factors as well as the patient preference (7).

1.3 Physicochemical Background of Dialysis

All RRTs, except KT, are based on semipermeable membranes that allow size and charge selectivity. The necessary mass transport is a consequence of diffusion, osmosis and/or ultrafiltration, i.e. convection (7).

1.3.1 Diffusion

Diffusion is described as the movement of dissolved particles following a concentration gradient due to the random Brownian motion. In dialysis, size- and charge-selective diffusion occurs across the semipermeable membrane. This means, that only particles that are small enough can pass the membrane pores and thus participate in the diffusion process. The speed of diffusion thereby depends on multiple factors such as molecular size, electric charge, or the difference in concentration. Following the fact, that small molecules move faster and collide more often with the membrane, the concentration equilibrium of small particles is reached faster than for large particles (16,17). For this reason diffusion is particularly effective to clear small molecules such as potassium, creatinine or urea (18) and thus plays an important role in conventional HD.

1.3.2 Osmosis

Osmosis is the movement of fluids through a semipermeable membrane due to a concentration gradient between both sides of the membrane. The different concentrations of dissolved particles that are unable to pass the membrane create an osmotic pressure toward the higher concentration, which leads to a fluid-shift in this direction (7). This mechanism ceases when the concentration in both compartments is identical, due to dilution and concentration. In patients receiving PD this mechanism enables the removal of fluid by adjusting the osmotic pressure of the dialysate. In patients receiving HD, osmosis plays a subordinate role in fluid removal (7).

1.3.3 Ultrafiltration

Filtration is the selection of dissolved or undissolved particles by applying a hydrostatic pressure to a filter (7). While the fluid and some dissolved particles are able to pass the filter, depending on the pore diameter, larger particles will be retained. The rate of ultrafiltration can be increased by increasing the applied pressure difference (17).

1.3.4 Convection

The effect on particles, which get carried through the membrane by the fluid suction during filtration, is called convection ("solvent drag") (8). This effect does not depend on concentration gradients and is only depending on the pore size and the ultrafiltration rate (17). For very small solutes, the concentration of particles in the filtrate is almost equal to their concentration in the original fluid (16).

1.4 Uremic Toxins

Uremic toxins are molecules that are physiologically cleared by the kidneys. In patients with decreasing renal function, these substances accumulate and cause uremic symptoms such as pruritis, uremic odor or nausea and emesis (1,3,19). These symptoms are the result of the attributed ability of uremic toxins to cause inflammation, disturbance of the immune system and vascular changes.

One can divide more than 80 different uremic toxins, which can be classified in three different groups. Beside the small water-solute compounds (<500 Da) that can be subclassified depending on their protein binding, and middle size compounds (0,5-60 kDa), there also exists a group of large toxins (>12.000 kDa) (20). Since this classification does not consider clinical characteristics and only focuses on biochemical features, Kashani *et al.* (21) proposed a classification into two groups depending on the origin of the toxin. While those uremic toxins such as urea, creatinine or β_2-microglobuline which are a product of metabolism, are classified as endogenous and are elevated due to a decreased renal elimination. Uremic toxins that are the result of pathophysiological changes in result of the decreased renal function, such as inflammation (i.e. interleukins) and gut dysbiosis, are classified as exogenous toxins. The categorization in endogenous and exogenous toxins enables a new path in the clinical management of ESRD patients (21).

Although the newer classification into endogenous and exogenous forms provides a new clinical context, the biochemical features are still a relevant factor in understanding transport processes in the context of RRT. Particularly the clearance of middle size molecules and protein-bound toxins represent an ongoing challenge as result of their poor diffusion capacity in common dialyzers (22).

1.5 Hemodialysis

HD is a common invasive, extracorporeal RTT mainly based on selective diffusion and to a smaller proportion on ultrafiltration. The dialysis machine consists of two circuits, one for blood and one for dialysate. In the blood circuit, the anticoagulated blood leaves the body via an "outflow" line and is then pumped through the dialyzer. The online produced or prefabricated dialysate gets pumped in the dialyzer in counterflow to the blood, divided by a semipermeable membrane. Due to the concentration gradient between blood and dialysate, selective diffusion occurs and leads to the elimination of small molecules in the blood, such as urea. The counterflow thereby ensures maximal clearance of uremic substances (17).

The diffusion rate depends on various factors, such as the membrane structure, the flow rates of blood and dialysate in the dialyzer, the applied concentration gradient, duration of the therapy and further factors (16,23). Larger molecules and those bound to proteins cannot pass the membrane due to their size and therefore remain in the blood.

While ultrafiltration plays a role in removing excess fluid from the body, the elimination of toxins by convection depends on the used dialyzer (16). While dialyzers with small permeability, so called low-flux (LF) dialyzers, do only allow low volumes of convection, newer dialyzers with higher permeability, referred to as high-flux (HF) dialyzers, allow more elimination of larger molecules such as β_2-microglobulin and myoglobin through convection (24).

1.6 Hemofiltration

Due to the restricted elimination of larger molecules during HD, the process of Hemofiltration (HFIL) was implemented. The method is purely based on convection by ultrafiltration of blood due to a hydrostatic pressure across a semipermeable membrane. Following the solvent drag, all solvents smaller than the membrane's cut-off are filtered through the membrane (12,16). The clearance of a substances is thereby proportional to the ultrafiltration rate (8). While HD and HFIL show approximately the same rate of small molecule removal, larger molecules are removed at a much higher rate in HF due to convection (16,18). As a result of the high amount of lost ultrafiltrate, partially or completely compensation by infusing a substitution fluid is necessary (18). In patients with acute hypervolemia, the HFIL can be used without reinfusion to enable the elimination of excess fluid (25).

1.7 Hemodiafiltration

Hemodiafiltration (HDF) is a method combining HD and HFIL to make use of both solute transport mechanisms. This combination of ultrafiltration and diffusion optimizes the clearance of uremic toxins and might show higher cardiovascular stability in comparison with exclusive HD (26). To achieve the necessary ultrafiltration rates, the choice of the dialyzer is crucial. Requirements include a high permeability for water and a high mechanic resistance to the applied transmembrane pressure in order to enable the desired ultrafiltration rates (27). Due to the high ultrafiltration rate, fluid substitution is crucial. While substitution fluid was packaged in bags in the past, modern online-HDF machines enable the production of sterile substitution fluid from ultrapure water and therefore can provide the dialysate on-demand (8,27). This modern method permits a convective volume of up to 25-30l per session in post-dilution mode which has been shown to lead to improved overall outcome in comparison with pure HD in selected patient populations (27–29).

Depending on the side of infusion of the sterile substitution fluid relative to the dialyzer, two modes of HDF can be distinguished. While in post-dilution-HDF the substitution fluid is added behind the dialyzer, pre-dilution-HDF describes the injection of fluid upstream of the dialyzer. Post-dilution HDF is presumably more efficient mode and allows the ultrafiltration of blood in an undiluted state, while pre-dilution-HDF can be indicated in certain situations, for example when patients present with high hematocrit levels and thus to prevent excessive hemoconcentration and thrombosis in the dialyzer (12,16).

1.8 Peritoneal Dialysis

PD is an intracorporal method to eliminate toxins and fluid by diffusion, ultrafiltration, and convection. In contrast to conventional HD, the serous membrane of the peritoneum and the capillary walls form the necessary semipermeable membrane. At the beginning of every PD-session, a solution of electrolytes, osmotically active molecules and buffer substances is instilled into the peritoneal cavity and after a certain time, the solution is drained. One can distinguish a variety of procedures of PD, that are described elsewhere (4,8,16).

1.9 Dialyzer and Membranes

Dialyzers are the central component of the dialysis machine and enable the elimination of toxins and excess fluid from the blood. HD treatments are nowadays exclusively performed

using hollow-fiber dialyzers. These consist of a thousand of tightly packed fibers which are run through by blood. The walls of the blood-carrying vessels build the semipermeable membrane which enables the actual dialysis. The fibers are surrounded by a separate space enclosed by a plastic capsule which is flowed with dialysate. The dialysate thereby flows in the opposite direction to the blood, increasing the efficiency of the dialyzer (so called "counterflow") (8,16).

Depending on the used materials and the structure, the membranes show different characteristics and enable different procedures such as HDF (8). Hence, a wide variety of membranes are available depending on the requirements.

1.9.1 Materials

The first dialysis membranes used were made from cellulose, which led to a high rate of bioincompatibility. Currently, the majority of membranes in clinical routine are manufactured from synthetic materials and rarely out of modified cellulose. This leads to less immunological reactions (higher biocompatibility) and enables higher ultrafiltration coefficients (8,16). Furthermore, most of the modern membrane materials have hydrophobic qualities and can absorb proteins and toxins to a certain extent (8).

1.9.2 Structure

Synthetic membranes are built with an asymmetric wall that consists of two layers. While the inner layer so called skin layer, of the membrane is thin and responsible for filtration and high permeability, the outer layer, so called support structure, is thicker and has big pores. The outer layer is responsible for the stability of the membrane and has minor influence on the filtration (8,12).

1.10 Membrane characteristics

The manufacturing procedure, structure and materials used, result in differing properties of dialysis membranes, which define membrane characteristics.

1.10.1 Sieving Coefficient (SC)

The sieving coefficient (SC) is the measure for the permeability of a membrane in relation to a specific molecule and is defined as ratio of the concentration of a dissolved substance

S_X in the filtrate and the concentration of a dissolved substance S_X in the plasma water (8,12). Therefore, the SC varies between 0 (no molecules can pass the membrane) and 1 (all molecules can pass the membrane).

1.10.2 Membrane Cut-off and Retention Onset

Following the SC, one can define two values that enable the description of membrane characteristics. While the membrane cut-off is defined by the molecular weight that results in a SC of 0.1, the retention onset is the molecular weight at a SC of 0.9 (30,31). These two parameters play an important role in the classification of dialyzers, which is discussed below.

1.10.3 Clearance

The clearance is defined as volume of blood which is completely cleared from a substance S_X over specific time (ml/min). It depends on a variety of factors, such as the membrane characteristics, the size and electric charge of the molecule, the flow of blood and dialysate as well as the overall composition of these two fluids (8,17).

1.10.4 Mass Transfer Area Coefficient

The mass transfer area coefficient (K_0A) is a specific constant of each dialyzer. It is defined as the maximal clearance of a membrane with maximal blood and dialysate flow to a given substance. The K_0A depends on the size of the membrane and the permeability for the specific substance (16).

1.10.5 Ultrafiltration Coefficient (KUF)

The K_{UF} is a measure to describe the permeability of a membrane for water. It is one of two features to predict the ultrafiltration quantity of a membrane. K_{UF} is defined as number of milliliters of fluid that will be transferred across a membrane in one hour per mmHg pressure difference at the membrane. The most significant influence for the K_{UF} is the pore size of the membrane (12). The higher the K_{UF}, the higher the permeability for water and reversely. Membranes with a high K_{UF} also show a higher permeability for larger molecules and thus enable convection (8,16). A commonly used marker is β_2-microglobulin (11.8 kDa) which only crosses membranes with higher K_{UF} due to their larger pore-size (16).

1.10.6 Pore-size Distribution

Due to the manufacturing process, the pores of a membrane do not have an identical diameter but rather vary around a certain size. This variation is called pore-size distribution and shows a normal distribution around the declared diameter. By minimizing the pore-size distribution, it is possible to widen the general pore-size to eliminate larger uremic toxins without increasing the loss of large molecules such as albumin due to pore-size variants bigger than their diameter (32).

1.10.7 Flux

Flux as a membrane specification is a frequently used, although an inconsistently defined term. The common and general definition of flux in relation to membranes is the permeability rate for volume in relation to area and time (Volume/Area/Time [L m^{-2} hr^{-1}]) (33). The so defined flux is influenced by biochemical characteristics of the used membrane and solutes as well as the applied transmembrane pressure. Latter represented in the K_{UF} (34).

Beside the purely phenomenological definition as a unit for the permeability of a membrane, the term “flux” is commonly used interchangeably with other measures in daily practice. These various definitions were implemented by membrane manufacturers, professional association guidelines and state approval bodies. Presently, flux serves as a measure of a dialyzers capability to eliminate medium or large-sized uremic toxins. Furthermore, pore size, SC, and K_{UF} are commonly used as indicators of membrane flux, despite their lack of direct correlation with the hydraulic permeability of a membrane. The use of adjectives to describe the flux i.e. "low-" or "high-flux", with heterogeneous definitions, leads to even greater inconsistency in the use of the term (34).

1.11 Types of Membranes

Membranes can be classified due to their K_{UF} and additional factors such as pore-size distribution (24). The different permeability by different pore sizes leads to a different spectrum of mass transport through the membrane. While smaller pores allow diffusion of small uremic particles, larger pores enable further the convective clearance of larger uremic molecules and in some cases even protein-bound toxins (8,35).

1.11.1 Low-flux Membranes (LF)

The first generation of cellulose membranes had small pores and therefore a poor K_{UF}. This kind of membranes with small pores and a K_{UF} <8 ml/mmHg/h of water are called LF membrane following the classification of the Food and Drug Administration (FDA) of the United States (8,18). The main transport process through these membranes is diffusion of especially small molecules (<500 Da) such as urea, while larger molecules cannot pass the membrane. Since LF membranes present with a low permeability, they allow very little convective transport, although ultrafiltration is possible to a low extent (8).

1.11.2 High-flux Membranes (HF)

High-flux membranes were the first development step in relation to improved elimination of larger uremic molecules, especially β_2-microglobulin (36). Therefore, the pores of HF membranes have a larger diameter and consequently show a higher permeability for water. Following the FDA-classification for HF membranes, the K_{UF} needs to be ≥8 ml/mmHg/h (8) and further classifications require an additional sieving coefficient for β_2-Mikroglobulin, for example a SC >0.6 according to the European Dialysis Working Group (24). Due to the higher K_{UF}, HF membranes allow a higher rate of ultrafiltration and enable convection of medium-sized molecules (8). Additionally, some HF membranes might be able to absorb larger solute molecules which further improves their ability to eliminate uremic toxins (24).

1.11.3 High cut-off Membranes

These so-called protein-leaking membranes contain large pores, and thus have a very high permeability to enable the elimination of larger molecules that can occur in sepsis (cytokines), rhabdomyolysis (myoglobin) or in some hematologic diseases (37). While the elimination of bigger molecules remains one goal of dialyzer development, the maximized permeability leads to the loss of albumin and therefore can cause hypoalbuminemia (24). Thus, high cut-off membranes can only be used for a limited number of sessions and specific indications.

1.11.4 Medium Cut-off Membranes (MCO)

MCO membranes are an evolution of HF membranes with an optimized permeability and thus enable the clearance of larger middle-size uremic toxins with a cut-off that is almost equal to the cut-off of HF membranes (37,38). As opposed to HF membranes, MCO

membranes show a much steeper decrease of the SC and thus enable a more efficient clearance of molecules with medium molecular size (≥15 kDa) without increasing the loss of albumin. In other words, MCO membranes present with an equal or higher retention onset than high cut-off membranes combined with a cut-off comparable to HF membranes (31). The clearance of medium-size molecules is of interest due to their potential influence on the development of uremic anemia, osteodystrophy and cardiovascular complications such as atherosclerosis (36,37). D. Zickler *et al.* (39) showed that MCO membranes can lower the inflammatory level to a greater level than conventional HF membranes and thus might lead to a better outcome in patients. Another study (40) investigated the elimination of various medium-sized molecules (i.e. free immunoglobulin light chains, α_1- and β_2-microglobulines) and found a significantly improved or equal reduction ratio in patients treated with MCO dialyzers compared to common HF-HD and HDF.

In contrast to the previously mentioned high cut-off membranes, MCO membranes are furthermore able to retain albumin to a greater extend due to their small pore-size distribution and lower cut-off values (22,35,37,40,41). While most of the albumin is retained, minor losses of albumin (avg. 2-4 g per session) might even be beneficial, due to the higher clearance of protein-bonded uremic toxins (24). It is important to note, that the minimal loss of albumin does not affect the overall concentration of albumin in the blood (37). Nevertheless, Yang *et al.* (42) described that MCO-membranes do not show higher elimination of protein-bound uremic toxins compared to other established procedures.

Ronco (31) proposed the term expanded HD for the use of MCO membranes in HD due to the new mechanism that occurs in this application. HD with MCO membranes allows the combination of diffusion and convection without the need of complex dialysis machines. Additionally, there is no need for high volumes of substitution fluids in contrast to HDF. This is the result of the higher SC of MCO membranes and their small fiber diameter which consequently leads to a new profile of cross filtration. While in the proximal part of the dialyzer a large amount of ultrafiltration and convective transport occurs, the back filtration in the distal part of the dialyzer makes the substitution of fluids superfluous. However, it must be noted that the high rate of back filtration makes it necessary to use ultrapure water in order to prevent the back filtration of pyrogens or toxins. Another positive effect is that a lower rate of ultrafiltration is necessary to achieve the same clearance for middle-size molecules based on the higher SC for larger molecules (31,37,41).

1.12 Parameters of Dialysis Quality

1.12.1 Urea Reduction Rate

The urea reduction rate is a simple tool to evaluate dialysis adequacy by determining the relative change in urea concentration before and after dialysis treatment (26). Therefore, the concentration before and after the session are subtracted and then divided by the urea concentration at the beginning of the treatment (16).

1.12.2 Dialysis Dose (Kt/V)

This dimensionless ratio, introduced in 1985 by Gotch and Sargent, is used to evaluate dialysis effectiveness and is calculated using the dialyzer urea clearance (K), dialysis time (t), and urea distribution volume (V) (8). The product of K and t represents the total volume cleared of urea during a dialysis session. This volume is divided by the total volume loaded with urea (V) and thus allows a statement to be made about the proportion of purified body water in one dialysis session.

A variety of factors influences the dialysis dose. Besides the efficient dialysis duration (t), recirculation and tissue perfusion influence the Kt/V as well as the blood and dialysate flow as well as the ultrafiltration (17).

Since this model represents a simplified relationship between clearance, HD duration and the distribution volume, and does not account for the new synthesis of urea during dialysis neither volume removal, adapted formulas, such as the Kt/V Daugirdas formula have been developed (43).

1.13 Complications in Dialysis

While HD is a routine and valuable treatment for millions of patients with acute kidney injury or ESRD, complications may occur. The etiology of these events is versatile and depends on multiple factors, including the primary disease, the general constitution of the patient, the dialysis procedure as well as human error. Common acute complications are intradialytic hypotension (IDH), muscle cramps, headache or nausea and emesis (8). Long-term complications result from the missing renal endocrinal function including anemia or mineral and bone disorder due to insufficient erythropoietin and calcitriol synthesis as well

as dysfunction of metabolic processes (e.g., metabolic acidosis) and cardiovascular complications (8,25).

1.13.1 Intradialytic Hypotension (IDH)

The occurrence of IDH is the most common complication during dialysis and occurs in 10-30 % of all sessions (44,45). While the K/DOQI guidelines define IDH, as a blood pressure (BP) drop under a certain nadir (systolic ≥20 mmHg; mean arterial pressure ≥10 mmHg) that coincide with clinical symptoms, other authors include the necessity of medical interventions for the definition (44,46,47).

Causal mechanisms for the occurrence of IDH are a reduction in effective circulating blood volume during HD due to ultrafiltration, changes in blood temperature during the session and the high burden of comorbidities in ESRD patients, that weaken physiological adaptation processes that usually compensate volume loss. The resulting loss of perfusion pressure leads to reduced tissue perfusion and thus to tissue ischemia. The resulting ischemia is the critical factor which leads to multiple adverse effects such as underdialysis, adverse cerebral outcome and raised mortality in patients with IDH (44,46,47). The appearance of IDH is also associated with a wide range of cardiovascular complications such as MI, decompensated heart-failure and overall cardiovascular mortality (45). Therefore, IDH is a relevant clinical factor influencing outcome and wellbeing of patients.

1.13.2 Cardiovascular Complications in Dialysis Patients

A decrease in GFR presents an independent risk factor for the development of cardiovascular diseases (CVD) (48). Thus, in patients undergoing long-term dialysis, the risk for CVD is drastically increased and therefore a major factor that influences the mortality and morbidity in this group of patients (12,25,49). In 2021, 25.6 % of all deaths in patients receiving HD in Austria were due to cardiac causes while 5 % died due to vascular causes (13). Therefore, prevention, diagnosis, and therapy of CVD is essential in this population. The most frequent manifestations are left ventricular hypertrophy (LVH), arrhythmias, sudden cardiac death, ischemic heart disease and valve stenosis (8).

1.13.2.1 Cardiorenal syndrome

While five types of cardiorenal syndrome (CRS) have been described and their detailed discussion exceeds this thesis, CRS type 4 will be discussed in greater detail to understand

the high prevalence of CVD in patients with ESRD. Following the consensus conference from 2010, CRS type 4 is characterized as secondary dysfunction or disease of the heart resulting from CKD (50). Mechanisms that lead to this secondary alteration remain incompletely understood but several studies have identified multiple potential risk factors and mechanisms. Alongside the classic risk factors for CVD (such as higher age, hypertension, diabetes mellitus and dyslipidemia) which show a higher prevalence in CKD patients than in the normal population, a variety of non-traditional risk factors in dialysis patients occur due to the impaired renal function (16,51). These additional risk-factors include albuminuria, volume overload, anemia, endocrine disturbances, chronic inflammation and the accumulation of uremic toxins as well as changes in the lipid metabolism (16,52–54). In patients with ESRD undergoing HD or HDF, the dialysis procedure itself poses an additional burden to the heart due to intradialytic hemodynamic instability and fluid shifts (51,55). The sum of these factors leads to an increased rate of CVD and a higher risk of cardiovascular events such as ACS in patients with CKD and ESRD.

1.13.2.2 Coronary artery disease

About 40-50 % of chronic HD patients show signs of ischemic heart disease, also referred to as coronary artery disease (CAD) (12,49). Management of this cohort of patients is complex due to untypical symptoms and the high rate of comorbidities (54). This is aggravated by the fact, that most studies covering the diagnosis and therapy of CAD exclude advanced CKD and ESRD patients.

One big factor complicating the diagnosis of CAD in this population, is that patients with CAD often present asymptomatic and show no typical signs such as angina pectoris. Thus, Ohtake *et al.* (56) showed that 16 of 30 asymptomatic patients at the initiation of RTT showed CAD in coronary angiography, from which 5 patients had severe stenosis (≥90 %). Possible causes for this high rate of silent myocardial ischemia might be diabetic and/or uremic polyneuropathy.

The therapy of CAD in CKD patients remains a further challenge since only limited knowledge is available on whether commonly used therapies are effective in this specific population. (57). While statins show a significant effect in reducing mortality and morbidity in the general population, patients with ESRD do not universally benefit from low-density lipoprotein reduction (58). Other drugs, such as acetylsalicylic acid or beta blockers were

not examined in large randomized trials and their usage is based on observations from the general population (57).

1.13.2.3 Acute myocardial infarction

Due to the high prevalence of CAD, the occurrence of ACS is a common complication in ESRD patients (59). The resulting need to differentiate MI and other causes of ACS presents a major challenge in this group of patients due to several factors. Firstly, the clinical presentation of MI in patients undergoing HD is atypical and different compared to the general population. While 68 % of the general population with MI presents with chest pain, only 44 % of patients with ESRD show this typical symptom. On the other hand, shortness of breath and dyspnea are more common in CKD patients compared to a comparative group, but this symptom also occurs in ESRD patients suffering from overhydration. Furthermore, ST-elevations in ECG are more frequent in non-dialysis patients than those with ESRD and cardiological disorders, such as LVH, that occur in CKD patients, additionally complicate the diagnosis (60,61). Another factor that complicates the objective diagnosis of ACS in HD patients is the uncertainty surrounding the interpretation of biochemical markers, such as troponin.

While clear cut-offs for the general population are available, these values cannot be extrapolated for ESRD patients due to various factors which are discussed below.

Potentially also as a result of this, mortality during the hospital stay due to MI is almost doubled in ESRD-patients compared to the general population (21.3 vs. 11.7 %; $p<.0001$) and in addition the long-time mortality remains high (73 % at two years). A potential explanation might be the higher rate of inaccurate diagnosis (44.8 vs. 21.2 %; $p<.0001$) and the fact, that patients with CKD are less frequently considered eligible for acute coronary angiography interventions (60,62).

1.14 High-sensitivity Cardiac Troponin

High-sensitivity cardiac troponin (hs-cTn) is a sensitive biochemical marker that indicates myocardial damage and is inter alia used in the diagnosis of MI. The term “high-sensitivity” refers thereby to the newest generation of assays with the ability to identify smallest myocardial injuries and the capability to detect hs-cTn in 50 % of all healthy individuals, although there is no generally accepted definition (63,64).

One can distinguish between two clinically relevant forms of hs-cTn following their physiological function and molecular size. While cardiac troponin T (cTnT) is relevant for the attachment to the actin filament and has a molecular weight of 37 kDa, troponin I (cTnI) has a smaller size (24 kDa) and acts as inhibitor for the ATPase in the muscle (64,65). Together with a third molecule (troponin C), these molecules regulate the contraction of the myocardium. Beside the cardiac forms, there are another subtype of troponin in smooth and striated muscles of the body.

There are a variety of causes for an elevation in hs-cTn, the most commonly described is ischemic heart damage. Following the universal definition of myocardial infarction from 2007, an elevation of hs-cTn above the 99th percentile with other signs of myocardial ischemia is defined as MI (66). Furthermore, the dynamic elevation of hs-cTn is part of the diagnosis of non-ST elevation MI (NSTEMI) according to the 2023 ESC Guidelines (67).

On the other hand, congestive heart failure, hypertrophic cardiomyopathy or cardiac arrhythmia can also lead to elevation in hs-cTn (68). In addition, Turer *et al.* (69) were able to show a significant increase in hs-cTn following rapid atrial pacing, comparable with medium physical stress, due to temporary ischemia.

Beside these cardiovascular causes, a large portion of CKD patients and a majority of patients undergoing HD show significantly elevated levels of hs-cTn independent from any sign of CVD or ACS (70–72). It therefore is important to note, that an elevation in hs-cTn does not allow an etiopathological categorization and consequently not every elevation of hs-cTn is a sign of cardiomyocytic damage or ischemia (73,74).

1.14.1 Troponin and Acute Coronary Syndrome

The measurement of hs-cTn levels plays an important role in the diagnostic workup of patients presenting with ACS beside the 12-channel ECG. While an elevation of the ST-segment in ECG is sign of a “ST-segment elevation myocardial infarction” (STEMI) and those patients should be treated immediately, patients presenting without ST-segment elevation must be further diagnostically clarified. Following the ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, the measurement of hs-cTn is recommended in this group of patients (67). Therefore, the current guidelines recommend a 0/1 h or 0/2 h-algorithm with the widely available hs-cTn assays (75).

If the first hs-cTn obtained is below a predefined cut-off level, depending on the used assay, patients can be ruled out and other causes for their symptoms should be taken in consideration. On the other hand, a one-time increase of hs-cTn above the 99th percentile of upper reference level is referred to as myocardial injury and a second testing is necessary to differentiate acute and chronic processes. While dynamics between the two sampling points in hs-cTn above the reference change value are a sign of acute myocardial damage and thus indicate MI, the absence of changes is usually a sign of chronic injury or a variety of conditions discussed above (66,76).

The determination of hs-cTn therefore does not only allow a fast and precise diagnosis, but also allows risk stratification of patients presenting with chest pain. Thus, this algorithm enables an even faster rule-in and rule-out and reduces the time to diagnosis and necessary intervention (76).

1.14.2 Comparison of Different Troponin Assays

When comparing two commercially available assays for hs-cTn for the both clinically used subtypes of hs-cTn (e.g. ARCHITECT High Sensitive *STAT* Troponin I assay (Abbott Laboratories) vs. Elecsys 2010 (Roche Diagnostics)), there are no significant differences in their diagnostic accuracy. Thus, a study from Gimenez *et al.* (77) showed that both forms of hs-cTn have almost similarly high diagnostic accuracy for MI, whereby hs-cTnI had a small advantage in the diagnosis of patients with very early presentation. On the other hand, high-sensitive cardiac troponin T (hs-cTnT) was more precise in patients presenting in a later stage of ACS. Limiting in relation to the subject of this thesis is the fact, that patients with CKD were excluded from the study.

1.15 Troponin in Dialysis Patients

1.15.1 Baseline Characteristics

Asymptomatic patients undergoing HD frequently present with elevated hs-cTn compared to the general population (70,71,78,79). Following Snaedal *et al.* (70), dialysis patients with negative hs-cTn assays are rare and only make up less than 0.5 % of all patients. Different studies measured hs-cTnT pre-HD and describe average values between 49-70 ng/l in this group of patients. Moreover 95-99 % of HD-patients in these studies presented with hs-cTnT above the 99th percentile which is the cut-off value for the diagnosis of MI (70,71,78–81).

In comparison, hs-cTnI increases are rarer and have a less pronounced manifestation (14,0-54,3 ng/l and 20-73 % above the 99th percentile) (70–72,80,82). The reason for this dissimilarity is not conclusively clarified but might be partly explained due to the adsorption of hs-cTnI at the dialysis membrane (83).

Beside the common elevation of hs-cTn, different authors observed large intraindividual changes over time. These biological changes were greater, the higher the baseline was (70,84,85). Additionally, patients presenting with CAD have bigger intraindividual changes than those without CAD (85).

Higher levels of hs-cTn are associated with a variety of factors. Kumar *et al.* (84) showed that patients with CVD such as CAD, LVH or reduced left ventricular ejection fraction presented with higher hs-cTnI baseline levels. The association of CAD and hs-cTn was confirmed in a further study, especially in hs-cTnI (85). With regard to hs-cTnT, a publication describes a relation of hs-cTnT to diabetes, CAD and peripheral artery disease (81).

The causal mechanisms that lead to these findings described above, are controverse and targeted by multiple studies. While some authors consider a decreased renal elimination of troponin fragments as causal (86), other authors point out, that this might not be the case, due to the persisting elevation of troponin in patients after undergoing KT (87). Chauin (73) summarizes the main mechanisms as decreased renal elimination of troponin fragments, the direct damage of cardiomyocytes by uremic toxins and the myocardial hypertrophy due to volume overload.

The commonly elevated levels of hs-cTn in this population have demonstrated predictive value in asymptomatic patients, and therefore after adjusting for other risk factors, hs-cTnT has been shown to possess prognostic value for long-term morbidity (70,80,88,89). Furthermore a 2012 published work from Breidthardt *et al.* (90) showed that elevated hs-cTnT is a prognostic factor for the incidence of myocardial stunning during HD. On the other hand, hs-cTnI correlates with the severity of CAD in asymptomatic patients (82) and is associated with the risk of long term major adverse cardiovascular events (89).

1.15.2 Troponin Dynamics during Dialysis

Different studies tried to determine changes in hs-cTn during and after HD in asymptomatic patients. The already published data from our research (91) described a significant decrease

in hs-cTnT compared to baseline in HD with HF (-6.8 % in the first hour and -8.3 % post-dialytic) and MCO dialyzers (-21.9 % 1 h, -33 % post-dialytic) as well as in HDF (-21.2 % 1 h, -28.9 % post-dialytic). In patients dialyzed with LF dialyzers, there was neither a significant change in hs-cTnT over the period of one hour nor one session. Chen *et al.* (92) showed a decrease of hs-cTnT during HD in 10 asymptomatic patients to -11.7 % of the baseline after two hours and -12 % at the end of the HD session, which the authors attribute to the elimination of small cTnT fragments. Another study from 2008 showed, that cTnT decreases significantly after HF-HD, while LF-HD does not lead to a significant drop in cTnT (78). However, the before mentioned study was conducted previous the implementation of hs-cTn assays and therefore might not reflect current conditions. A further study from New Zealand showed a decrease of hs-cTnT (average -16 %) in 78 patients undergoing a session of HDF (79). Cardinaels *et al.* (93) likewise described a decrease in hs-cTnT that occurred in HF-HD over eight hours and HDF but was only significant in HDF, especially in eight-hour sessions . The causal reasons for this finding are unclear and remain the object of further research. One discussed mechanism beside the elimination of troponin due to diffusion, convection or adsorption is the reduced release of hs-cTn as a result of reduced volume strain and thus a decreased burden to the heart (81). On the other hand Wongcharoen *et al.* (71) describe a significant increase of hs-cTnT during HD in a study with 200 asymptomatic patients. A limiting factor for the interpretation of the studies from Chen *et al.* (92) and Wongcharoen *et al.* (71) is the lack of more detailed information on dialysis membranes used.

The changes in cTnI during HD have been subject to multiple studies published. A 2021 trial from Croatia, that included 122 anuric patients and compared the effects of LF- and HF-HD on cTnI levels, showed an increase in patients undergoing LF-HD, while there was no kinetic observed in patients dialyzed with HF dialyzers (94). A second research from 2013 (95) also described a significant increase in cTnI during LF-HD in 66 % of patients, while other publications showed no change or even a decrease. The above-named group of Wongcharoen *et al.* (71) describes no significant increase, nor decrease of cTnI in patients undergoing HD. The authors presume a potential adsorption of cTnI to the membrane as being causal, which was shown in an investigation from Gaze *et al*. (83). Limiting for the significance of this study is the fact, that the authors do not clarify what kind of membrane has been used.

Another investigation from 2019 conducted by Tarapan *et al.* (72) found a decrease in hs-cTnI during HD. Thereby, the majority of the 100 patients treated with HF-HD or HDF

showed a decline (median -36 %) in cTnI after the session, while 25 % of the patients showed elevated cTnI values after HD without any signs of ACS, this might be due to asymptomatic myocardial stunning (72). Likewise, the above-mentioned study from Cardinaels *et al.* (93) also showed a significant decrease of hs-cTnI in patients undergoing HDF for eight hours. However, a described decrease of hs-cTnI in patients undergoing HD for eight hours and HDF for four hours was not significant.

Thus, the kinetic of cTnI during dialysis varies significantly between the studies and there is still no definitive consensus on the dynamics of troponin during HD.

1.15.2.1 Factors influencing troponin dynamics during HD

The dynamics in hs-cTn during HD depend on multiple factors, such as the used membrane, the ultra-filtration rate (HD vs. HDF), the dialysis duration and the type of troponin. However, the individual contribution of these factors to the large variability of hs-cTn during HD remains inconclusive.

Four researches (78,84,94,96), two of which conducted without high-sensitive assays, investigated the effect of different dialyzers on the dynamics of cTnT and/or cTnI. Although most analysis showed a decrease in troponin during HF-HD, the effect of LF-HD is ambiguous. While two studies describe an increase in Trop T (96) respectively in hs-cTnI (94), Lippi *et al.* (78) describe an insignificant decrease of troponin in patients undergoing LF-HD. An older analysis from 2011 did report no significant change in hs-cTnI during HF-HD (84).

Another factor influencing the troponin dynamics, is the convection occurring during the session. Patients undergoing HDF show significantly higher rates of troponin decrease, than patients undergoing conventional HD (-41 vs. -23 % in HDF vs. HF-HD) (96). This was also shown in an additional study, which only found significant troponin dynamics in HDF, not HF-HD (93). The duration of dialysis also seems to have an influence on the dynamics of troponin. Thus, longer dialyses sessions lead to higher reduction rates in hs-cTn (93).

1.15.3 Assessment of Troponin in CKD/ESRD in View of ACS

Twerenbold *et al.* (97) investigated the diagnostic performance of hs-cTn assays in patients with CKD (<60 mL/min/1.73m^2) presenting with suspected NSTEMI. They found good diagnostic performance with both hs-cTn assays, especially if the ESC 0/1h-algorithm was

performed. Although sensitivity for MI following the 0/1h-algorithm was comparable with non-CKD patients, the frequently elevated hs-cTn values decreased the specificity significantly. To improve specificity, other studies propose adapting higher cut-off values depending on the GFR (98). Consequently a higher cut-off increases the specificity comparable to non-CKD patients, but decreased sensitivity in return (99). However, the analysis from Twerenbold *et al.* did not find increased efficiency (proportion of rule-in and rule-out) for modified cut-offs or modified algorithms in CKD patients (97).

In relation to HD-patients, Huang *et al.* (100) showed, that a one-time elevation of hs-cTnT above the 99th percentile in HD patients presenting with chest pain or dyspnea, had only a small specificity (3%) for the presence of an MI. On the other hand, the evaluation of dynamics in hs-cTnT increased the diagnostic accuracy significantly and should therefore be the main tool for diagnosing MI in patients with ESRD.

A previous publication (85) tried to establish reference levels for hs-cTn in ESRD patients with and without CAD. Patients without CAD had a 99th percentile of 204 ng/l for cTnI and 212 ng/l for hs-cTnT ($p<.05$). The 99th percentile for patients suffering CAD were significantly higher in cTnI and hs-cTnT (620 ng/l and 252 ng/l; $p<.05$). They also determined the 95th percentile of biological change (cTnI 117 ng/l; hs-cTnT 77 ng/l) to determine a cut-off for unphysiological troponin dynamics. Due to the large inter- and intraindividual changes in troponin levels, the authors however prefer the use of relative changes.

In contrast, other authors propose GFR-dependent cut-off values (101) or an hs-cTnI above 75 ng/l as ideal cut-off value for patients undergoing HD (102).

To conclude, the determination of hs-cTn for MI is a useful tool in patients with CKD and ESRD, although several factors demand consideration.

1.16 Pitfalls in the Diagnosis of MI in HD Patients

The above-mentioned situation represents a major challenge in the diagnosis and sufficient therapy of myocardial damage, especially infarction, in patients with CKD and ESRD. Beside the atypical clinical presentation in this group of patients described above, which complicates the diagnosis in an early stage and reduces the diagnostic accuracy, the assessment of hs-cTn is rendered even more challenging due to the significant uncertainty that exists based on the missing standard and cut-off values for hs-cTn in this population.

The differentiation of baseline elevations and clinically relevant changes presents an ongoing challenge. This situation gets further complicated, due to the uncertainty concerning the changes of hs-cTn values during HD and HDF.

1.17 Aim of this Thesis

While some inconclusive studies for the dynamics in hs-cTn in patients undergoing LF-HD, HF-HD and HDF are available, until this day no study for the kinetic of hs-cTn in patients treated with novel MCO-membranes. The higher permeability and the bigger cut-off value of 45 kDa lead to the assumption that both clinically relevant forms of hs-cTn can pass the membrane due to their smaller molecular size. In result, this finding leads to the hypothesis, that dialysis with MCO-membranes might - in some situations - lower hs-cTn and therefore might mislead the interpretation of hs-cTn dynamics during HD. This assumption is substantiated by the fact, that other studies were able to show, that these membranes can decrease the concentration of molecules with similar molecular sizes to hs-cTn (40).

While both forms of hs-cTn are used in clinical practice and show almost identical diagnostic accuracy (77,97), hs-cTnI is less commonly elevated above the 99th percentile and might be better suited for the diagnosis of acute myocardial injury in CKD and ESRD patients (71,80,93). Therefore, this thesis focusses on dynamics in hs-cTnI during HD.

Consequently, the aim of this study is to compare the relative change of hs-cTnI at baseline to after one hour of treatment with different HD modalities including MCO-membranes and to compare the relative change from baseline to after completion of the dialysis sessions.

2 Material und Methods

2.1 Ethical Statement

The study has been approved by the Ethics Committee of the University of the Medical University of Graz, Austria (34-306 ex 21/22) and the Austrian Federal Office for Safety in Health Care (101037133). All data was anonymized, and all informed consent was obtained from all patients before entering any study related activity.

2.2 Data Management

In order to protect patient data, all participants were assigned an individual identification number after informed consent and all further activities were performed in this anonymized way. The collected data was encrypted or if printed, stored in a locked room, and therefore was only accessible by the study team. All study related data and materials were stored according to current laws and regulation to protect the identity of all patients participating.

2.3 Literature Research

The literature search was performed in the period from November 2022 to August 2023, using the PubMed, DOAJ, and Europe PMC biomedical databases. Used MESH-terms were among others “Renal Dialysis” AND “Membranes” AND “Troponin”. Further literature was selected based on the references of the literature used. In addition, literature was obtained from the reference collection of the Library of the Medical University Graz.

2.4 Study Design

This was a controlled, prospective, randomized single-center trial carried out at the dialysis unit of the LKH-Universitätsklinikum Graz, Division of nephrology.

2.4.1 Patient Population

Patients for the study were recruited by clinicians during their regular HD sessions in the dialysis center of the LKH-Universitätsklinikum Graz. Only patients fulfilling the inclusion criteria and none of the exclusion criteria listed in table 1 were recruited.

Table 1

Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Pregnancy
ESKD patients undergoing HD for ≥ three months	No confirmed consent was obtained

ESKD = end-stage kidney disease; HD = hemodialysis

2.4.2 Study Procedure

After informed consent was obtained, patient data was collected in a study visit. Subsequently participants were randomized and therefore assigned to one of four sequences by an online randomization tool (Randomizer.at). After randomization, every patient participated in four study sessions, each with a different membrane or modality, respectively. The characteristics of the three membranes used in this study are listed in table 2.

Table 2

Membrane Characteristics

Session	Membrane	Manufacturer	Membrane material[a]	Effective surface area[a] [m^2]	K_{UF}[a] [ml/h x mmHg]
LF	FX 10	Fresenius Medical Care Austria GmbH	Helixone®	1.8	14
HF and HDF	FXCorDiax800	Fresenius Medical Care Austria GmbH	Helixone® *plus*	2.0	62
MCO	Theranova 400	Gambro Dialysatoren GmbH	Polyarylethersulfon-Polyvinylpyrrolidon	1.7	48

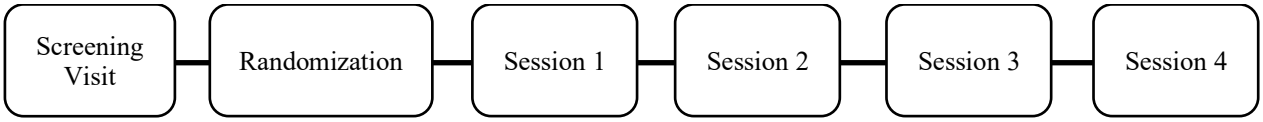
LF = low-flux dialysis; HF = high-flux dialysis; HDF = hemodiafiltration; MCO = medium cut-off dialysis

[a]According to manufacturer information

The study sessions were conducted following the randomization between September and December 2022 with consecutive sessions. The sessions were carried out after the short interval, thus on Wednesdays and Fridays as well as Thursdays and Saturdays, to prevent bias due to higher ultrafiltration rates on the first day after the longer interdialytic period. Furthermore, we assumed that hs-cTnI reaches a steady state after 48 hours. The study process is shown in figure 1.

Figure 1

Flowchart of Study Procedure



2.4.3 Data Collection

After informed consent was obtained, patient data was collected in the screening visit. The information was provided by the local hospital information system by manual search in discharge letters and diagnostic findings. The details included demographic data and medical history, that are listed in table 3. A preexisting cardiovascular disease was with the presence of at least one of the following diagnoses: cerebral, coronary or/and peripheral artery disease.

Table 3

Screening Visit

Demographics	• Age • Gender • Smoking habit
Comorbidities	• Cardiovascular disease • Diabetes mellitus • Arterial hypertension • Left ventricular hypertrophy • Status post myocardial infarction • Primary renal disease

Dialysis related data	• Euvolemic state • Residual renal function [ml/d] • Period since start of dialysis in months • Dialysis access

After every session the dialysis protocol was screened for the presence of IDH, chest pain and/or systolic BP drops that occurred without any symptoms. IDH was defined as a drop of the systolic BP ≥30 mmHg with the appearance of symptoms (e.g. nausea, headache, dizziness) or a resulting therapeutic intervention (e.g. stop of ultrafiltration or leg elevation). All decreases of the systolic BP ≥30 mmHg without symptoms or therapeutic intervention were defined as simple BP drops.

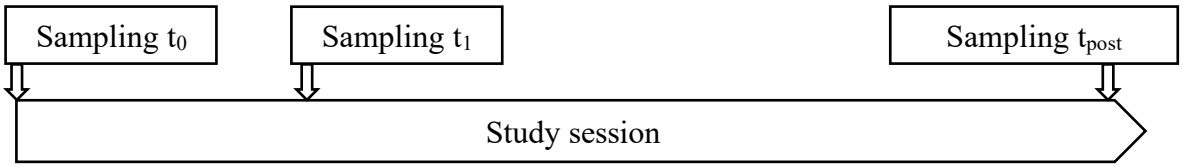
Additionally, dialysis-specific data, such as ultrafiltration volume, blood- and dialysate-flow and dialysis duration were collected from the dialysis protocol for every session.

2.4.4 Conduction of Individual Dialysis Sessions

Study sessions were performed with standardized settings with a dialysate temperature of 35.5 °C, dialysate calcium of 1.25 mmol/l and dialysate bicarbonate of 30 mmol/l. The concentration of sodium, potassium and the ultrafiltration rate were individually set by the physician on duty, depending on patient needs. In all study sessions two blood samples were taken at the beginning (t_0), after one hour (t_1) and at the end of the dialysis session (t_{post}) as shown in figure 2. Thus, 6 samples were taken each session which leads to 24 samples per patient. Blood draws were performed by the nursing staff of the dialysis center in Lithium-Heparin tubes (BD Vacutainer® Brand Tubes with Lithium-Heparin) and afterwards directly sent to the Biobank and the Clinical Institute for Medical and Chemical Laboratory Diagnostics of the Medical University of Graz. Intradialytic events, such as IDH, and possible interventions were noted in the dialysis protocol by the nursing team and later noted in the study protocol.

Figure 2

Sampling Points



Two samples each were taken at three different sampling points. At the beginning (t_0), after the first hour (t_1) and right at the end of the dialysis session (t_{post}).

2.4.5 Laboratory Analysis

The laboratory analysis was executed by the central clinical laboratory (KIMCL) of the LKH Universitätsklinik Graz with Alinity I STAT High Sensitive Troponin-I Reagent Kit (Abbott Ireland Diagnostics Division, Lisnamuck, Longford, Ireland). Additionally, the hematocrit was measured for all three sampling points.

Since the fluid removal during treatment leads to a concentration of substances dissolved in the blood, the hs-cTn concentrations were subsequently corrected for the occurring hemoconcentration at the final data analysis.

2.4.6 Statistical Analysis

The statistical analysis was conducted independently using IBM SPSS Statistics 28. All data were tested for normal distribution using the Shapiro-Wilk test. With the exception of a few parameters, the data was not normally distributed. Therefore, the median is used as central tendency in this thesis. Non-parametric data was analyzed using the Mann-Whitney-U-test and the Wilcoxon test. To compare multiple nonparametric data, the Kruskal-Wallis test was used. Furthermore, the Spearman correlation coefficient was used to analyze non-parametric correlations. A significance level of $p<.05$ was set for all conducted analyses. For hs-cTnI values below the lower limit of detection (<10.0 ng/l), a value of 10 ng/l was imputed. The correction of hs-cTnI values based on the hematocrit was performed using the correction formula published by Schneditz *et al.* (103).

3 Results

3.1 Baseline Characteristics

For this study, 22 patients were recruited, but two withdrew their informed consent before the first study visit. An additional patient was excluded during data analysis since the patient suffered a NSTEMI during the study period, and these disproportionately elevated levels of hs-cTn would have significantly impeded the interpretation of the data.

Of the 19 patients who were included in the final analysis, 47.4 % were female, and the median age was 66 years (IQR 59–78). While most participants were non-smokers (63.2 %), about one-third were former smokers (31.6 %) and one participant was an active smoker (5.3 %). The participants were on dialysis for a median of 19 months (IQR 5–58) and had a median renal residual urine volume of 250 ml/d (IQR 0-500). The majority was dialyzed via a percutaneous dialysis catheter (84.2 %) while three patients had a dialysis shunt (15.8 %). All patients were in euvolemic state at the time of the study. The specific baseline characteristics of the participants are shown in table 4.

The most frequent comorbidity was arterial hypertension (89.5 %), additionally 68.4 % of all patients had at least some form of CVD, 36.8 % already had at least one myocardial infarction and 31.6 % of the patients also suffered from diabetes mellitus. The most common primary renal diseases in this study population were diabetic and/or vascular nephropathy (36.9 %) and acute to chronic kidney failure (26.3 %). The frequency of underlying primary renal diseases in the study population are shown in figure 3.

Figure 3

Underlying Renal Disease

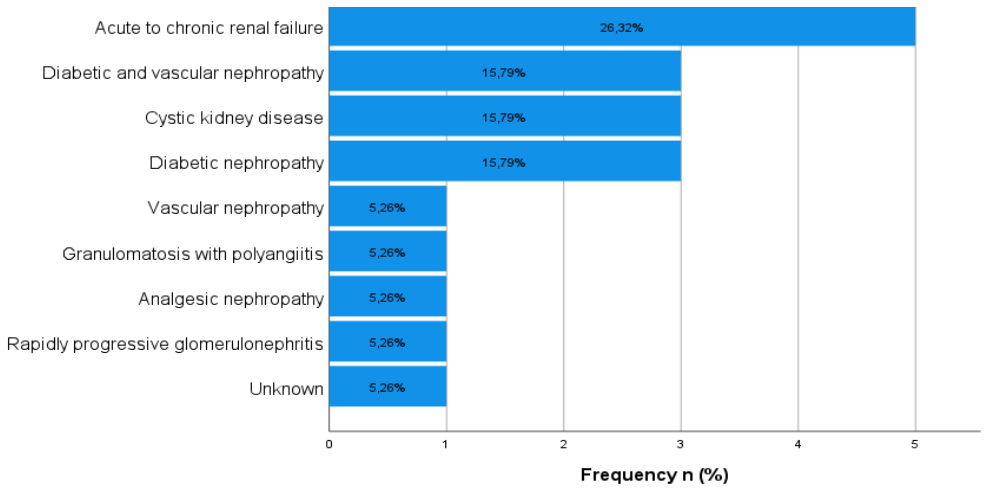


Table 4

Baseline Characteristics

age in years, median (IQR)	66 (59–78)
sex, n (%)	
male	10 (52.6)
female	9 (47.4)
smoking habits, n (%)	
non-smoker	12 (63.2)
former smoker	6 (31.6)
active smoker	1 (5.3)
comorbidities, n (%)	
arterial hypertension	17 (89.5)
cardiovascular disease	13 (68.4)
left-ventricular hypertropia	14 (73.7)
status post myocardial infarction	7 (36.8)
diabetes mellitus	6 (31.6)
dialysis treatment period in months, median (IQR)	19 (5–58)
renal residual urine volume in ml/d, median (IQR)	250 (0–500)
dialysis access, n (%)	
percutaneous dialysis catheter	16 (84.2)
dialysis shunt	3 (15.8)
euvolemic state, n (%)	19 (100)

IQR= interquartile range

3.2 Troponin I

Due to technical problems, some samples could not be analyzed completely and therefore these results were not included in the statistical analysis. In total, 5 samples for the determination of hs-cTnI and 8 samples for the determination of the hematocrit were excluded due to missing data.

The median baseline of hs-cTnI in the study population at the beginning of the dialysis sessions was 34.25 ng/l (IQR 15.25–121.96), 58.3 % of which were above the 99th percentile cut-off value for the diagnosis of MI with the used assay (overall ≥27 ng/l), according to the FDA approval document (104).

A significant difference in baseline hs-cTnI between patients with CVD and without CVD was found (U=216; Z=-3.976; p<.001). The patients with CVD had a median hs-cTnI of 47.7 ng/l (IQR 21.1–190.5) and patients without CVD presented with a median hs-cTnI of 16.6 ng/l (IQR 10.0–30.1), showing that CVD patients have a higher hs-cTnI level. The effect size was medium (r=.468).

In relation to LVH there was no difference in baseline hs-cTnI (p=.917) with a median of 33.15 ng/l (IQR 16.38–115.13) in patients with LVH and 39.65 ng/l (IQR 10–131.47) in patients without LVH.

Additionally, patients with diabetes mellitus did not have differences in baseline hs-cTnI (p=.785) compared to those without. The median hs-cTnI in patients with diabetes mellitus was 29.7 ng/l (IQR 11.9–138.9) while patients without diabetes mellitus presented with a median hs-cTnI of 36.4 ng/l (IQR 15.4–114.95).

Furthermore, there was no difference (p=.520) in baseline hs-cTnI in patients with a residual renal function of 500 ml/d or less (median 27.6 ng/l; IQR 10–64.8) compared to those with a residual renal function of more than 500 ml/d (median 35.5 ng/l; IQR 15.55–139.78). There was no statistically significant correlation between residual renal function and the baseline hs-cTnI levels ($\rho(70)$=-0.87; p=.470). Also the age and baseline hs-cTnI did not have a correlation ($\rho(70)$=-0.124; p=.298).

3.3 Intradialytic Events

While BP drops ≥30 mmHg were recorded during 19 sessions (25 % of all sessions), these drops were only accompanied by symptoms such as nausea and emesis in 4 sessions (5,3 %) and therefore classified as IDH.

Blood pressure drops occurred on an almost equal level with each membrane (HF=5; LF=5; MCO=5; HDF=4) and therefore no further investigation in the interrelation between used membrane type and the occurrence of BP drops and IDH was conducted.

3.4 Changes and Dynamics

3.4.1 High-flux Dialyzer

The median hs-cTnI at baseline before starting dialysis with HF-membrane was 34.60 ng/l (IQR 10.1–157.80). The median dialysis time with the HF membrane was 242 minutes (IQR 228–249), and a median blood flow of 290 ml/min (IQR 260.50–291.50) and dialysate flow of 490 ml/min (IQR 475.00–499.50) were applied. At the end of dialysis treatment with the HF membrane, the median ultrafiltration volume was 2900 ml (IQR 1900–3500).

There was no difference in hs-cTnI at baseline compared to the second measurement one hour after the start of dialysis (p=.408). The median hs-cTnI at baseline was 34.6 ng/l (IQD 10.1–157.8) and after one hour the median was 46.0 ng/l (IQD 10.0–105.1). On top, regarding the dynamics between baseline and the final measurement, no difference could be observed (p=.65; median end 39.95 ng/l; IQD 15.78–155.7). The median hs-cTnI values, maximum and minimum values of hs-cTnI for the different sampling points as well as their changes are listed in Table 5. Figure 6 illustrates a boxplot for the median hs-cTnI at the three different sampling points in patients dialyzed with HF membrane.

While 10 patients (52.6%) showed a decrease of hs-cTnI with a median of -15.50 ng/l (IQR -176.28–-8.28) in the first hour, 6 patients (31.6 %) showed an increase with a median of +45.3 ng/l (IQR 3.70–360.53) and 3 had no change (15.8 %) in the first hour. Between baseline and the post-dialytic hs-cTnI, 10 patients had a decrease (52,6 %; median -16.00 ng/l; IQR -125.70–-1.70), 5 patients an increase (26.3 %; median 106.20 ng/l; IQR 42.65–441.05) and 3 patients (15.8 %) did not have different hs-cTnI values between baseline and the end of the session.

Table 5

Values and Kinetics of hs-cTnI in High-flux Dialysis

	Baseline	First hour	End of Session
hs-cTnI (IQR)	34.60 ng/l (10.1–157.80)	46.00 ng/l (10.00–105.10)	39.95 ng/l (15.78–155.78)
Absolute change to baseline (IQR)		-0.10 ng/l (-17.30–4.5)	-0.60 ng/l (-43.15–33.88)
Relative change to baseline (IQR)		-0.99 % (-36.27–13.01)	-0.72 % (-51.60–139.32)
Minimum	10.0 ng/l	10.0 ng/l	10.0 ng/l
Maximum	593.9 ng/l	501.1 ng/l	794.9 ng/l

hs-cTnI = high-sensitivity troponin I IQR= interquartile range

3.4.2 Low-flux Dialyzer

In the sessions in which the LF membrane was used, the median hs-cTnI value at baseline was 35.20 ng/l (IQR 11.42–119.23) and the session lasted for a median of 242 minutes (IQR 237–244). A median blood flow of 284 ml/min (IQR 247–290) and a dialysate flow of 491 ml/min (IQR 479–502) were observed. The post-dialytic ultrafiltration volume amounted to a mean of 2300 ml (IQR 1600–3400).

While there was no difference between hs-cTnI at baseline and one hour later (p=.227), with a baseline median of 35.2 ng/l (IQR 11.43–119.26) and a median of 74.6 ng/l (IQR 35.5–165.4) after one hour, a difference was found (Z=2,12; p=.034) with a median post-dialytic hs-cTnI of 56.4 ng/l (IQR 33.9–355.2). Therefore, patients dialyzed with the LF-membrane showed higher hs-cTnI levels after finishing the dialysis session compared to baseline. The observed effect size was medium (r =.499).

In the first hour, 6 patients showed a decrease (31.6 %; median -15.20 ng/l; IQR -114.35–-6.40), 11 patients presented with an increase (57.9 %; median 66.90 ng/l; IQR 3.60–155.40) and one patient (5.3 %) did have no change in their hs-cTnI. Between baseline and the end of the dialysis session 11 patients had an increase (57.9 %; median 197.00 ng/l; IQR 24.40–269.30), 5 persons a decrease (26.3 %; median -4.00 ng/l; IQR -122.75–-3.6) and 2 patients (10.5 %) no change in hs-cTnI. Table 6 displays the median hs-cTnI values, along with the maximum and minimum values for hs-cTnI at various sampling points, as well as the corresponding changes during the session. Figure 7 displays

the median levels of hs-cTnI at the three sampling points for patients undergoing dialysis with a LF membrane.

When comparing patients with an intradialytic increase to those without such increase, there was no difference in ultrafiltration volume (p=.860), dialysis duration (p=.536), blood flow (p=.659), dialysate flow (p=.791) nor age of the patients (p=.069). The median relative change in patients with increasing hs-cTnI levels was +234 % (IQR 59–454) and -11 % (IQR -27–.00) in patients without rises in hs-cTnI.

Table 6

Values and Kinetics of hs-cTnI in Low-flux Dialysis

	Baseline	First hour	End of Session
hs-cTnI (IQR)	35.20 ng/l (11.43–199.23)	74.60 ng/l (35.50–165.40)	56.40 ng/l (33.90–55.20)
Absolute change to baseline (IQR)		3.45 ng/l (-8.45–81.25)	14.60 ng/l (-3.45–250.50)
Relative change to baseline (IQR)		18.14 % (-13.17–306.52)	53.74 % (-6.71–268.08)
Minimum	10.0 ng/l	10.0 ng/l	10.0 ng/l
Maximum	238.7 ng/l	324.1 ng/l	480.6 ng/l

hs-cTnI = high-sensitivity troponin I IQR= interquartile range

3.4.2.1 Influences on hs-cTnI dynamics with low-flux dialyzer

Since there was a difference observed between baseline and end of session, a multiple regression analysis was conducted. With the predictor's dialysis duration, blood flow per minute, dialysate flow per minute and ultrafiltration volume and the dependent variable difference in hs-cTnI comparing baseline and the end of the session. However, none of the above-mentioned predictors explain any of the variants in the hs-cTnI between baseline and the end of the session ($F(4, 13)=1.395$; p=.290).

3.4.3 MCO Dialyzer

Prior to treatments with the MCO dialyzer, patients had a median hs-cTnI of 37.60 ng/l (IQR 16.38–102.23) and were dialyzed for a median of 245 minutes (IQR 239.00–247.00). The median blood flow amounted 287 ml/min (IQR 271–290) and the median dialysate flow was

486 ml/min (IQR 470–504). The median post-dialytic ultrafiltration volume was 2400 ml (IQR 1300–3400).

There was no difference from the baseline hs-cTnI either in terms of change after one hour (p=.193) nor to the end of dialysis (p=.469). After one hour the median was 42.5 ng/l (IQR 10-220.5) and at the end of the dialysis session the median was 49.7 ng/l (IQR 18.6–246.1).

The different median values for hs-cTnI together with relative and absolute changes between the sampling points are shown in table 7. A graphical representation of the median hs-cTnI at the three sampling points during dialysis with MCO membrane is shown in Figure 8.

While 11 patients showed an increase (57.9 %; median 12.00 ng/l; IQR 3.70–114.30) in hs-cTnI during the first hour, 6 patients had a decrease (31.6 %; median -24.10 ng/l; IQR -58.63–-2.73) and one (5.3 %) did not show any dynamics during this time frame. Regarding the changes in hs-cTnI occurring during one session with MCO-membrane, eight patients showed an increase (42.1 %; median 75.30 ng/l; IQR 9.53–313.48) or decrease (42.1 %; median -24.80 ng/l; IQR -51.13–-2.78) each. Two patients (10.5 %) showed no dynamics over the period of one treatment.

Table 7

Values and Kinetics of hs-cTnI in MCO Dialysis

	Baseline	First hour	End of Session
hs-cTnI (IQR)	37.60 ng/l (16.38–102.23)	49.70 ng/l (18.60–246.10)	42.50 ng/l (10.00–220.50)
Absolute change to baseline (IQR)		2.55 ng/l (-7.13–93.35)	0.00 ng/l (-19.20–51.60)
Relative change to baseline (IQR)		8.13 % (-11.11–77.14)	0.00 % (-21.09–107.98)
Minimum	10.0 ng/l	10.0 ng/l	10.0 ng/l
Maximum	314.2 ng/l	477.4 ng/l	500.6 ng/l

hs-cTnI = high-sensitivity troponin I IQR= interquartile range

3.4.4 Hemodiafiltration

The median hs-cTnI at baseline before HDF treatments was 28.50 ng/l (IQR 10.0–114.20) and these sessions lasted for a median of 241 minutes (IQR 226–247). The median blood

flow was 284 ml/min (IQR 255–497) and the dialysate flow was 484 ml/min (IQR 449–497). The median ultrafiltration volume was 2000 ml (IQR 1800–2800).

There was no difference in hs-cTnI from baseline to the second measuring point one hour after the start (median 44.6 ng/l; IQR 25.53–381.38; p=.551). No difference could be observed between baseline and the end of the session eighter (p=.272; median end 34.3; IQR 10.9–147.7). Table 8 shows the median hs-cTnI as well as the relative and absolute change between the different sampling points. A boxplot illustrating the median hs-cTnI at the three different sampling points in patients dialyzed with HDF is shown in figure 9.

In the first hour, 7 patients had an increase (36.8 %; median 15.60 ng/l; IQR 5.10–289.60) and other 7 patients a decrease (36.8 %; median -7.30 ng/l; IQR -80.60–-0.90) in hs-cTnI during the first hour. Another two patients (10.5 %) did not show any dynamics during the first hour of HDF. In relation to one session, the majority of patients had an increase (n=11; 57,9 %; median 24.80 ng/l; IQR 1.40–141.20), three (15.8 %) had no dynamics and other three patients had a decrease in hs-cTnI (15.8 %; median -417.40; IQR -469.10–-104.60).

Table 8

Values and Kinetics of hs-cTnI in Hemodiafiltration

	Baseline	First hour	End of Session
hs-cTnI (IQR)	28.50 ng/l (10.00–114.20)	44.60 ng/l (25.53–381.38)	34.30 ng/l (10.90–147.70)
Absolute change to baseline (IQR)		0.0 ng/l (-6.08–14.20)	1.40 ng/l (0.00–93.95)
Relative change to baseline (IQR)		0.0 % (-6.85–82.39)	9.00 % (0.0–186.68)
Minimum	10.0 ng/l	10.0 ng/l	10.0 ng/l
Maximum	479.1 ng/l	567.7 ng/l	572.5 ng/l

hs-cTnI = high-sensitivity troponin I IQR= interquartile range

3.5 Comparison of Changes with Different Treatments

The relative change in patients dialyzed with the HF membrane was -0.99 % (IQR -36.27–13.01) in the first hour and -0.72 % (IQR -51.60–139.32) at the end of the session compared to the baseline. In sessions that were conducted with LF membranes, the relative change from baseline amounted to +18.14 % (IQR -13.17–307.52) after the first hour and +53.74 %

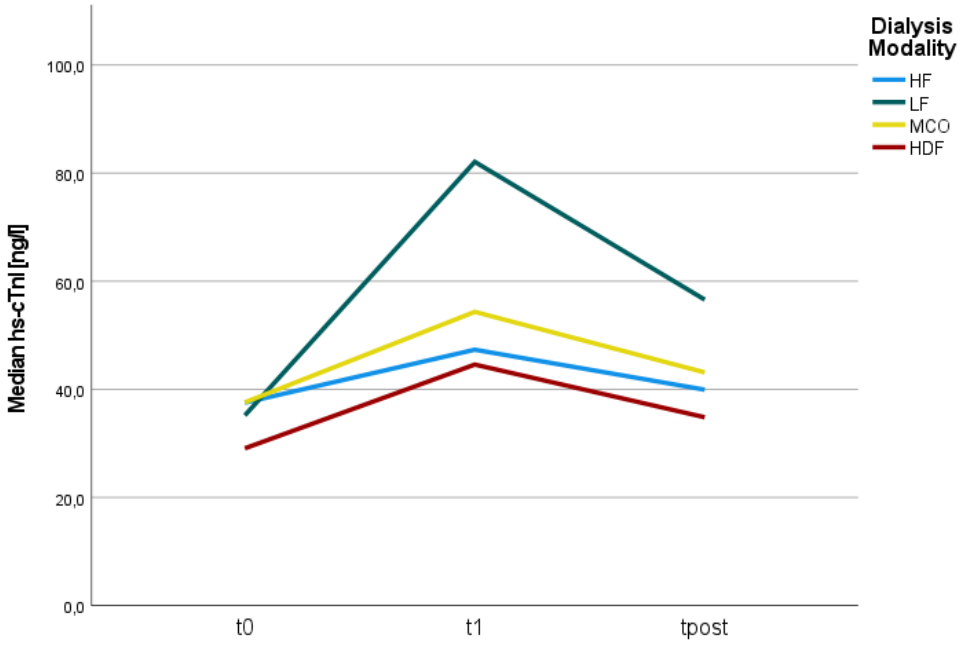
(IQR -6.71–268.08) at the end of the session. The hs-cTnI measured during sessions with the MCO membrane showed a relative change of +8.13 % (IQR -11.11–77.14) after one hour and 0.00 % (IQR -21.09–107.89) compared to baseline. In patients dialysed with HDF the median relative change was 0.00 % (IQR -6.85–82.39) after one hour and +9.0 % (IQR 0.0–186.68) at the end.

There was no significant difference between the four treatment types in relation to the relative changes of hs-cTnI at baseline compared to one hour after the beginning of the session (H(3)=3.026; p=.388). In regard to the relative changes between baseline and the end of the session, no difference was found between the four membranes (H(3)=3.368; p=.338) eighter.

Figure 4 shows the median hs-cTnI concentrations for each membrane at the three different sampling points.

Figure 4

Median hs-cTnI in Different Dialysis Modalities at Different Sampling Points



LF = low-flux dialysis; HF = high-flux dialysis; MCO = medium cut-off dialysis; HDF = hemodiafiltration; t_0 = baseline; t_1 = after the first hour; t_{post} = end of the session

3.6 Changes and Dynamics Corrected for Hemoconcentration

3.6.1 High-flux Dialyzer

The median hs-cTnI value corrected for hemoconcentration after the first hour was 45.74 ng/l (IQR 10.0–113.43) and 34.93 ng/l (IQR 16.99–144.66) at the end of the session. There was no difference between hs-cTnI values at baseline compared to the first hour (p=0.196; median baseline 34.60 ng/l; IQR 10.1–157.80), nor from baseline to the end of the session (p=0.356).

3.6.2 Low-flux Dialyzer

In session conducted with the LF membrane, the corrected median of hs-cTnI was 64.47 ng/l (IQR 29.71–178.80) after the first hour and 45.51 ng/l (IQR 29.33–321.02) at the end of the session. There was no difference from the baseline hs-cTnI either in terms of change after one hour (p=.381; median baseline 35.20 ng/l; IQR 11.42–119.23) nor to the end of dialysis (p=.134).

3.6.3 Medium Cut-off Dialyzer

In patients dialyzed with MCO membranes, the corrected median value of hs-cTnI after the first hour was 47.63 ng/l (IQR 14.29–234.06) and 37.59 ng/l (IQR 9.53-194.23) at the end. Regarding dynamics between baseline (median 37.60 ng/l; IQR 16.38–102.23) and the first hour, there was no difference (p=.500), nor between the end of the session (p=.938).

3.6.4 Hemodiafiltration

In HDF sessions the corrected median hs-cTnI after the first hour was 42.50 ng/l (IQR 21.34–78.64) and 29.13 ng/l (IQR10.16–152.30) after the end of the session. No dynamics were observed between baseline (28.50 ng/l; IQR 10.0–114.20) and the first hour (p=.807) nor between baseline and the end of the session (p=.427).

The corrected median hs-cTnI values for each used modality and at the different sampling points are listed in table 9. The course of the median hs-cTnI over the course of the various sampling points for each modality is shown in figure 8.

Table 9

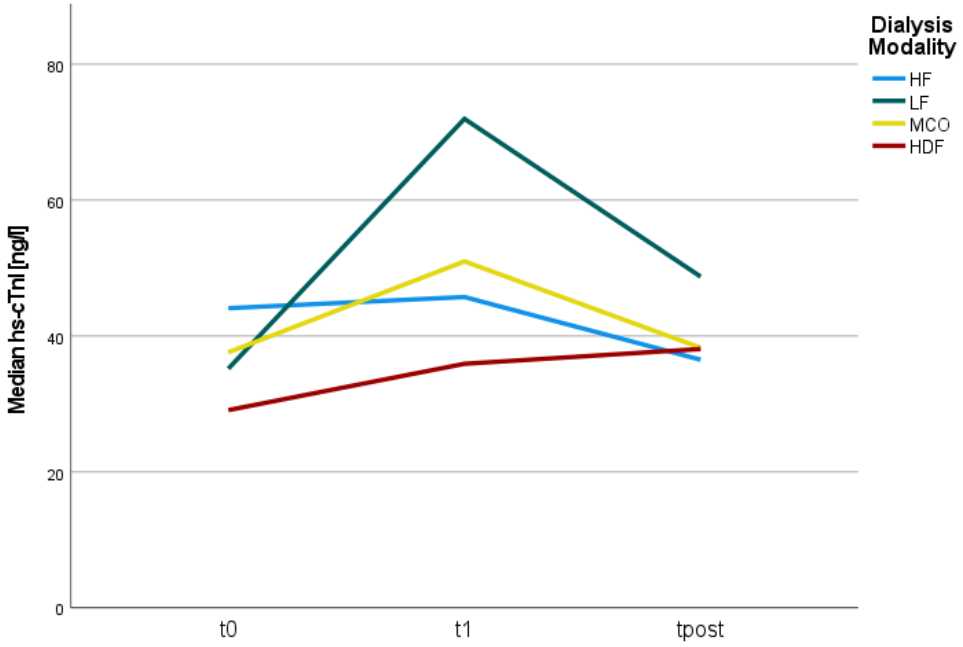
hs-cTnI Values Corrected for Hemoconcentration

	Baseline	After one hour	End of session
HF	34.60 ng/l (IQR 10.10–157.80)	45.74 ng/l (IQR 10.0–113.43)	34.93 ng/l (IQR 16.99–144.66)
LF	35.20 ng/l (IQR 11.43–199.23)	64.47 ng/l (IQR 29.71–178.80)	45.51 ng/l (IQR 29.33–321.02)
MCO	37.60 ng/l (IQR 16.38–102.23)	47.63 ng/l (IQR 14.29–234.06)	37.59 ng/l (IQR 9.53-194.23)
HDF	28.50 ng/l (IQR 10.00–114.20)	42.50 ng/l (IQR 21.34–78.64)	29.13 ng/l (IQR 10.16–152.30)

LF = low-flux dialysis; HF = high-flux dialysis; HDF = hemodiafiltration; MCO = medium cut-off dialysis; hs-cTnI = high-sensitivity troponin I; IQR= interquartile range

Figure 5

Median hs-cTnI Corrected for Hemoconcentration in Different Dialysis Modalities at Different Sampling Points



LF = low-flux dialysis; HF = high-flux dialysis; MCO = medium cut-off dialysis; HDF = hemodiafiltration; t_0 = baseline; t_1 = after the first hour; t_{post} = end of the session

4 Discussion

The aim of this thesis was to evaluate the relative changes of hs-cTnI in the first hour of dialysis, depending on different membranes, with a special focus on MCO membranes. Secondary endpoints were dynamics in hs-cTnI between baseline and the end of each dialysis session.

When considering the relative change of hs-cTnI depending on the membrane used, no significant relative change was found either in the first hour or over the course of an entire session. Therefore, the MCO membrane did not lead to any significant dynamics in either of the two measurement periods, regardless of whether a correction was made for the hemoconcentration or not. An exception was the HD with LF membrane which showed a significant increase in hs-cTnI. Nevertheless, this increase was no longer significant after correction for the hemoconcentration that occurred during the session.

The previous published observation of frequently elevated baseline hs-cTnI values in ESRD-patients and some of the previously publicized correlations, were also present in this patient population.

4.1 Baseline Cardiac Troponin Values

The baseline hs-cTnI level of this study population was in the range of previously published studies. While the median hs-cTnI baseline in this study was 34.25 ng/l other authors reported baseline values between 14.0–54.3 ng/l. Also, the proportion of patients with a baseline value that exceeds the test-specific cut-off value (99^{th} percentile ≥27 ng/l) was within the range of previous publications (70–72,80,82). The reason for these findings might be the impaired renal elimination of cTnI in patients with ESRD, nevertheless a correlation of baseline hs-cTnI depending on the residual renal function could not be shown in this study population. However, this might also be due to the relatively small number of patients included in the study and the fact that residual renal function was quantified merely based on residual daily urine production without any assessment of remaining renal excretory function. Another underlying reason for elevated hs-cTnI baseline levels could be the higher rate of, partly asymptomatic, CVD in HD patients (56).

The previously published connection between the presence of CVD and elevated baseline hs-cTnI could be confirmed in our group of patients. The elevated baseline values in patients with CVD might reflect the higher rate of CAD in this group and a therefore elevated rate of

asymptomatic myocardial damage that occurs during HD (105). The correlation between the severity of CAD and the baseline level of hs-cTnI has been shown by others previously (82).

Other factors such as diabetes mellitus or LVH did not show a significant influence on the measured baseline values (84,85). This stands in contrast to authors, that described a further impact from LVH on hs-cTnI in dialysis patients (84). Reasons for this finding could be the small sample size and the heterogeneity of our study population.

4.2 Troponin Kinetics in Dialysis with MCO Dialyzers

Since MCO dialyzers show significantly better elimination of larger middle sized molecules up to 45kDa (38,40), it was expected that hs-cTnI with a size of 24 kDa would also be eliminated to a greater extent compared to other membranes with smaller pore-size such as HF or LF. This assumption was supported by the fact that middle sized molecules with a similar or bigger molecular size than cTnI (i.e. kappa free light chains ~22.5 kDa or lambda free light chains 45 kDa) were eliminated to a greater extent in MCO membranes compared to HF-HD or even HDF (40,106).

Contrary to the assumption of an increased elimination of cTnI with MCO dialyzers, the median hs-cTnI levels did not differ between baseline compared to one hour after start and to the end of the session in our study population. Even after correction for hemoconcentration, there was no significant kinetic, neither after one hour nor after the end of the session.

One reason for this finding might be the increased release of troponin during dialysis due to myocardial stunning and cardiovascular stress (90,107). Another factor might be the fact, that the elimination of medium-size molecules depends not only on size but also on charge, hydrophilic properties and binding to other molecules (108). This theory is supported by the fact, that the pro-inflammatory molecule interleukin-6 which presents with a similar size to cTnI (24.5 kDa) does not decrease significantly during HD with MCO membranes (38,108). It seems therefore, that the changes on hs-cTnI during HD does not only depend on permeability respectively the flux of the membrane but rather on multiple factors that might include the material of the used membrane and their chemophysical characters, the structure and chemophysical characteristics of hs-cTnI fragments as well as the *de-novo* release of hs-cTnI during HD depending on the individual patient and comorbidities.

4.3 Troponin I Dynamics during LF, HF and HDF

In this thesis no significant dynamics in relation to relative changes between baseline and one hour into the session nor to the post-dialytic values could be shown. The only observed dynamics occurred in patients dialyzed with LF dialyzers between baseline and at the end of the session. This result is consistent with other publications that showed an increase of hs-cTnI in patients after dialysis with LF dialyzers (94,95). However, the observed increase was only detectable in the analysis without correction for the hemoconcentration and therefore may be a mere consequence of hemoconcentration.

The proportion of patients with hs-cTnI elevations during LF-HD is comparable previously published data (95). Despite the fact that the elevation of hs-cTnI in LF-HD was shown in other publications, a conclusive explanation for this finding remains elusive. Since HD puts a strain on the cardiovascular system and shows negative effects on myocardial perfusion and function, i.e. myocardial stunning (105), the release of cTnI might be elevated in all HD sessions. Due to the small pore size of LF membranes, the additional cTnI might be eliminated to a smaller extent and therefore a net increase in hs-cTnI is observed. On the other hand, the findings of Gaze *et al*. (83) showing adhesion of TnI in LF membranes, might even reduce the observed hs-cTnI increase during LF-HD.

A significant decrease of hs-cTnI during HF and HDF that has been published by different authors before (72,93), was not observed in this group of patients. While Cardinaels *et al.* (93) presented a non-significant decrease of hs-cTnI in dialysis sessions lasting four hours, the median hs-cTnI in patients dialyzed with HF and HDF in this study showed a non-significant increase in hs-cTnI at both measuring points that also was persistent after correction for hemoconcentration.

4.4 Mechanisms Influencing Troponin I Dynamics in Dialysis

While neither the flux of the used membrane, nor the ultrafiltration volume, has a significant impact on hs-cTnI, except for LF-HD, there remains uncertainty about the cause of this observation. In particular, since hs-cTnT does significantly decrease during HF-HD, HDF and MCO-HD, even though the molecule is bigger and therefore should be cleared in smaller extend compared to hs-cTnI (91).

One factor that comes into play could be the increased release of troponin that counteracts the elimination during HD and HDF. Thus, any dialysis treatment causes stress on the heart

and circulatory system, resulting in the release of troponin independently of ischemic damage to the myocardium (51,55,105). The effect of increased release of troponin may be amplified by hemoconcentration that occurs during HD and HDF and lead to a distorted picture in the laboratory analysis. Even though, the correction for hemoconcentration did not show any significant effect on the results.

On the other hand, the increased release and the concentration of troponin might be compensated by the filtration of troponin during dialysis but also by the absorption of troponin fragments to the membrane (83). Since the filtration of molecules in dialysis does not only depend on size but many other factors, such as charge, three-dimensional structure and protein-binding, the dynamics of cTnI during dialysis depends on an interplay of several factors that are not understood completely until now (108).

Furthermore, a study from Labugger *et al.* (109) showed substantial modification processes of cardiac troponin within patients suffering MI. Thus, the authors showed a degradation of cTnT and cTnI in fragments as well as an increased amount of phosphorylation in cTnI molecules in their cohort. The authors discuss that the fragmentation of cardiac troponin is not the result of proteolytic activity in the blood but rather intracellular processes in damaged myocytes. Since patients with ESRD also present with higher levels of cTnI, potentially due to myocardial stunning, the published fragmentation in combination with negative charge due to phosphorylation might also lead to an impaired elimination during dialysis. Another factor influencing the dynamics of hs-cTnI during HD and HDF seems to be the individual patient. Although a significant increase in troponin was observed in the study population during LF-HD, several patients showed a decrease in troponin levels in LF-sessions. The reason for this observation could be the different constellation of comorbidities, individual tolerability of dialysis, cardiovascular fitness, and other unidentified factors.

Since LF membranes have the smallest pore size of the examined membranes and might not even allow the passage of the smallest hs-cTnI degradation fragments (~14.3 kDa), the additional hs-cTnI release that occurs during HD might not be counteracted by the previously shown adsorption of cTnI fragments at the LF membrane (83) and therefore result in a small but significant net increase of hs-cTnI during LF-HD. Nevertheless, the observed increase in hs-cTnI vanished after the correction for hemoconcentration and therefore might only be a mere consequence of fluid retention.

4.5 Strengths and Limitations

Our study has several strengths. To our knowledge, this was the first clinical trial that investigated the effect of the newly introduced MCO dialyzers on hs-cTnI in comparison to other HD modalities. The randomized, cross-over study design did provide a direct comparison of the effect of different modalities and dialyzers on hs-cTnI values. The sampling schema, which included baseline measurements and subsequent sampling points at one hour into the session and immediately post-dialytic was used the first time. This approach allowed the evaluation of short-term dynamics of hs-cTnI during the initial hour.

There are some limitations to this study. The biggest limitation is the small cohort of patients included and the number of potential confounders, such as the wide range of residual renal function and pre-existing conditions that lead to an inhomogeneous study population. Since this study only included patients without ACS or MI, the main target group of the focused topic was excluded and therefore reduces its clinical implication.

4.6 Conclusion

The effect of different dialyzers and dialysis modalities on hs-cTnI levels in patients that receive chronic HD remains uncertain. While we could confirm the previously reported elevation of hs-cTnI in patients receiving LF-HD, the effect of other dialyzers, especially MCO dialyzers remains unclear. Analysis, conducted with values corrected for the hemoconcentration did not show any significant changes in hs-cTnI levels during HD regardless of the modality used.

Thus, the persisting uncertainty regarding the evaluation of hs-cTnI values in dialysis patients and the management of dialysis patients presenting with symptoms of MI and elevations in hs-cTnI remains. Due to the observed large variabilities of hs-cTnI dynamics during HD, diagnosis of MI based on established cut-offs of cTnI appears of limited use in this population. The proposed definition of personal cut-offs and ranges for acceptable variations in hs-cTnI might be beneficial to improve the sensitivity and specificity in the diagnosis of MI during HD, but there remains the uncertainty of interindividual dynamics of hs-cTnI during HD.

In order to enhance the sensitivity and specificity of MI detection in this patient cohort, it would be advantageous to identify a biomarker that would remain stable or shows a predictable dynamic during therapy. But since such biomarker has not been identified yet

and likely will not be in the future, the already established combination of clinical, electrocardiographic, and laboratory analyses should be utilized to maximize diagnostic precision for MI in this population.

4.7 Future Perspective

Since this study included only a small number of patients with multiple confounders, further investigations including a larger sample size and greater homogeneity may be helpful to address the uncertainty surrounding the assessment of hs-cTnI in dialysis patients during treatment.

To examine, whether the effect of missing dynamics in hs-cTnI in HD is the result of an elevated release of troponin during dialysis or the unexpected small transmembranous elimination further investigation is necessary. Consequently, a study investigating hs-cTnI levels in dialysate might be useful. Moreover, an investigation of the *in vitro* elimination of hs-cTnI with different membranes could provide further information to explain intradialytic hs-cTnI dynamics.

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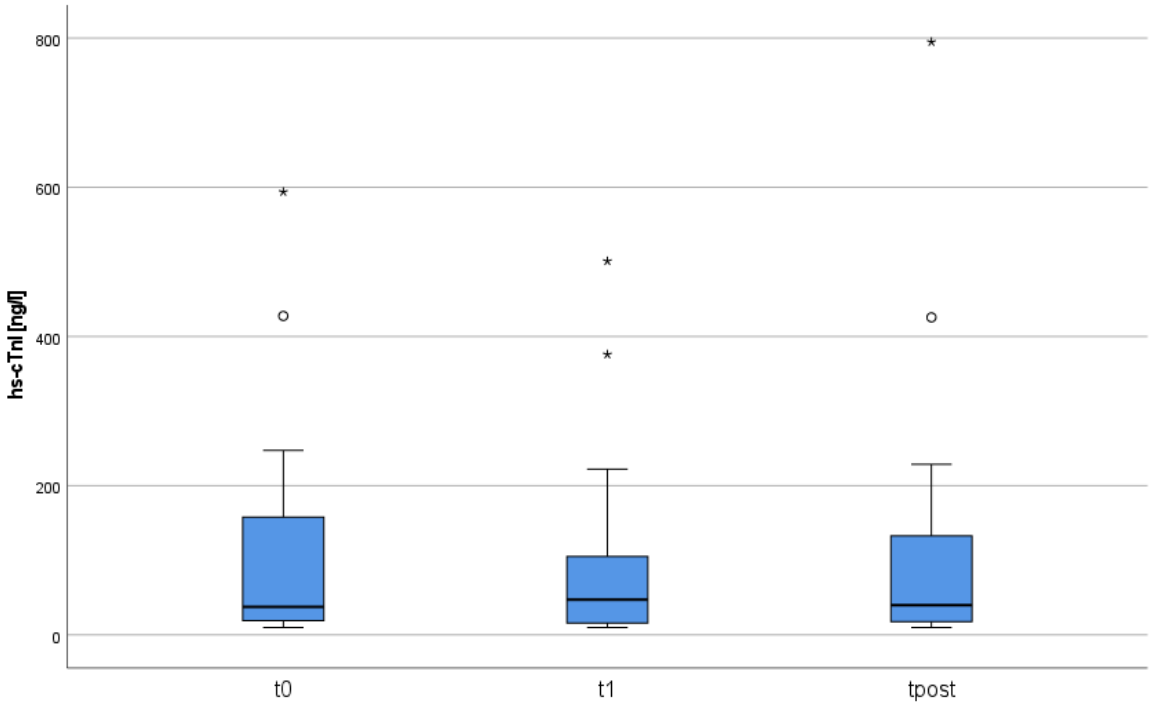
Appendix

Figure 6

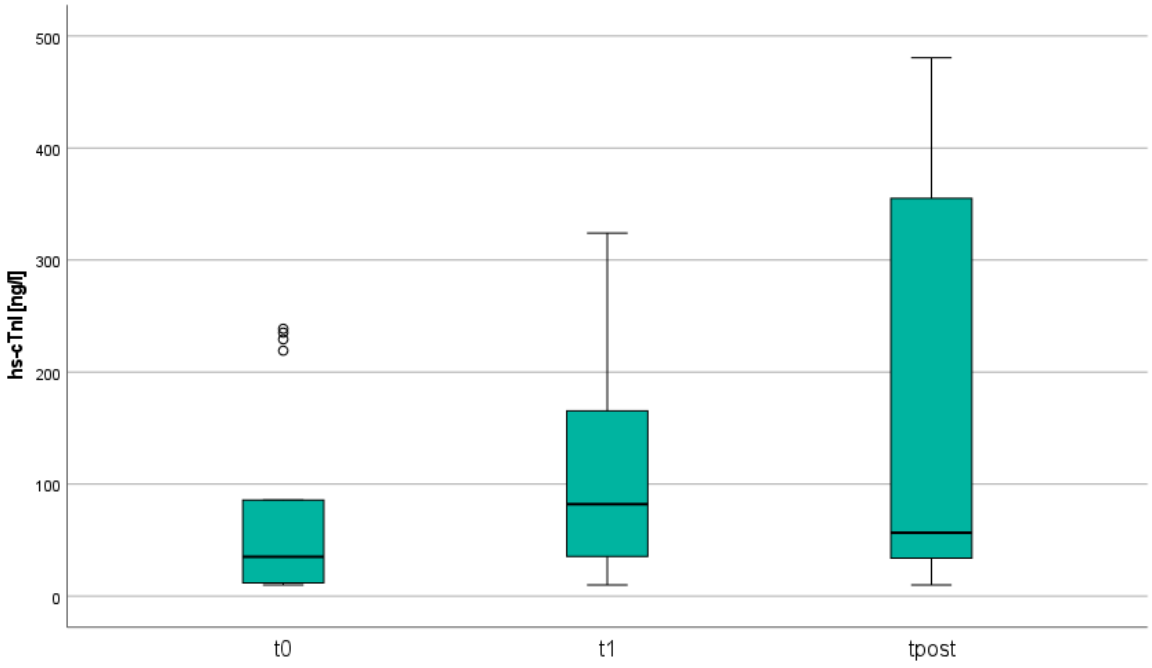
Median hs-cTnI in Patients Dialyzed with HF Dialyzer at Different Sampling Points



t_0 = baseline; t_1 = after the first hour; t_{post} = end of the session

Figure 7

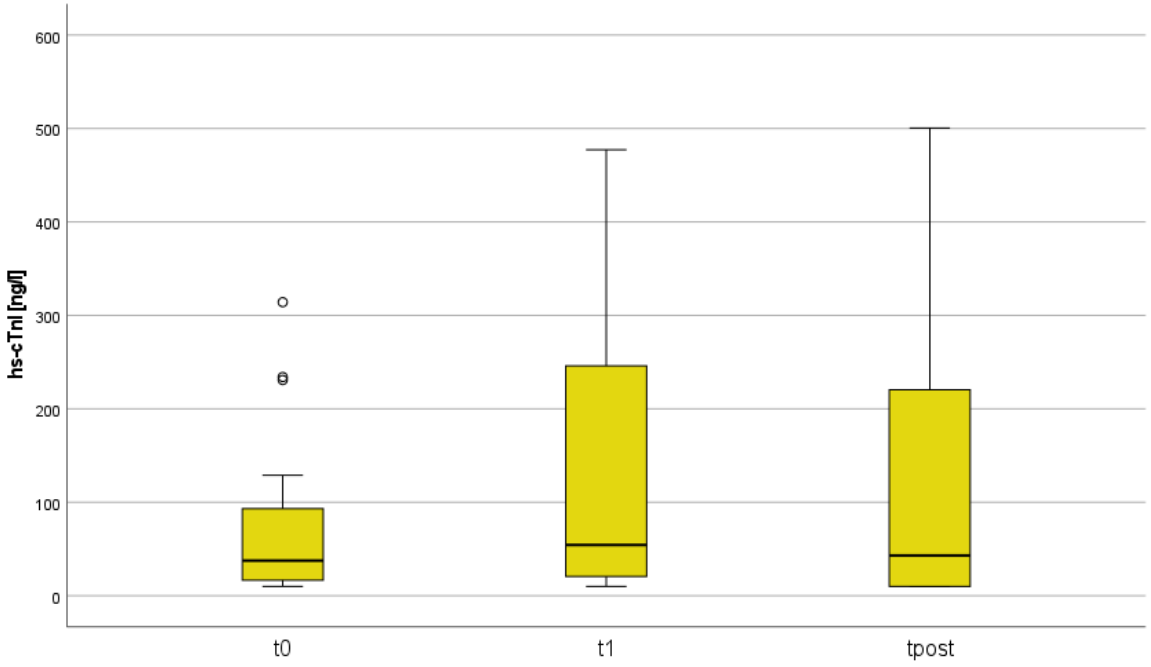
Median hs-cTnI in Patients Dialyzed with LF Dialyzer at Different Sampling Points



t_0 = baseline; t_1 = after the first hour; t_{post} = end of the session

Figure 8

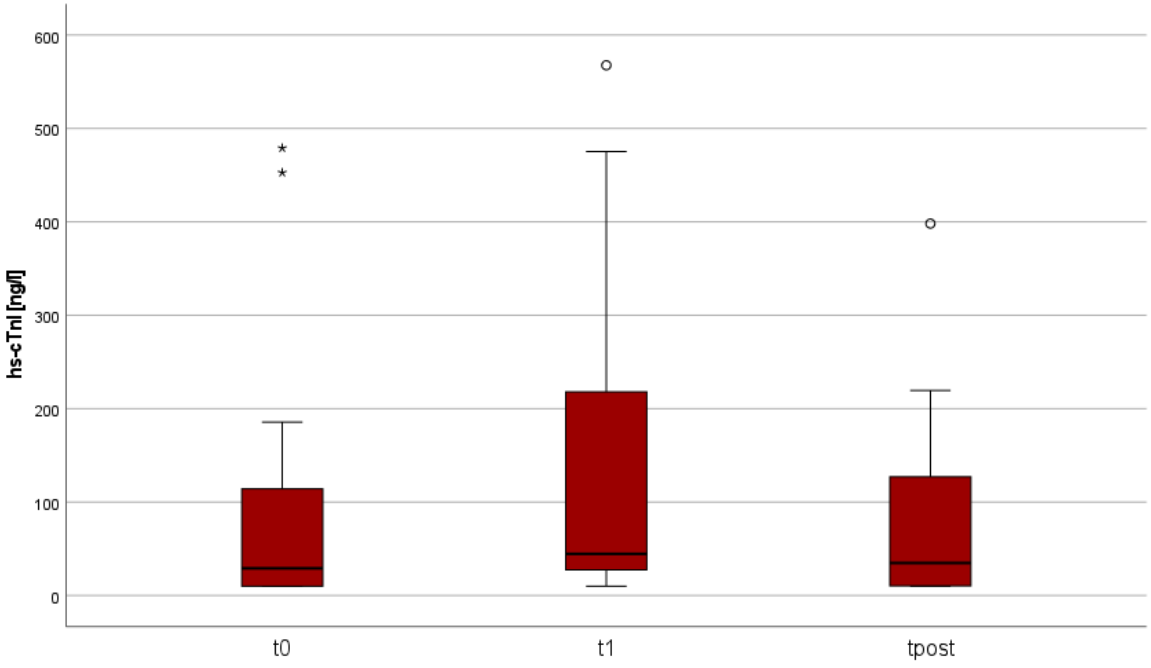
Median hs-cTnI in Patients Dialyzed with MCO Dialyzer at Different Sampling Points



t_0 = baseline; t_1 = after the first hour; t_{post} = end of the session

Figure 9

Median hs-cTnI in Patients Dialyzed with HDF at Different Sampling Points



t_0 = baseline; t_1 = after the first hour; t_{post} = end of the session