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Exploring Novel Intradialytic Techniques to Identify & Ameliorate of Hemodialysis-induced Myocardial Ischemic Injury

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Medical Biophysics

Abstract

Patients with chronic kidney disease requiring hemodialysis to sustain life have extremely high rates of cardiovascular morbidity/mortality. This is both a consequence of the disease process and treatment. Hemodialysis induces systemic circulatory stress largely due to the extracorporeal circuit and volume removal. The stress induced by intermitted hemodialysis is repetitive with cumulative cardiovascular effect and is the principal driver of heart failure and sudden death in this vulnerable population. The insults imposed by hemodialysis result in left ventricular regional wall motion abnormalities and lead to myocardial stunning with permanent damage to the vasculature and myocardium. Currently, the adversity caused by hemodialysis remains underappreciated and largely ignored. The aim of this thesis is to explore intradialytic methods to detect and ameliorate hemodialysis-induced circulatory stress (myocardial stunning).

The utility of a non-invasive intradialytic hemodynamic monitoring system using photoplethysmography to detect hemodialysis-induced circulatory stress through the skin was explored. In the first thesis project, we determined that reductions in pulse strength, an output generated by PPG technology was associated with the development of myocardial stunning.

Building on this initial finding, the second thesis project supported the significance of the pulse strength variable as a signal to the development of regional wall motion abnormalities/myocardial stunning during hemodialysis. Additionally, we determined that intradialytic changes in cutaneous perfusion were detected earlier in treatment and were associated with direct measures of global cardiac perfusion using intravenous contrast/computerized tomography imaging. Both findings were associated with rates of ultrafiltration (fluid removal) during dialysis (previously identified as principal drivers of hemodialysis-induced acute cardiac injury).

Exercise pre-conditioning, a phenomenon that provides cardio-protection against ischemic-reperfusion injury was explored, in the form of intradialytic exercise. In the third project, we found there to be a reduction in the number of treatment-induced regional wall motion abnormalities at the peak of hemodialysis stress when intradialytic exercise was incorporated

into treatment. Moreover, any amount of exercise had an immediate influence with no detrimental effect on treatment tolerability.

This work describes the utility and benefit of non-invasive microcirculatory monitoring for the early detection of hemodialysis-induced circulatory stress and demonstrates the pre-conditioning benefit that intradialytic exercise has on the reduction of myocardial stunning in the hemodialysis population.

Keywords

Hemodialysis, circulatory stress, myocardial stunning, cardiovascular injury, photoplethysmography, preconditioning, intradialytic exercise, microcirculation

Summary for Lay Audience

Patients with kidney disease have a higher risk of cardiovascular problems than people without kidney disease. When about 90% of kidney function is lost, patients need dialysis to live. Hemodialysis cleans the blood and also removes large amounts of fluid (because of low urination) with each hemodialysis treatment (four hours, three times weekly). Hemodialysis puts stress on the blood vessels and hinders the ability of the heart to pump blood throughout the body (circulatory stress). This causes long term damage and can lead to sudden death. The goals of this thesis were to see if a monitoring system that is placed on the skin during dialysis could detect the circulatory stress (myocardial stunning) and to test whether or not exercise (cycling) during dialysis could prevent or reduce circulatory stress (myocardial stunning).

The blood vessels in the body, more specifically the very small vessels of the microcirculation are affected by low blood flow during dialysis. In the first project we found that changes in blood flow in the skin during dialysis was predictive of myocardial stunning.

The second project, in addition to the findings above, we found that the changes in blood flow in the skin represented changes in blood flow in the heart and that the rate of fluid removal contributed to these changes.

Previous research has shown that small repeated amounts of exercise protected the heart from harm during a heart attack (pre-conditioning effect). The third thesis chapter tested exercise during dialysis, using a stationary bike to see if it provided the same protection. We found that when patients cycled during dialysis, they had less myocardial stunning than when they did not exercise.

These results help us to understand what type of monitoring would help detect the stress caused by dialysis and what activities may reduce or prevent stress on the heart.

Co-Authorship Statements

Chapter 1 - Parts of this chapter has been published in *Current Opinions in Nephrology and Hypertension*, 31, 553-559. October 2022. The title of the review article is "Assessment of Microcirculatory Function During Dialysis", by Penny, Moradshahi, McIntyre. *The permission to reproduce this manuscript are provided in Appendix A.*

Chapter 2 - The content of this chapter have been adapted from an original research manuscript entitled "Percutaneous Perfusion Monitoring for the Detection of Hemodialysis-induced Cardiovascular Injury", which was published in *Hemodialysis International* in 2018 and co-authored by Jarrin D. Penny, Clair Grant, Fabio R. Salerno, Anne Brumfield, Marcus Mianulli, Lori Poole and Christopher W. McIntyre. *Research ethics board approval is provided in Appendix B. The permission to reproduce this manuscript are provided in Appendix C.*

Chapter 3 – The contents of this chapter have been adapted from a manuscript submitted to *Frontiers in Nephrology (Blood Purification)*, 2022. The title of the manuscript is "Non-invasive Intradialytic Percutaneous Perfusion Monitoring: a view to the heart through the skin: by Penny, Hur, Salerno, Wong, Jan, McIntyre. Hur and Penny collected the data. The data were analyzed by Hur, Salerno, Wong, Jan and Penny. The data were interpreted by Penny. Each author contributed important intellectual content during the drafting and revising of the manuscript and accept accountability for the overall work by ensuring that questions pertaining to the accuracy and integrity of any portion of the work are appropriately investigated and resolved. *Research ethics board approval is provided in Appendix D.*

Chapter 4 - The content of this chapter have been adapted from an original research manuscript entitled "Intradialytic Exercise Preconditioning: an observational study on the effects on myocardial stunning", which was published in *Nephrology Dialysis Transplant* in 2019 and co-authored by Jarrin D. Penny, Fabio R. Salerno, Ranveer Brar, Eric Garcia, Krista Rossum, Christopher W. McIntyre and Clara J. Bohm. *Research ethics board approval is provided in Appendix E. The permission to reproduce this manuscript are provided in Appendix F.*

Acknowledgments

"Let us never consider ourselves finished nurses…we must be learning all of our lives."
Florence Nightingale

I would like to thank my ***colleagues, mentors, employers, educators*** and especially ***my patients*** from past and present who have taught me the meaning of nursing. The teachings and learnings over the years have been fundamental to my achievements and success. I am grateful for each and every one of you.

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I dedicate this work to my Daughters,

Paige Julie Daniele and Raegan Pauline 'Rae'

As a Mother, I strive to teach you, through example, that learning never ends; whether it be professionally, personally, emotionally or through lived-experiences.

Life will throw you many curves - believe in yourselves and your decisions, never look back; explore, redirect and challenge the status quo.

May you always know that my love for you remains constant through all adversity.

Reach for the stars...dream…and grow your own future!

Xo

"I think the hardest thing for a mother is to make it possible for a child to be independent and at the same time let the child know how much you love her, how much you want to take care of her, and yet how truly essential it is for her to fly on her own".

Madeleine Albright

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List of Abbreviations

Abbreviation	**Definition**
HD	Hemodialysis
PPG	Photoplethysmography
PS	Pulse Strength
CT	Computerized Tomography
IDE	Intradialytic Exercise
RWMA	Regional Wall Motion Abnormalities
CKD	Chronic kidney disease
RRT	Renal replacement therapy
CV	Cardiovascular
BP	Blood Pressure
RBC	Red Blood Cells
KDIGO	Kidney Disease Improving Global Outcomes
GFR	Glomerular filtration rate
ESRD	End stage renal disease
PD	Peritoneal dialysis
UF	Ultrafiltration
AVF	Arteriovenous Fistula
AVG	Arteriovenous Graft

CVC	Central venous catheter
IDWG	Interdialytic weight gain
IDH	Intradialytic Hypotension
LV	Left Ventricle
LS	Longitudinal Strain
SDF	Side-stream darkfield imagine
LDF	Laser doppler flowmetry
LDI	Laser doppler imaging
NIRS	Near infrared spectroscopy
TcP02	Transcutaneous oxygen tension
BP	Blood Pressure
RBV	Relative Blood Volume
CVI	CVInsight ® (InteloMed Inc)
RIPC	Remote Ischemic Preconditioning
GLS	Global Longitudinal Strain
EF	Ejection Fraction

Chapter 1

1 Introduction

1.1 Co-authorship Statement

Part of this chapter has been published in *Current Opinions in Nephrology and Hypertension,* November 2022, 31(6), 553-559. doi: 10.1097/MNH.0000000000000831 The title of the review article is "Assessment of Microcirculatory Function During Dialysis", by Penny, Moradshahi, McIntyre.

The permission to reproduce this manuscript are provided in Appendix A.

1.2 Overview of Thesis

The purpose of this thesis was to study methods to: identify hemodialysis (HD)-induced circulatory stress through non-invasive intradialytic monitoring of the cutaneous microcirculation; and to ameliorate HD-induced circulatory stress through intradialytic exercise. The studies presented in this thesis applied techniques including echocardiography to identify HD-induced circulatory stress in the form of myocardial stunning, photoplethysmography (PPG) for cutaneous microcirculatory monitoring and intradialytic cycling as an intradialytic intervention.

Section 1.2 provides a brief summary of the concern at hand and thesis overview. Background information can be found in section 1.3. Section 1.4 summarizes the functions of the kidney. Section 1.5 provides information on chronic kidney disease. Section 1.6 describes the principles and types of renal replacement therapies. Sections 1.7 explains the concept of HD-induced circulatory stress. Sections 1.8-1.10 summarized the functions of the microcirculation, microcirculatory dysfunction and methods of non-invasive microcirculatory monitoring. Section 1.11 describes strategies to ameliorate HD-induced circulatory stress and section 1.12 summarizes currently used methods of intradialytic

monitoring. Finally sectional 1.13-1.14 describe the motivation for this thesis, overall hypothesis, aims/objectives as well as my research approach.

Thesis project are then described in the following three chapters. Chapter 2 examines the intradialytic utility of PPG technology for continuous intradialytic microcirculatory monitoring as a means of identifying HD-induced circulatory stress (myocardial stunning) in a timely and representative manner. It was hypothesized that the cutaneous microcirculation could be used as a surrogate vascular bed for the early identification of circulatory stress using PPG technology. In line with this hypothesis, myocardial stunning was associated with reductions in PPG pulse strength (PS) signal.

Chapter 3 of this thesis further explores the relationship between PPG PS and the development of myocardial stunning and compares changes in PS to direct measures of myocardial perfusion. It was hypothesized that cutaneous microcirculatory changes during HD would reflect direct measures of myocardial perfusion using computerized tomography (CT). In line with this hypothesis myocardial stunning was associated with reduction in PPG PS and changes in PS were associated with changes in myocardial perfusion.

Chapter 4 of this thesis explores the effectiveness of intradialytic exercise (IDE) as an intervention to ameliorate HD-induced circulatory stress/myocardial stunning. It was hypothesized that intradialytic exercise would have a pre-conditioning effect similar to remote-ischemic preconditioning and could ameliorate the development of regional wall motion abnormalities (RWMA) and myocardial stunning. In line with this hypothesis, when IDE was incorporated into HD, the number of HD-induced RWMA was reduced and myocardial stunning was ameliorated.

Chapter 5 of this thesis summarizes the contribution of this work to the scientific community and discusses options for further investigation.

1.3 Background

Chronic kidney disease (CKD) is a progressive condition affecting more than 10% of the global population, and has been listed as one of the most predominant causes of death worldwide.[1] In Canada, four million Canadians are diagnosed with CKD and more than 50,000 are living with end-stage kidney disease with 58% requiring dialysis.[2] Institutional-based HD is the most costly treatment option ($100,000 per patient/per year), which is chosen by approximately 75% of patients requiring renal replacement therapy (RRT).[2] However HD itself contributes to further healthcare concerns and disease burden, including cardiovascular (CV) disease, vascular complications, frequent hospital admissions and low survival – most patients will die within five years of starting HD.[3]

The intent of RRT is to clear (filter) the blood of built-up toxins and remove excess fluid from the body in the absence of native kidney ability/function – the intent is to 'replace' kidney function to sustain life. Although HD does sustains life, it also causes additional pathological processes resulting in extreme physiological burden, and socio-economic challenges to patients, caregivers, and the healthcare system as a whole. Despite technological advancements to therapy in the past few decades, there has unfortunately been no appreciable improvement in survival rates for this population.[4] This is in part due to progressive loss of kidney function (over many years) causing inherent CV complications which are present upon the initiation of HD. Furthermore, it has become increasingly evident over the past decade that the HD procedure itself plays a large role in poor clinical outcomes and high mortality rates.[5] The physiological stress caused by HD cumulates over time with repetitive insults inducing damage systemically to the entire circulatory system, resulting in changes to vital organ structure and function. It is therefore important to find strategies to *identify* (intradialytic monitoring) and a*meliorate* (intradialytic intervention) HD-induced circulatory stress to improve clinical outcomes and the delivery safer HD therapy.

1.4 The Kidneys

1.4.1 The Function of the Kidneys

The kidneys play an integral role in optimal bodily function and are essential to homeostasis within the body in order to sustain life. The kidneys are responsible for a number of crucial functions including: filtering the blood for metabolic waste product removal, maintaining fluid/electrolyte/pH balances and hormone secretion.

1.4.1.1 Waste Products

Once the body uses food for energy and bodily repair, the waste products are sent to the blood. The glomerulus (a series of specialized blood vessels withing the cortex of the kidneys) then filters the blood removing waste and toxins while returning any beneficial substances (vitamins, amino acids, glucose, hormones) back into the bloodstream to be utilized by the body. The filtered fluid goes through a series of tubules that extend into the medulla (inner core) of the kidneys where substances needed by the body are retained and those not needed are excreted - producing urine. When kidney function declines, waste products begin to rise to toxic levels, resulting in systemic impairment.

1.4.1.2 Water and Electrolyte Balance

Every cell in the body is surrounded by extracellular fluid which requires a stable composition of fluid/electrolyte/acid/base balance in order for the body to function properly. This is a very intricate balancing system whereby the kidneys are able to continuously concentrate or dilute urine depending on demand and bodily requirements, ensuring levels remain within optimal safe limits at all time. When kidney function declines this system is unbalanced with consequences of excess fluid accumulation (e.g., dependent and pulmonary edema), electrolyte and/or acid/base imbalances; causing emergent life-threatening conditions.

1.4.1.3 Hormones

The kidneys are also responsible for the secretion of several important hormones:

Renin is required for blood pressure (BP) regulation. Renin is normally secreted by the kidneys in response to pressure changes in the vasculature (low BP). When renin is released blood vessels respond by constricting, increasing pressure within the blood vessel and maintaining tissue perfusion and oxygenation. When kidney function declines, renin is often unregulated and often secreted in excess resulting in difficult to manage/uncontrol hypertension.

Erythropoietin is a hormone that stimulates bone marrow to produce red blood cells (RBC), enabling the delivering of oxygen to tissues. When kidney function declines, fewer RBC are produced and those that are tend to be immature and unable to transport oxygen properly – causing anemia and poor tissue oxygenation.

Vitamin D metabolism. The kidneys are responsible for changing vitamin D from its in-active form to it active form so that it can be used by the body. Active vitamin D is essential for calcium absorption, normal bone formulation and effective muscle function. When kidney function declines, active vitamin D availability and calcium levels drop resulting in muscle weakness and structural/functional bone disease.

1.5 Chronic Kidney Disease

Kidney Disease Improving Global Outcomes (KDIGO) defines CKD as the presence of structural and functional abnormalities of the kidney for more than three months. A diagnosis of CKD includes multiple factors including: a reduction in glomerular filtration rate (GFR) which is a measure of kidney function, anatomical abnormalities, proteinuria and elevated electrolyte levels.[6–8] CKD is classified into five stages which are based on GFR *(Table 1-1)* and is calculated based on serum creatinine (or Cystatin C) levels. The evaluation of kidney injury is made according to albumin/creatinine ratio levels *(Tables 1-2).*

Table 1-1: Stages of Chronic Kidney Disease

GFR category	GFR value (ml/min/1.73m^2)	Terms
Stage 1	≥ 90	Normal or high
Stage 2	60-89	Mildly decreased (*for young adults)
Stage 3a	45-59	Mildly to moderately decreased
Stage 3b	30-44	Moderately to severely decreased
Stage 4	15-29	Severely decreased
Stage 5	<15	Kidney failure

GFR = Glomerular filtration rate. *Adapted from 2013 KDIGO guidelines.*[8]

Table 1-2: Stages of Albuminuria

Category	AER (mg/24 hours)	ACR (mg/mmol)	ACR (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased (*for young adults)
A3	>300	>30	>300	Severely increased

AER= albumin excretion rate, ACR=albumin/creatinine ratio. *Adapted from 2013 KDIGO guidelines.*[6,8]

CKD is a condition that progresses over many years. CKD is often 'silent', meaning that often people don't realize they have CKD until kidney function is reduced by half. By this time CKD is associated with multifactorial complications including chronic inflammation, CV disease, anemia, bone/mineral abnormalities, malnutrition and edema. As a result, patients may begin to experience psychological distress, symptom burden, poor quality of life, other comorbid conditions.

1.5.1 End Stage Kidney Disease

The progression of CKD to stage five (GFR of < 15ml/min/m^2) is considered to represent kidney failure or end-stage renal disease (ESRD). This stage of renal disease will characteristically result in symptoms of uremia which may include: nausea, anorexia, fatigue, weakness, confusion, edema and/or shortness-of-breath. Additionally fluid/electrolyte imbalances cause greater risk of CV events and cardiac arrest. A combination of GFR <15ml/min/m^2, elevated levels of urea/creatinine/potassium, intractable fluid overload and clinical symptoms typically warrant a decision to begin RRT (dialysis).

1.6 Principles of Dialysis

The principles of dialysis were first described in the 18^{th}/19^{th} century by Thomas Graham, a chemist from Glasgow, at the same time as Dr. Richard Bright, a physician from Edinburgh, described the clinical features of renal failure. Graham, who discovered the law of diffusion and osmotic forces within fluid, and studied the behaviour of biological fluids, initially build a compartmental bell-shaped vessel using the bladder of an ox, urine and distilled water. He placed urine inside the vessel which he covered with ox bladder, and placed the vessel into a larger container filled with distilled water. After several hours, Graham removed the inner vessel and boiled down the distilled water solution discovering the presence of sodium-chloride and urea (components found in urine). This was the foundational discovery that solutes can pass through a semi-permeable membrane (ox bladder) which formulated the discovery of dialysis. Graham continued his work creating numerous alternative semi-permeable membranes of different designs and materials. At that time, it was predicted by Graham/Bright that the evolution of dialysis for the safe treatment of human kidney failure would take approximately 60 year to refine.[9,10]

1.6.1 Peritoneal Dialysis

1.6.1.1 History of Peritoneal Dialysis

Peritoneal dialysis (PD) was in fact discovered prior to the discovery of HD, however due to extensive complication and difficulty accessing the peritoneal cavity, it's contribution to patient care at that time was quickly disregarded. It was not until the late 1940's that Fine and his colleagues reported the first successful peritoneal irrigation in an anuric patient who went on to survive for four days with peritoneal lavage. This success highlighted the potential of the peritoneum to be used as a semi-permeable membrane and that PD could be used as a treatment option for uremia. In the late 1960's, intermittent PD was available in expert centers only (Seattle, Paris, Toronto) and was offered to those unable to receive HD (due to availability). At this time, PD was thought to be an inferior therapy and therefore, as HD patients died, PD patients would transition to the available HD space.[11]

1.6.1.2 Peritoneal Dialysis Procedure

Today PD is the most cost-effective form of dialysis allowing patients to perform their own treatments within their home environment. PD utilizes a patient's own abdominal cavity which houses a natural occurring and highly vascular semi-permeable membrane (peritoneal membrane). A catheter (Tenckhoff) is placed through the skin of the abdomen into the peritoneal cavity. A fluid containing solutes and an osmotic agent is instilled into the patient's abdomen through the catheter. The fluid is allowed to dwell in the abdomen for several hours. During this time, the peritoneal membrane allows the transfer of solutes, toxins and water (from the circulation) to cross the membrane (concentration gradient). Solutes and water, through diffusion and osmosis are transferred from the circulation into the PD solution. After several hours, the waste solution (effluent) is drained from the abdomen and discarded. The cycle then continues with fresh dialysate instilled into the peritoneum.

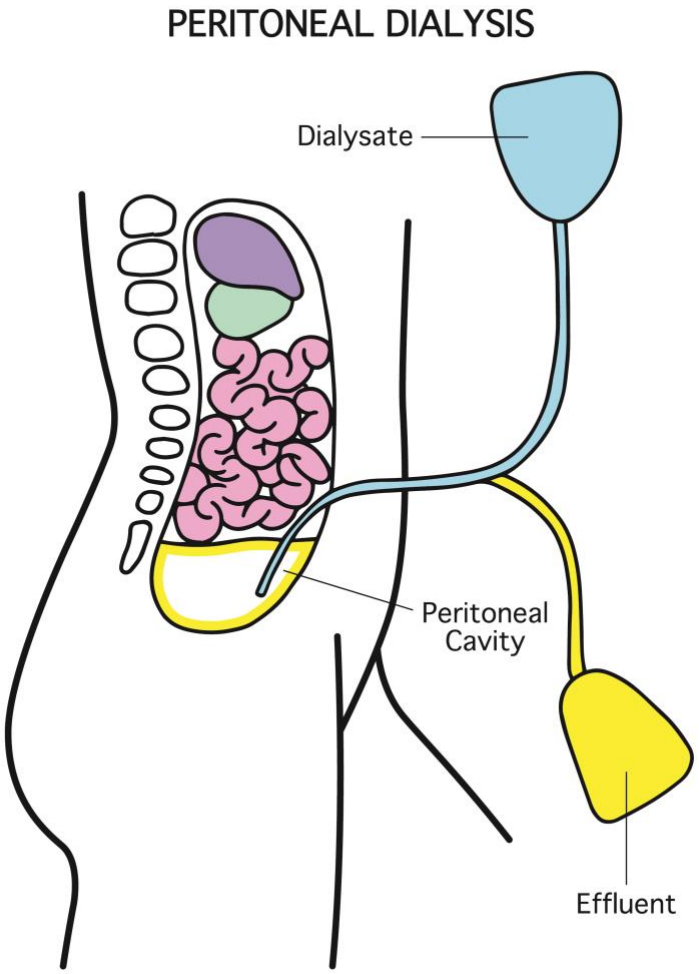

Figure 1-1: Peritoneal Dialysis Graphic (drawn by T. Tamasi RPN, S. Tamasi)

PD is a viable option for many patients (absolute limitation only to those with unrepaired abdominal herniations or severe adhesions from previous surgeries/intraperitoneal inflammation). There can be barriers to the uptake of PD as a treatment (e.g., fearful of home modality, limited resources/support systems, body image concerns). Although PD is known to be a somewhat 'gentle' form of dialysis (regular exchanges throughout the day/night and lower ultrafiltration (UF) requirements, high glucose levels (osmotic agent in dialysate) can lead to associated complications as a result of metabolic stress. Many patients who start PD often require transition to HD for varying reasons including infection,

dialysis adequacy, catheter malfunction, inability to meet UF requirements, patient/care-giver burnout or lack of home support.

1.6.2 Hemodialysis

1.6.2.1 History of Hemodialysis

The initial concept of dialysis described previously (Graham/Bright), gave rise to various technological adaptions, developments and designs by numerous researchers over the next several decades (tested in dogs/rabbits). In 1924, the first human HD was performed in Germany by Haas and by 1926 he had treated a total of six patients. However, due to short treatment times, low blood flows and small dialysate volumes there was very little therapeutic effect due to limited clearance. Several years later, Kolff, a Dutch investigator, interested in uremic syndrome and acute renal failure introduced a rotating drum dialysis system (cellophane membrane and dialysate fluid). In 1943 he treated the first patient which was followed by a successful treatment regime with recovery from acute renal failure in 1945.[9,10] Meanwhile in Canada, simultaneously and independent to the work of Kolff, Gordon Murray a cardiac surgeon in Toronto took interest in renal failure after seeing several patients die of renal failure due to no treatment options. Between 1945-46, Murray and his partners developed a dialysis system which they tested on uremic animals. In 1946, Murray agreed to experimentally treat a 26-year-old women who was declared to be a 'hopeless' case, in a uremic coma, with no options. Over the following weeks three treatments were delivered, each time the patient was revived from coma after treatment, yet relapsed into a coma the following days. After the third treatment however, her kidney function was restored and the patient was discharged from hospital one month after admission. Eleven patients were treated with this 'experimental therapy/system', until 1949 when Murray went on to pursue other interests (cardiac surgery) due to the lack of support/interest from his colleagues.[10,12] In 1960, Scribner and his team in Washington reported on the development of an implantable cannula (made of synthetic material) which they used to connect an artery to a vein in order to gain repeated access to a patient's systemic circulation, the 'Scribner Shunt' opened a pathway for long-term chronic kidney disease treatment.[9,10,13] Later in the 1960's Cimino and Brescia developed the native

‘arterio-venous fistula’ surgically connecting a vein with an artery - a significant improvement to the Scribner shunt.[9]

Over the past four decades researchers have adapted these original concepts advancing dialysis therapy beyond experimental. HD is now an accepted treatment for both acute and chronic kidney failure with many improvements made to semi-permeable membrane (dialyzer) design, biocompatibility, technology, monitoring systems, volume controls, and dialysate composition. Today, HD is largely administered intermittently (four hours/three times weekly) in-hospital by regulated healthcare providers which are specially trained to deliver HD making it the costliest form of RRT [although, HD can also be administered by patients at home (cost savings) the uptake remains quite limited due to patient stability and home modality acceptability].

1.6.2.2 Components of Hemodialysis

HD is the process of removing waste products and excess fluid from a patient’s blood. The following components are necessary for HD to occur.

1.6.2.2.1 Functional Vascular Access

HD requires repeated access to a patient’s circulation for extended lengths of time. An access must be able to maintain blood flows of 300-400ml/minute in order to achieve optimal HD clearance. There are three main types of vascular access used for HD.

Arterio-venous Fistula (AVF) – The AVF is the desired access. The AVF is created by a surgeon who surgically connects a patient's artery to a vein (anastomosis). The high blood flows coming from the artery flows through the vein enlarging the vein, and enabling cannulation with two large bore dialysis needles (one for blood removal, the second for blood return). Because there are no synthetic materials permanently embedded in the patient, the AVF is the desired vascular access and associated with fewer infections. The figure below is a graphic representation of an AVF.

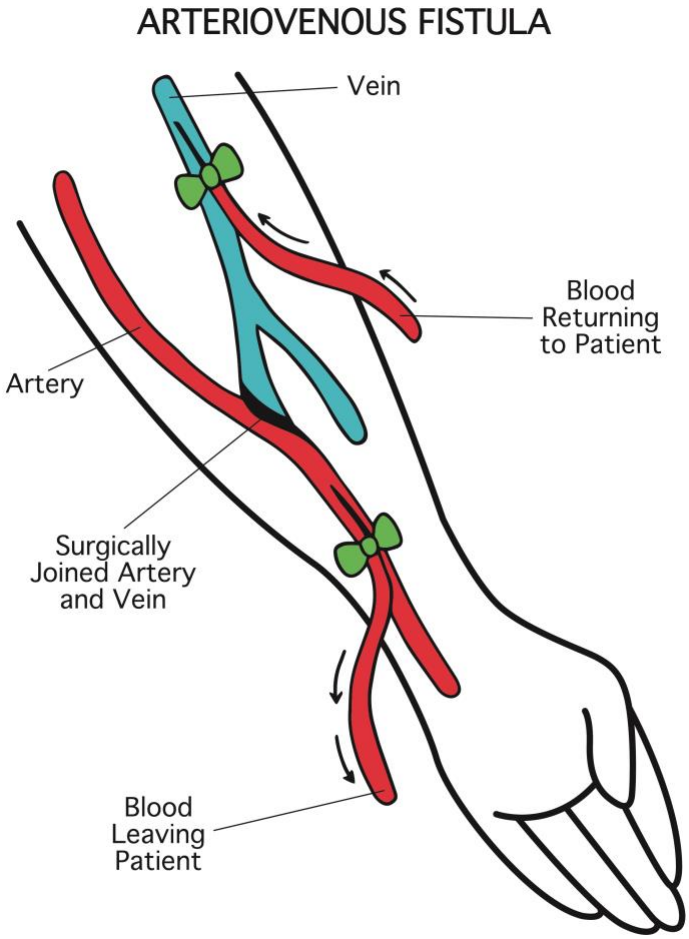

Figure 1-2: Arteriovenous Fistula Graphic (drawn by T. Tamasi RPN, S. Tamasi)

Arterio-venous Graft (AVG) – Using a piece of synthetic material (gortex), a surgeon connects an artery to a vein so that blood flows from the arterial circulation, through the synthetic tube to the venous circulation. The graft is then cannulated with two large bore dialysis needles (one for blood removal, the second for blood return) for HD. There is a greater risk of infection and thrombosis with the AVG due to biocompatibility. The figure below is a graphic representation of two types of grafts (determined by surgeon) Radial-cephalic and Loop AVG.

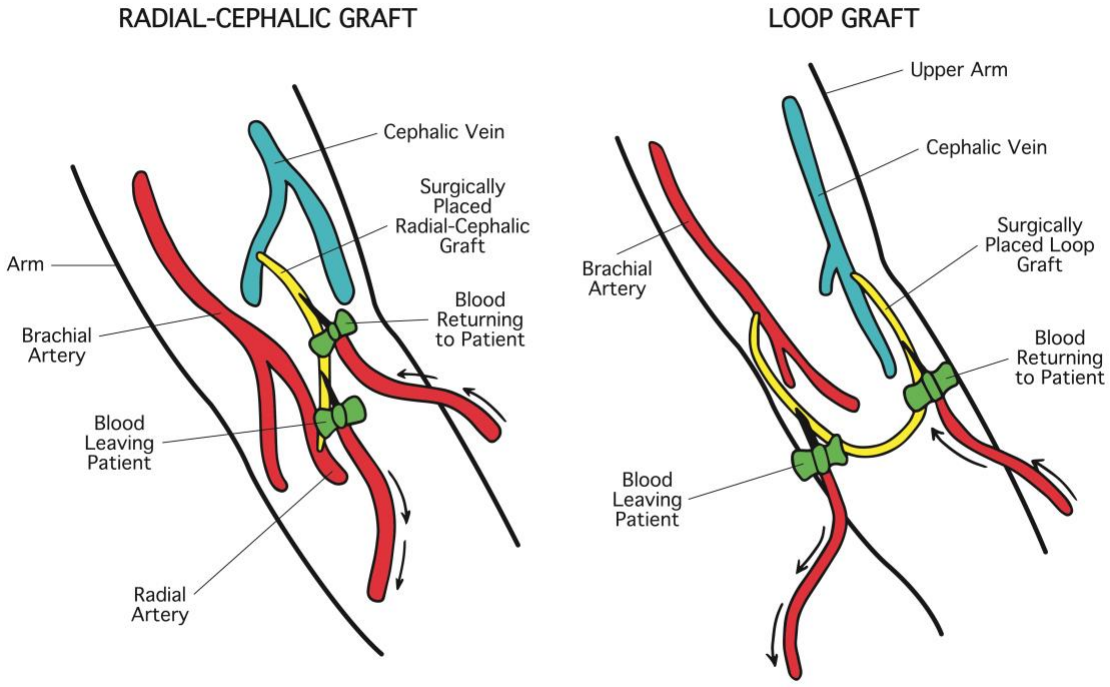

Figure 1-3: Arteriovenous Graft Graphic (drawn by T. Tamasi RPN, S. Tamasi)

Central-venous Catheter (CVC) – A duo-lumen central line is place in the patient's subclavian or intrajugular vein which extends so that the tip of the catheter sits in the right atrium of the heart. The duo-lumen allows blood to be removed in one lumen and returned in the second during HD. Although largely the most common vascular access, there is a high risk of infection, thrombosis and vascular stenosis with CVC. The figure below is a graphic representation of the placement of a CVC.

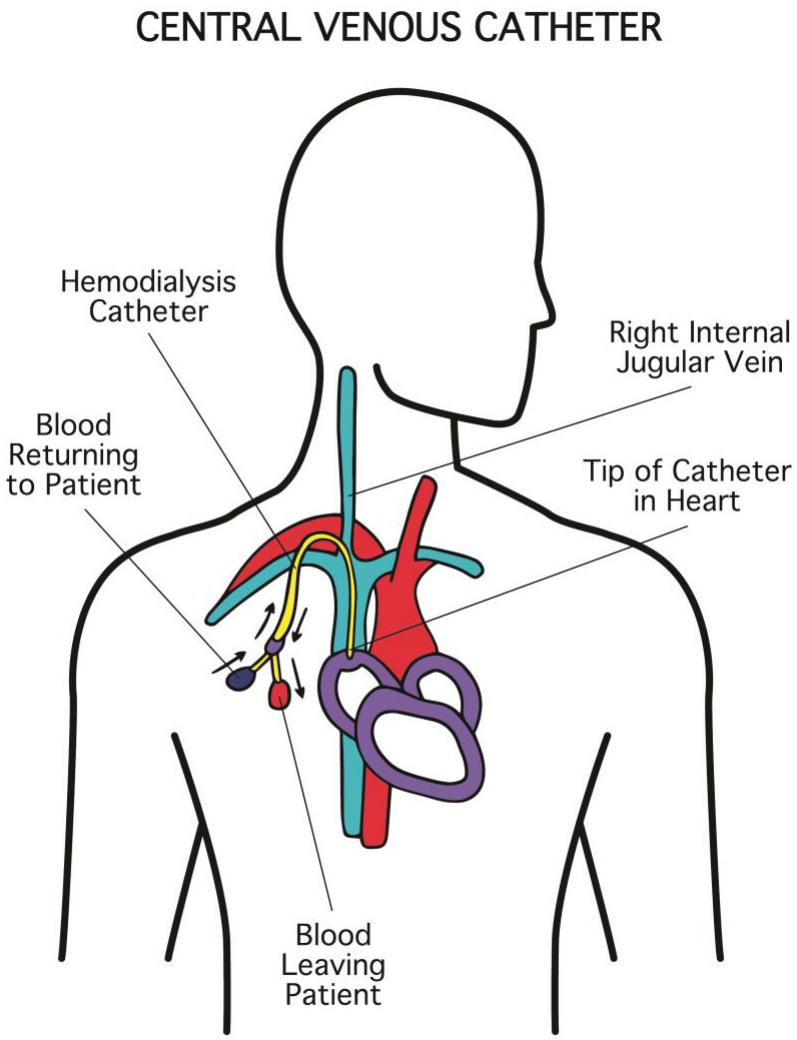

Figure 1-4: Central Venous Catheter Graphic (drawn by T. Tamasi RPN, S. Tamasi)

1.6.2.2.2 Hemodialysis Monitor

The HD monitor is the technology/mechanics required for modern safe HD. The monitor consists of a pump which pumps blood from the patient's circulation, through the fibres in the dialysis membrane, and back to the patient's circulation forming a circuit. There are several other components in the HD machine with the purpose to maintain regularity and safety (pressure sensors, additional pumps, regulators, air/leak detectors, temperature monitor, heater, flow monitors).

1.6.2.2.3 Semi-permeable Dialysis Membrane

The dialysis membrane is essentially an artificial kidney, a disposable apparatus containing approximately 18,000 hollow straw-like fibres of semi-permeable material (typically made of polysulphone) which are encased in a plastic cylinder. It is the dialysis membrane that functions as the filtering system (in place of the native kidneys). The dialyzer connects the blood compartment to the dialysate compartment (although the two compartments never come in contact with one another – blood runs through the fibres, dialysate surrounds the fibres). These are currently considered single use items.

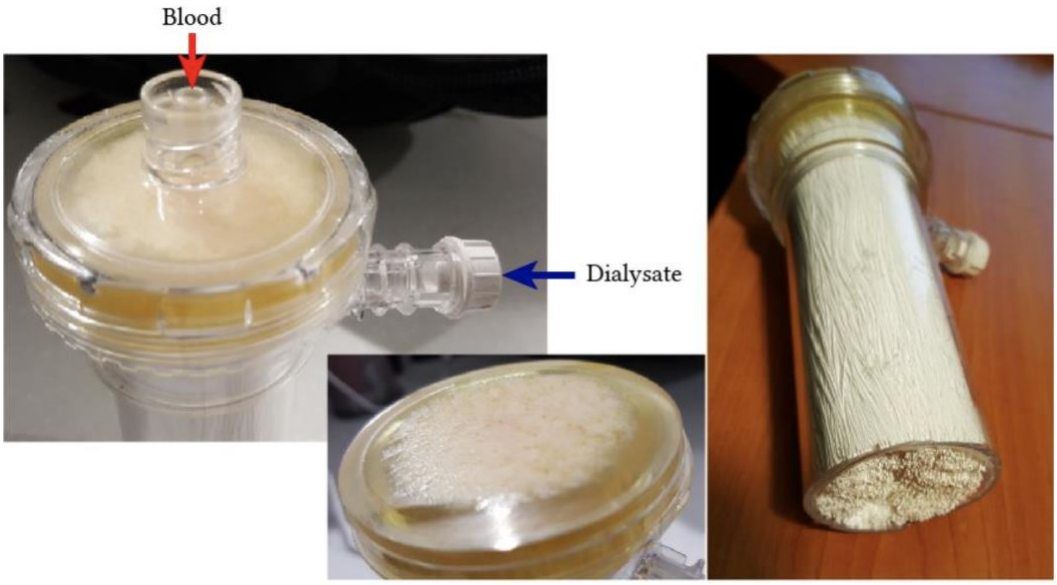

Figure 1-5: Semi-permeable Dialysis Membrane. Individual straw-like hollow fibres of semi-permeable membrane.

1.6.2.2.4 Blood Compartment

The blood compartment consists of a set of disposable tubing which is secured onto the outside of the HD monitor. The blood compartment (tubing and the internal surfaces of the dialyzer fibres) is connected to the patient's circulation housing the patient blood (approximately 350ml) for the length of the HD treatment.

1.6.2.2.5 Dialysate Compartment

The dialysate compartment is largely embedded within the HD monitor and connected to the dialysis membrane. The HD monitor mixes and monitors the conductivity of the dialysate composition (made up of bicarbonate, solute solution, purified water) ensuring it is mixed proportionately to the desired safety parameters. Temperature sensor, heater, pressure sensors, flow controls, blood leak detector, air detector, pumps, and hydraulics work together to deliver dialysis with UF.

1.6.2.3 Hemodialysis Procedure

The tubing of the blood circuit is connected to the dialysis membrane (prescribed specifically for the patient by their physician/nurse practitioner), mounted onto the HD monitor and primed with a solution of either normal saline or dialysate mixture. Once the dialysate is mixed proportionately and conductivity is within safe parameters, the dialysate hoses are connected to the dialysis membrane and the dialysate compartment is primed. Both compartments are allowed to circulate to ensure all air is removed. The patient's circulation is then accessed (via their vascular access) and blood circuit tubing is connected. The pump is then turned on and begins to pull blood from the vascular circulation through the circuit and returning to the patient circulation. Blood passes through the dialysis membrane (inside the hollow fibres) while purified dialysate runs counter-currently surrounding the fibres (where diffusion/osmosis occur). The filtered blood is returned back to the patient's circulation and the dialysate (with toxins/fluid) is deposited as waste (drain). A patient's entire blood volume is circulated approximately 15 times in the course of a typical four hours treatment. The figure below is a schematic of the HD procedure with components of each compartment.

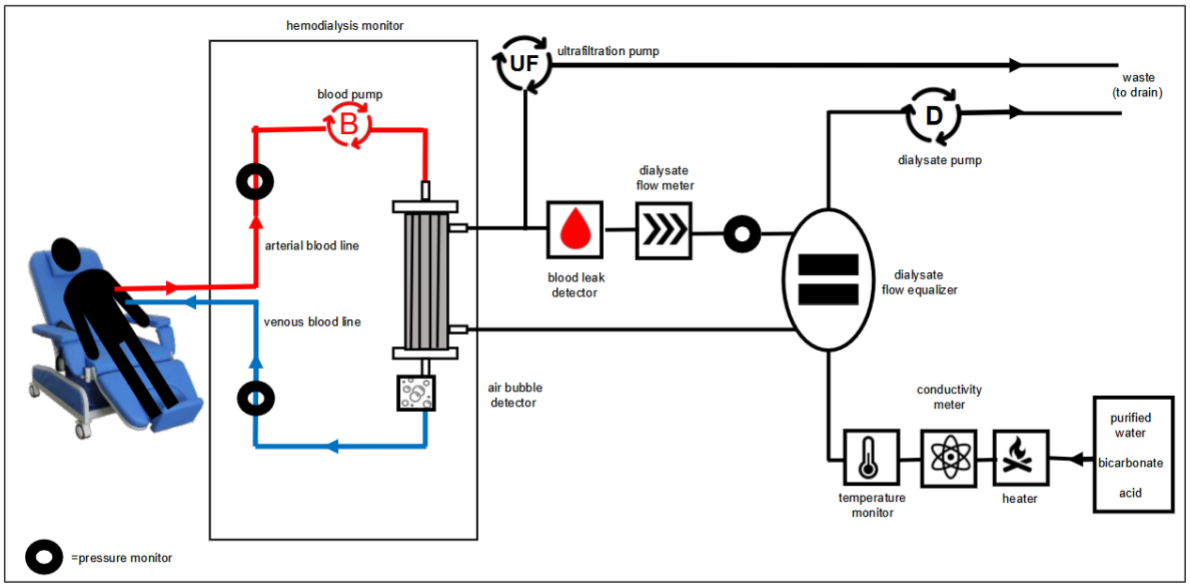

Figure 1-6: Hemodialysis Circuit made up of two compartments. Blood compartment (red/blue) and dialysate compartment (black).

1.6.2.4 Principles of Hemodialysis

HD uses the principles of diffusion to transfer solutes from an area of high concentration to an area of low concentration along a concentration gradient. Typically, the blood has a higher concentration of urea, creatinine, potassium and other toxins which pass through the semi-permeable membrane to the lower concentration environment of the dialysate solution. The counter-current flow of the dialysate to the blood provides maximum concentration gradient and solute removal. Conversely, higher concentration components in the dialysate are transferred into the circulation (e.g., bicarbonate – correcting acidosis). The composition of dialysate plays an integral role in stable HD delivery whereby levels can be adjusted according to the patient's individual requirements (e.g., sodium levels, potassium levels, bicarbonate levels, calcium levels).

Negative pressure within the dialysate compartment generates UF (fluid removal) causing a pressure gradient where free water can move. The amount of fluid removal is determined based on:

a. Patient's 'dry' weight- individual prescribed weight based on optimal blood BP, absence of extra fluid accumulation (lungs/edema), absence of intradialytic hypotension/symptoms and feelings of well-being. Otherwise termed the target weight to restore the patient to at the end of the HD treatment.

b. Interdialytic weight gain (IDWG) - the accumulation of fluid between dialysis sessions (dependent on residual renal function (urine output) as well as the ingestion of salt and fluid).

The calculation is made and the total UF volume to be removed for the treatment is entered into the HD machine.

UF volume = incoming weight – 'dry' weight + circuit volume + fluid consumption

Measures of solute clearance is based on small solute (urea) measurements and used for optimal dialysis dose. The reliance on small solute clearance has become increasingly controversial. However, *Kt/V* is used in many centers to measure dialysis adequacy *(K=urea dialyzer clearance, t=dialysis time, V=volume of distribution of urea)*. Kt/V is calculated automatically by software embedded in the HD monitor. Target/sufficient dialysis dose is said to be Kt/V is 1.2, however striving for a higher Kt/V has been recommended, primarily opinion-based and not evidence based.[14] Strategies that may improve Kt/V include extended HD time/frequency, vascular access modifications, and choice of dialyzer (design, membrane and surface area).

Although tremendous progress has been made to HD therapy over the past several decades (moving from a 'last ditch effort' experiment to a widely accepted life sustaining treatment), it is certainly not perfect. Intermittent therapy cannot match the efficacy of continuous natural kidney function. Dialysis prescriptions can be altered (e.g., dialysate composition, length/frequency of treatment times, dialysis membrane, modality) in order to improve efficiencies/effectiveness of treatment however, modifications to therapy are

quite limited. The physiological needs of the patient must be carefully balanced in order to maintain HD tolerability and acceptability of treatment regimes. Even in our developed health care system, there are varying limitations to resources, supplies and acceptance to modified treatment regimes. This is largely due to institutional infrastructure, financial constraints and policy which dictate how we delivery therapy. The individuality of the patient, specific needs and personal requirements do not fit into this 'standard of care' model. As a result, improvement and advancement is stifled - and adversity, morbidity and mortality continue.

1.7 HD-induced Circulatory Stress

Intradialytic hypotension (IDH) is a serious and common complication of HD effecting 20-30% of treatments. All HD patients are at risk of developing IDH at any time, however additional vulnerability may include factors such as progressive age, longer HD vintage, presence of diabetes, low BP before dialysis and lower serum albumin levels.[15,16] IDH results when UF demands during HD exceed the rate of vascular refill, resulting in a reduction in circulating volume within the vasculature. In addition, HD patients often have impaired compensatory mechanisms. As a result, the body's ability to autoregulate and increase vascular tone in response to deterioration in BP in stunted reducing perfusion to vital organs. IHD is directly associated HD-related adversity including intra/interdialytic symptoms, vascular dysfunction (micro and macro levels), vascular access thrombosis due to hypoperfusion, inadequate dialysis dose (need to abort treatment early), end-organ damage and mortality.[15–19]

1.7.1 Ischemic-reperfusion Injury

The repetitive nature of intermitted HD with high UF demands cause vascular insults which last beyond the cessation of the HD. Initially organ reperfusion and recover however, over time, repeated insults cumulate impairing physiological responses to the point that full recovery is no longer possible. This eventually leads to permanent damage to the structure and function of various vital organs. These transient interruptions in blood supply and tissue oxygenation is known as ischemic-reperfusion injury. Ischemic-reperfusion injury is

directly associated with the degradation of the glycocalyx, endothelial damage and overall breakdown of the microvasculature further altering vascular reactivity, permeability, oxygen delivery and hemodynamic coherence[20,21] which will be described further in sections 1.8 and 1.9.

1.7.1.1 Effects of HD-induced Circulatory Stress on Vital Organs

1.7.1.1.1 The Heart

CKD associated cardiomyopathies are characterized by cardiac structural and functional abnormalities (left ventricular (LV) dilation, LV hypertrophy and systolic dysfunction), which worsen with advancing stages of CKD advance.[19] Maladaptive processes within the myocardium lead to capillary rarefaction impairing coronary flow reserve, and limiting the patient's ability to increase blood flow in response to demand (stress of HD).[19] Intermittent HD treatments induce recurrent episodes of myocardial ischemia and myocardial contractile dysfunction, which persists long after the return of normal perfusion, with eventual recovery. This phenomenon is known as myocardial stunning – a form of ischemic-reperfusion injury in the myocardium.[22]

More than 65% of patients receiving conventional thrice weekly HD experience HD-induced myocardial stunning.[23–26] Recurrent myocardial stunning can lead to permanent loss of global and segmental LV contractile function. Patients who develop myocardial stunning are at even greater risk of developing heart failure and succumbing to CV mortality.[23,27,28] Myocardial stunning can induce arrhythmic changes in the heart with direct correlation to sudden cardiac death as a result of UF and episodic IDH.[5,19] The association between myocardial stunning and cardiac perfusion using positron emission tomography, demonstrated that myocardial blood flow significantly declines during HD (associated with UF) by as much as 30% and LV regions with the greatest reduction in perfusion mirror segments that develop LV-RWMA resulting in myocardial stunning.[23,29]

The pathological processes leading to CV mortality in the HD population can be summarized as:

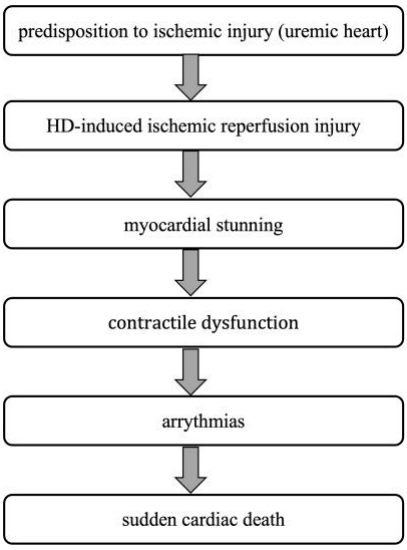

Figure 1-7: Pathological Cardiovascular Processes

1.7.1.1.1.1 Myocardial Sunning

Myocardial stunning and the development of HD-induced RWMA can be identified using serial 2D echocardiography and specialized speckle tracking strain analysis software (described further in the next chapter – section 2.3.5.1). Longitudinal strain (LS) can be assessed both globally (entire LV) and segmentally (12-LV segments). In order to establish that HD is responsible for the development of LV functional changes, echocardiography images are obtained before the initiation of dialysis and repeated again nearing the end of dialysis (peak HD-stress) at the time when fluid removal goals (due to UF) are achieved. Longitudinal myocardial strain is the percentage of change between the length of LV myocardial fibres during contraction (systole), and their original length (diastole), pre-HD segmental strain values are then compared to segmental strain values at peak HD-stress. The development of a RWMA is defined as any LV segment that has undergone a reduction in LS of ≥20% (at peak HD-stress). Following segmental strain analysis, the presence of HD-induced myocardial stunning is established if two or more RWMA develop.[30]

1.7.1.1.2 The Brain

In CKD, cognitive function synergistically declines with kidney function. The initiation of HD elicits further cognitive impairment with loss of functional status which contributes to mortality.[31] The presence of pathological processes (evidenced by magnetic resonance imaging) has been seen in the brains of HD patients including the presence of silent cerebral infarcts and generalized cerebral atrophy.[5,32,33] Changes to, and loss of white matter in the brains of HD patients as a result of ischemic injury is likely to contribute to the development of depression, dementia, mobility issues, and accelerated vascular aging.[5,34] Additionally, cognitive testing demonstrates that HD patients score poorly in the area of executive functioning which is known to be associated with changes to white matter.[34,35] Subclinical HD-injury tends to occur in the watershed area of the brain where intradialytic perfusion changes would be typically seen. This discovery highlights the importance of maintaining hemodynamic stability during HD.[5]

1.7.1.1.3 The Spleen, Gut and Liver

In health, reductions in cardiac output triggers the spleen to compensate and respond by emptying stored blood (splenetic reservoir) into the systemic circulation thereby increasing pre-load and circulating volume. A secondary mechanism is then triggered, inducing vasoconstriction, again increasing blood flow and the maintenance of perfusion to vital vascular beds, including the heart and brain.[36] During HD however, splenetic perfusion falls in response to UF impeding the autoregulatory function of the spleen, promoting the risk of IDH.[37–40]

The gastrointestinal tract is an important organ in many pathological processes. HD patients are prone to gastrointestinal dysbiosis, increased gut derived toxin production (endotoxins) and intestinal permeability (leaking). The translocation of circulating endotoxin levels is prevalent in patients with CKD, with levels tripling within months of starting HD.[41] There is often a reduction in blood flow to the gut of HD patients with mucosal ischemia present during HD.[36,42–44] Using CT imaging, intestinal perfusion has been shown to decrease acutely during HD with restoration after the completion of HD.

This has been shown to be associated with circulatory stress and severity of HD-induced cardiac injury.[41,45]

Working together with the spleen and gut, the liver is primarily responsible for endotoxin clearance. The duo blood supply of the hepatic circulation is a system of adaptive response however, the presence of heart failure, hypoxic injury, hypervolemia, endotoxemia and increased myocardial demand with ischemic-reperfusion injury compromises optimal liver functionality.[36] Intradialytic CT imaging has shown us that hepatic perfusion tends to remain constant (compliments of the unique blood supply), however the ability of the liver to function properly is compromised during HD.[36]

1.7.1.1.4 The Kidneys

The preservation of RRF is a key component to optimal outcomes for patients with CKD. Preserved renal function is associated with fewer uremic symptoms, better quality-of-life, hemodynamic stability and improved survival. However, the ability to maintain RRF for extended periods in the presence of HD is extremely challenging and eventually futile. Repetitive episodes of aggressive fluid removal to maintain optimal volume status results in the loss of RRF in a short period of time. Serial intradialytic imaging (using CT) has shown that even blood flow to the already damaged kidneys declines during HD. This phenomenon is suggestive that circulatory stress also occurs within the kidneys contributing to the dramatic loss of protective RRF as a result of HD.[45]

1.8 Microcirculation

The microcirculation is the terminal network of the vasculature consisting of micro-vessels of less than 20ug in diameter (arterioles, post-capillary venules and capillaries). This network of vessels covers a surface area measuring approximately 350m2, which makes up close to 99% of the entire circulation.[46,47] The microvasculature is the endpoint of the cardiovascular system responsible for the transport of oxygen via RBC within the capillaries to parenchymal cells where oxygen is delivered to the cells of tissues meeting energy requirements necessary for optimal functionality.[46]

RBC travel through the capillaries carrying oxygen (transport) which is then delivered (through diffusion) to the mitochondria of tissue cells – a function completely dependent on optimal flow and capillary density. Additionally, the microcirculation is also responsible for the regulation of solute/nutrient exchange between the intravascular environment and tissues, transporting hormones to tissues, maintaining cellular hemostasis and regulating immune responses.[46]

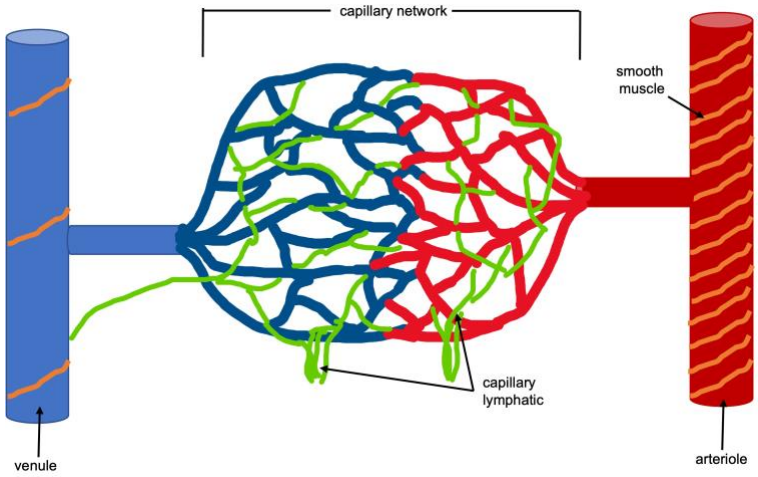

Figure 1-8: Microvascular Anatomy - consisting of small blood vessels (arterioles, capillaries, venules). The lymphatic system (green) carries fluid from vasculature to venous system. Arterioles surrounded by smooth muscle for vascular regularity/tone. *Adapted from Microcirculation: Physiology, pathophysiology and clinical application. Guven, Hilty, Ince, 2020.*[46]

1.8.1 Structure and Function

The internal luminal surface of all blood vessels (including the vessels of the microcirculation) are covered with a single cellular layer of endothelial cells (endothelium) followed by a basement membrane. Arterioles are then covered with a layer of smooth muscle whereby the endothelium and smooth muscle cells working together to regulate blood flow by adapting vascular tone and pressure within arterioles.[46]

Table 1-3: Features of Blood Vessels. Microcirculatory vessels include arterioles and capillaries.

		Vessels of the Microcirculation		
	Arteries	**Arterioles**	**Capillaries**	Veins
Number	• hundreds	• **half million**	• **ten million**	• hundreds
Features	• thick walls • elastic • large radius	• **muscular** • **small radius**	• **thin walls** • **single-cell radius**	• thin walls • large radius
Function	• passage from heart to organs	• **resistance vessels** • **vascular tone**	• **oxygen/nutrient/fluid exchange**	• passage from organs to heart • blood reservoir
Structure	• endothelium • basement membrane • elastic fibres • smooth muscle • elastic fibres • connective tissue	• **endothelium** • **basement membrane** • **smooth muscle** • **connective tissue**	• **endothelium** • **basement membrane**	• endothelium • basement membrane • smooth muscle (less) with elastic fibres • connective tissue

The endothelium produces a ‘gel-like’ protective layer made of negatively charged proteins/sugars (polysaccharides and peptidoglycans), forming a matrix that covers the luminal side of the endothelium, this protective ‘gel-like’ layer is called the glycocalyx. The glycocalyx comes in direct contact with the blood with properties that break down harmful substances and mediate shear-stress.[46,48] The glycocalyx is responsible for important regulatory processes including homeostasis, hemostasis, immune functions and vascular tone.[46,49] A healthy glycocalyx regulates vascular permeability preventing leakage/loss of water and macromolecules (essential proteins) into the extracellular space, it facilitates laminar blood flow forming a profibrinolytic/antithrombotic interface preventing RBC adhesion, coagulation/thrombosis formation and interaction between

leukocytes/platelets. The glycocalyx also acts as a mechano-sensor whereby passing blood flow rearranges the endothelial cytoskeleton inducing a shear stress response which triggers smooth muscle cell relaxation and vasodilation through nitric oxide release.[49] Pathological injury to the glycocalyx therefore results in abnormal vascular permeability, interstitial edema, platelet aggregation, leukocyte adhesion, a pro-thrombotic environment and maladaptive vascular tone with loss of autonomic compensatory mechanisms[49]. It is therefore well recognized that the health of the microcirculation with glycocalyx salvage is critical for optimal performance of bodily functions and overall circulatory health.[46,47]

1.9 Vascular/Microcirculatory Dysfunction

Endothelial dysfunction is considered to be one of the hallmark signs of hemodynamic collapse in critical illness.[46] CKD is progressive in nature, with a stepwise increase in CV complications as kidney function declines. In addition to 'traditional' pro-atherosclerotic conditions (dyslipidemia, obesity, smoking) and common disease processes (hypertension, diabetes), a diagnosis of CKD and state of uremia stimulate abnormal processes within the circulatory system.[48] Atherogenic changes in the vascular endothelium trigger the shedding of the glycocalyx, largely due to a oxidative stress and a chronic state of inflammation.[48] As a result, changes in nitric oxide autoregulation and smooth muscle tone disrupt the ability to physiologically regulate blood flow to vascular beds increasing shear-stress and endothelial degradation.[48] Consequently, capillary rarefaction occurs reducing the available surface area for oxygen/nutrient exchange with permanent tissue damage (fibrosis/remodeling) and capillary deterioration/death.[47,50–52]

Systemic microvascular impairment precedes macrovascular signaling and is directly associated with CV burden.[50,53,54] For the HD population, CV mortality extends beyond that of CKD and are on average 15 times greater than the general population.[55] 'Traditional' population based atherosclerotic risk does not account for the disproportionately high rates of mortality.[19,50] The acute effects of HD perpetuate the activation of pathological processes compounding vascular degradation as a result of several factors. During HD, the blood is in direct contact with multiple synthetic materials that make up the extracorporeal

circuit (tubing, dialysis membrane, dialysate, vascular access, supplies) causing oxidative stress and inflammatory responses (biocompatibility). Furthermore, the volume of blood outside of the patient's body (within the extracorporeal circuit) in addition to rapid and large amounts of fluid removal/UF during HD result in decreased systemic circulating volume which can lead to IDH where there is a reduction in perfusion to vascular bed resulting in HD-induced circulatory stress and ischemic/reperfusion injury.[46,48,50]

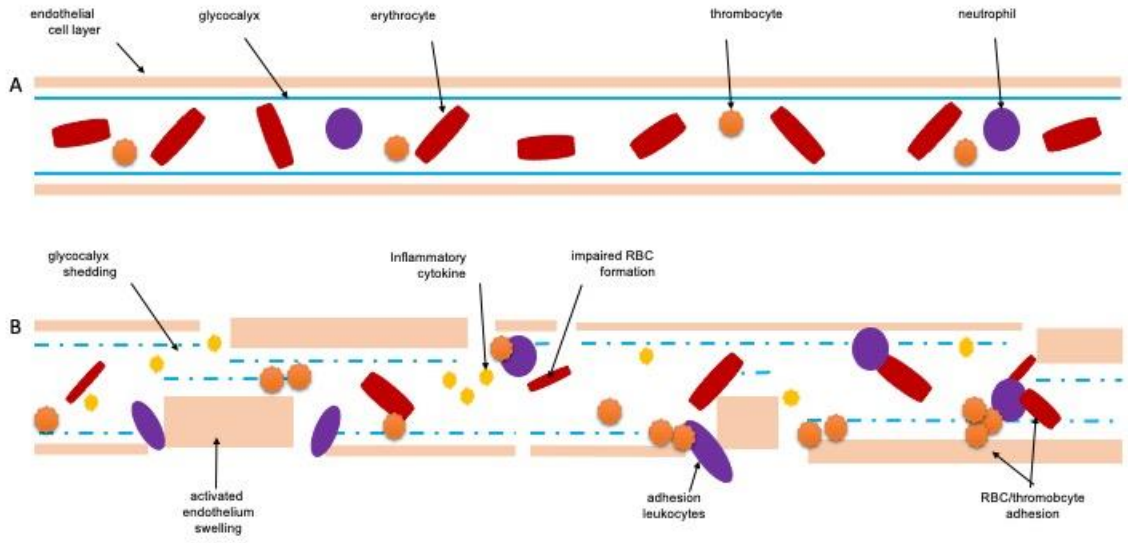

Figure 1-9: Microvascular Dysfunction and Vascular Endothelial Damage. Structure of healthy microvessel (A). Microcirculatory damage - caused by inflammation, hypoxia, ischemic-reperfusion injury (B). *Adapted from Microcirculation: Physiology, pathophysiology and clinical application. Guven, Hilty, Ince, 2020.*[46]

1.10 Non-invasive Evaluation of the Microcirculation

1.10.1 Sublingual Mucosa Vascular Bed Technology

1.10.1.1 Side-stream Dark Field Imaging

Direct in-vivo visualization of microvascular blood flow and morphology can be achieved through the sublingual mucosa, using side-stream dark field imaging (SDF). SDF has been used extensively in critical illness (sepsis/heart failure) and has proven to be a surrogate for both vital organ perfusion (gut) and clinical outcomes/survival.[56,57] In this setting, SDF has been used successfully to guide fluid resuscitation improving microcirculatory perfusion more effectively than macrovascular parameter guides. SDF is a microscopic technique that uses polarized green light to visualize RBC passing through the sublingual capillary bed in real-time,[58–61] facilitates assessment of erythrocyte flow and structure. SDF has proven to be an effective tool for the evaluation and assessment of vessel size, microcirculatory flow, vessel density, vessel perfusion and heterogeneity of flow.[58,60–63]

Total small vessel density, perfused small vessel density and proportion of perfused small vessels have been shown to be lower in HD patients, with improvement after kidney transplantation suggestive of both a uremic and volume causation for dysfunction.[64] UF during HD is strongly associated with microcirculatory blood flow reductions and heterogeneity of flow in the absence of macrohemodynamic changes at the systemic level.[58,62,65] It has been shown that by increasing pre-load, microcirculatory blood flow and perfusion of vessels improves (directly visualized by SDF).[65] Although the direct visualization of blood flow and quantification of perfusion would be extremely useful, the intradialytic utility of this technology is extremely limited (steep learning curve with image acquisition, unrealistic for continuous monitoring to drive HD delivery, expensive, resource intensive).

1.10.2 Cutaneous Vascular Bed Technologies

The cutaneous circulation is the most easily accessible vascular bed with a large surface area. Many diseased states (hypertension, diabetes, CKD, autoimmune disorders) alter the microvasculature, which can be detected locally in the skin circulation mirroring generalized systemic vascular dysfunction.[66,67] Impaired coronary microvascular function has been reflected as impaired peripheral microvascular function.[67] Skin biopsies from HD patients without macrovascular disease have shown there to be capillary rarefaction, fibrotic changes to the basement membrane, activation of the endothelium, structural changes and inflammatory cells within the microcirculation, all of which correlated with the length of time on HD.[50] Additionally, capillary rarefaction has been evident in the pediatric HD population with single renal causation and limited pathology.[50] Because the skin is responsible the temperature regulation, it is highly adaptive and able to change blood flow in response to stimuli. Several technologies have been used to assess the cutaneous circulation which largely rely on an optical light sources with absorption/reflective properties to quantify microcirculatory blood flow and oxygenation within the microcirculation.

1.10.2.1 Laser Doppler Technologies

Laser doppler is a non-invasive means to explore changes in microvascular blood flow. Laser doppler relies on detecting changes in wavelengths (doppler shifts) of interrogated laser light associated with velocity and the number of moving blood cells.[68–70] Laser doppler flowmetry (LDF) is a probe-based system that enables the temporal evaluation of microcirculatory blood flow at a fixed anatomical point. LDF has demonstrated that HD patients have significantly lower flowmetry measurements regardless of co-morbidities[71] than healthy controls with post-occlusion method. LDF was also found to show impairment in microvascular endothelial function in HD patients when compared to CKD patients that were not yet on HD which was seen to be ameliorated after a six-months course of AST-120 (an experimental uremic toxin absorbent).[72] Laser doppler imaging (LDI) provides non-contact spatial changes in the microcirculation over a larger surface area. LDI demonstrated that in 61% of evaluated surfaces (hand), there was a reduction in

microcirculatory blood flow with increased heterogeneity (fingers) during HD when compared to values before dialysis, which were proportional to UF.[73]

1.10.2.2 Near-infrared Spectroscopy

Near-infrared spectroscopy (NIRS) provides a more global assessment of tissue oxygen saturation and tissue perfusion. Infrared light is transmitted through the skin, where light is absorbed by RBC, with unabsorbed light reflected, measuring oxygenated hemoglobin concentration in relation to total hemoglobin concentration.[74] Largely used to evaluate oxygenation in the brain tissue, HD patients were shown to have a longer blood transit time in the cerebral microcirculation which corresponded to reductions in microvascular blood flow.[75]

1.10.2.3 Transcutaneous Oxygen Tension

Transcutaneous oxygen tension (TcP02) tension measures local peripheral arterial blood flow, skin oxygenation and tissue perfusion.[76–78] Diffusive oxygen, carried through the microcirculation to peripheral tissues is measured through heated electrodes providing indirect measurements of microcirculatory perfusion. TcPO2 is widely used to evaluate peripheral vascular disease, diabetic foot disease, wound healing, and to guide amputation levels.[76,77] HD patients (without peripheral arterial disease) have been shown to have significantly lover TcPO2 values when compared to healthy controls,[79,80] predictive of mortality.[81] HD patients (diabetic and non-diabetic) have micro and macro vasculature impairment during HD with TcP02 measures predictive of gangrene risk in peripheral extremities.[82] Reductions in TcP02 have also been shown to be associated with intradialytic BP and UF rates whereby the maintenance of peripheral vascular perfusion is entirely dependent on hemodynamic stability.[78] Dialysis membrane biocompatibility has also been shown to influence measures of microvascular peripheral circulation using TcP02.[79]

1.10.2.4 Photoplethysmography

PPG is a non-invasive technology used to measure blood volume changes in the microvascular tissue bed beneath the skin.[83] PPG requires a light source, photo detector and a biological material. The red/infrared light illuminates the tissue and the photo detector senses small changes in the light intensity associated with changes in perfusion to the area.[83,84] The different wavelengths of emitted light are absorbed by oxy and deoxyhemoglobin in the blood of the microvasculature with scattered light reflected back to the sensor creating a pulsatile plethysmograph waveform representative of volumetric changes.[84,85] When the heart pumps blood during systole, the amount of blood that reaches the capillaries in the skin increases (more light absorption). The blood is then returned to the heart thorough the venous network resulting in a decrease of blood volume in the capillaries (less light absorption). The PPG waveform has two components, the pulsatile component (AC) reflecting cardiac changes in blood volume and the baseline (DC) component representing information about respiration, venous flow, sympathetic nervous system activity and thermoregulation.[83] PPG can provide diverse physiological variables such as oxygen saturation, respiration rate, heart rate, heart rate variability, cardiac output and autonomic function.[83,84] In HD, PPG technology has been used to investigate physiological changes during fluid removal using various methodologies in varying cutaneous locations.[86–90] Moreover, researchers have used PPG in an attempt to create IDH prediction models using variables such as heart-rate variability,[91] heart rate turbulence,[91] pulse waveform reflective index,[92] pulse amplitude,[93] however, regardless of the low cost and accessibility of this technology, no consensus on variable importance nor clinical application has been pursued in the HD setting.[85,94] Comparative observations of these technologies can be seen in *Table 1-4*.

Table 1-4: Comparative Microcirculatory Technological Comparisons

Technology	Advantages	Drawbacks	Utility
SDF	Individualized Direct visualization Real-time analysis/outputs Point-of-care Glycocalyx measures	Cost No continuous measurement Accessibility/training Steep learning curve Pressure artifact Patient comfort Impractical in HD clinical setting	Can drive HD therapy Assess impact HD intervention
LDF	Temporal changes Real-time analysis	Poor reproducibility Varying measures between sites No continuous measures Ambient light/temperature sensitive Accessibility/training Impractical in HD clinical setting	Microcirculatory assessment Has not been used to drive HD
LDI	Non-contact No pressure artifact	No continuous measures Arbitrary units of measure Ambient light/temperature sensitive Accessibility/training Impractical in HD clinical setting	Microcirculatory assessment Has not been used to drive HD
NIRS	Continuous monitoring	No absolute measures Accessibility/training Impractical in HD clinical setting	Limited in HD Has not been used to drive HD
$TcPO_2$	Peripheral vascular status	Accessibility/training Requires baseline O_2 saturation Impractical in HD clinical setting	Peripheral vascular impact of HD Has not been used to drive HD
PPG	Availability Continuous monitoring Individualized Embedded algorithms* Real-time analysis* Point-of-care* Practical in HD clinical setting* Ease of use* No movement artifact*	Movement artifact (finger) Algorithms required Off-line analysis No consensus on output of value	Detect HD-induced circulatory stress* Can drive HD therapy* Assess impact HD interventions*

SDF=side-stream dark-field, LDF=laser doppler flowmetry, LDI=laser doppler imaging, NIRS=near infrared spectroscopy, $TcPO_2$=transcutaneous oxygen tension, PPG=photoplethysmography, *=technology used in Chapters 2 and 3.

1.11 Strategies to Ameliorate Circulatory Stress

It is well recognized that HD-induced circulatory stress begins at the microcirculatory level contributing to the development and progression of vascular complications and adverse outcomes for the HD population. Various intradialytic strategies have been explored to in an attempt to mitigate and/or reduce the negative consequences of HD therapy.

1.11.1 Extended Hemodialysis

Aggressive UF is one of the primary drivers of HD-induced circulatory stress. UF is a necessary part of the HD procedure where fluid that has accumulated between HD treatments must be removed in order to achieve the prescribed 'dry' weight and state of euvolemia. Conventional intermittent HD achieves this (if tolerated) in three-four hours, thrice weekly. The combination of high UF requirements and the inability of the vasculature to compensate during circulatory demand predisposes patients to episodes of IDH perpetuating systemic pathologic processes. Adaptation to current HD scheduling such as, extended HD treatment time (more than four hours reduces the rate of fluid removal per minute) and/or increasing the frequency of treatments (more than three times/week can reduce fluid accumulation between HD sessions) reduces systemic stress by lessening UF requirements for a 'gentler' dialysis. Frequent HD with lower UF requirements are associated with improved hemodynamic stability [improved blood pressure (BP)] with fewer episodes of IDH and less HD-induced myocardial stunning compared to conventional regimes[96]. Unfortunately, this strategy has its challenges. The current 'industrialized' models of care does not easily allow for changes to scheduling/resources, patients often do not accept the idea of longer/more frequent visits to the hospital and the uptake of home HD remains limited.

1.11.2 Hemodialysis Composition

Dialysate composition and delivery can be adapted by modulating dialysate sodium and UF rates in response to a significant reduction in a patient's relative blood volume (RBV) within defined limits to ensure that total UF and sodium depuration are unaffected. Biofeedback dialysis been shown to decrease episodes of IDH,[27,97,98] reduce the number of HD-induced RWMA[27] and improve post dialysis myocardial blood flow.[23] Although

promising, biofeedback dialysis required specialized equipment, training, education and a commitment from renal programs (acceptance and expenditure).

1.11.3 Cooling Dialysate

Body temperature commonly rises during HD due to heat exchange from the dialysate (traditionally set at 37 degrees), reductions in circulating blood volume causing cutaneous vasoconstriction and increased thermogenesis from inflammatory responses to circulating endotoxins.[99] Dialysate cooling involves lowering the temperature of the dialysate compartment (on the dialysis machine to 35-36 degrees), which in turn lowers the temperature of the blood during HD (heat exchange). Cooling has been shown to promote vasoconstriction/reactivity, improve vascular resistance and increase baroreflex sensitivity whereby peripheral blood supply is shifted to the vascular beds of vital organ.[19,100] Dialysate cooling has demonstrated intradialytic benefit by improving BP control and hemodynamic stability with lower incidence of IDH episodes by as much as 70%.[19] Cooling has also demonstrated reductions in HD-related circulatory stress by: 1) reducing RWMA and myocardial stunning[17,28]; 2) preserving cardiac function[17,28]; 3) reducing HD-related white matter changes[18]; 4) preserving hepatic perfusion/function[101]; 5) preserving renal perfusion.[45] Cooling is universally available on any HD-machine, it is also easy to implement with no additional costing to the healthcare system. Robust research focused specifically on the benefit of dialysate cooling on numerous vascular beds has led to international guideline recommendations for the prevention of IDH,[102] and was fundamental to the conduct of a recent cluster randomized clinical trial evaluating more than 15,000 patients and 4.3 million HD treatments (largest HD clinical trial to date).[103,104]

1.11.4 Ischemic Preconditioning

Organs vulnerable to acute ischemic injury by way of CV stress due to extensive microcirculatory disease (CKD/HD) are at risk for ischemic reperfusion injury. Tissues that are depleted of oxygen/nutrients have an inflammatory response with oxidative damage upon restoration.[105] Remote ischemic preconditioning (RIPC) is a strategy that protects tissues from this effect. The application of small controlled episodes of ischemia to remote areas (calf/wrist) prior to a larger ischemic insult leads to endogenous cardio-

protection, priming the heart to tolerate a larger injury and limiting reperfusion injury.[105] Physiologically, a cascade of intracellular kinases modify mitochondrial function within the cells preventing mitochondrial permeability and death.[105] Preconditioning has two separate protective windows – the first starts immediately lasting two-three hours with a second phase developing 12-24 hours later which lasts for two-three days.[105] In HD, a common BP cuff is applied to the non-vascular access wrist or calf, the cuff is inflated to a measurement of 200mmHg, applying pressure in 5 minute intervals (5 minutes inflated – 5 minutes deflated) for 3-4 cycles. This technique has proven to be cardio-protective whereby reducing troponin-t levels (a biomarker of cardiac stress) over a 28 day period.[106] Additionally, RIPC was found to reduce the number of HD-induced RWMA significantly preserving global longitudinal strain (LS) and increasing intradialytic BP, despite elevated UF rates – protection was maintained for 28 days.[107] The clinical application of RIPC in HD is promising and well tolerated however, challenges are met regarding patient acceptability, scheduling/resource management as patients must present to dialysis early than their scheduled treatment with added intervention to treatment regimes.

1.11.5 Exercise Pre-conditioning

A physically active lifestyle can reduce the risk of CV disease in the general population by as much as 44%, In those that do develop CV disease, physical activity is attributed to fewer hospitalizations, better prognosis and reduced mortality[108]. Physical activity promotes anti-atherosclerotic, anti-thrombotic, anti-ischemic and anti-arrhythmic properties.[109] Exercise induced cardio-protection is in part associated with adaptive processes in the heart and coronary arteries which occur within weeks to months and account for 30-40% of cardio-protective benefit.[108] Similar to ischemic pre-condition, the protective profile of exercise pre-conditioning is bi-phasic, an early phase occurring immediately lasting 2-4 hour, and a latent phase developing 24 hours later lasting several days - a response too short to induce physiological adaptive change. Exercise pre-conditioning has been shown to reduce infarct size (50%), risk of arrhythmias with fewer fatal cardiac events in both animals and humans.[108] The protection is present after the first dose of exercise with repeated exercise re-activating protective pathways for compounding effect, however immediate benefit is independent to duration of exercise (due to lack of

structural adaptations).[108,110] Repetitive episodes of brief exercise induce transient biochemical upregulation of protective cellular mediators[109] which have been found to reduce the degree of exercise induce myocardial stunning in patients with severe coronary artery disease.[111] Poor cardiorespiratory fitness levels are multifactorial and largely due to the chronic nature of the diseases processes including, anemia, malnutrition, metabolic disturbances, impaired autonomic control, muscle atrophy, disease burden and depression.[112] However, even exercise at sub-maximum effort carries physiological and psychological benefit. Exercise rehabilitation programs have been shown to improve exercise capacity, cardiac function and reduce the risk of sudden cardiac death.[113–115]

HD patients are bound to strict schedules and often feel unwell (dialysis fatigue, symptom/disease burden) limiting their ability and desire to incorporate exercise into their daily routines. The incorporation of exercise during dialysis although theoretically makes sense, is challenging to actualize and sustain. IDE programs are not routinely incorporated into HD regimes largely due to resources and lack of knowledge (work is currently underway to address barriers and promote the value of IDE).[116–118] However, it has been demonstrated that even IDE at moderate exertion results in better oxygenation, physical performance, physical function, nutritional status, dialysis adequacy, quality-of-life and less depression in as little as three-four months.[119–122] Thirty minutes of IDE over three months was found to improve cardiac function (ejection fraction, systemic arterial pressure, ventricular size),[123] reduce the incidence/severity of myocardial stunning,[124] and improve HD tolerability by reducing IDH events.[120,124]

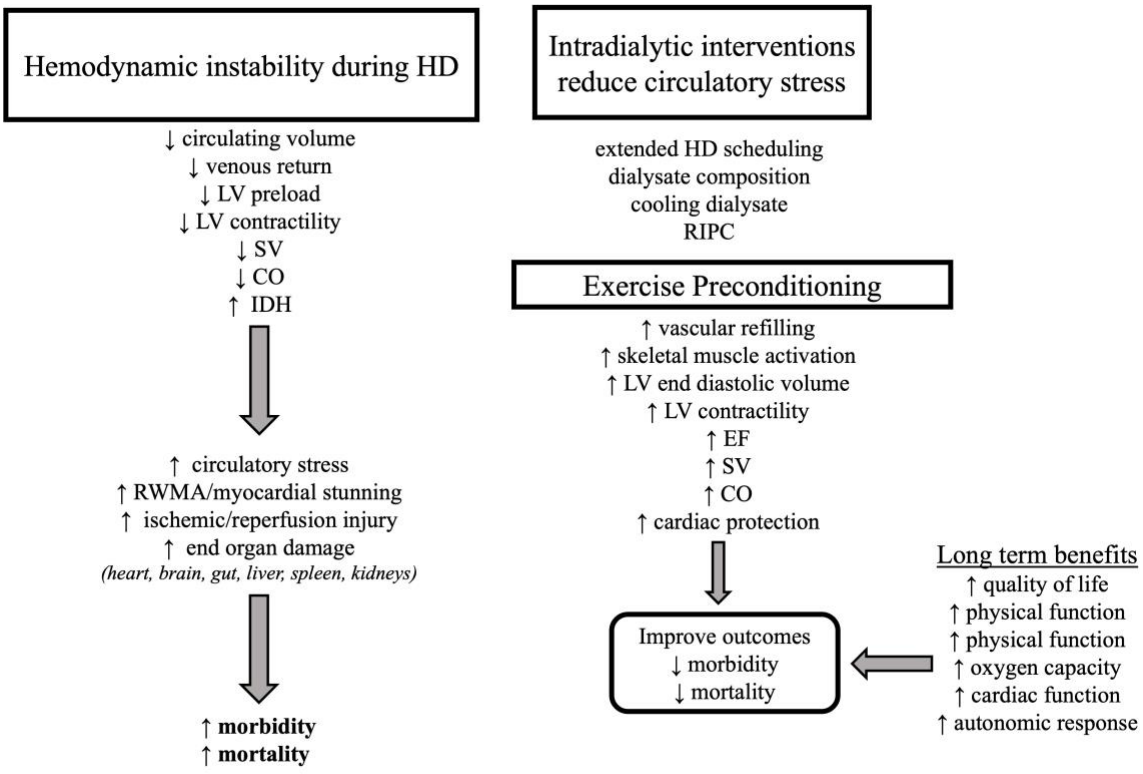

Figure 1-10: Effects of Hemodialysis Instability and Mode of Activation of Current Intradialytic Interventions. EJ=ejection fraction, SV=stroke volume, CO=cardiac output. *Adapted from Hemodynamic Instability during Dialysis: The role of intradialytic exercise. McGuire, Horton, Renshaw, Jimenez, Krishnan, McGregor, 2018.*[124]

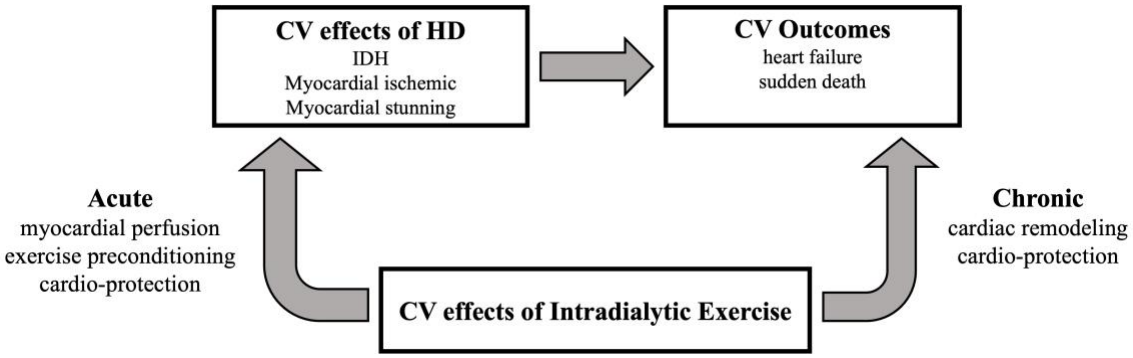

Figure 1-11: Conceptual Model of Beneficial Cardiovascular Effect of Intradialytic Exercise. *Adapted from Cardiovascular protection and mounting evidence for the benefits of intradialytic exercise. Hart, Johansen, 2019.*[122]

1.12 Intradialytic Hemodynamic Monitoring

Hemodynamics are measured routinely during the course of the dialysis treatment and more often when/if required based on variations in values or change in the patient's condition. Intradialytic monitoring currently includes parameters involving the macrovasculature including BP and pulse however, as we know, compensatory mechanisms are not intact in this population and therefore do not fully represent the circulatory changes that are occurring during HD. Moreover, changes in large vessel monitoring tend to be a 'latent' physiological response to circulatory changes. RBV, measures changes in blood volume related to time on dialysis, a technology available on many HD monitors. Different monitoring systems measure different blood constituents (hemoglobin, hematocrit, total plasma protein). Hemoglobin/hematocrit are measured by quantifying the amount of absorbed monochromatic light in blood while protein concentration is an estimate of sound wave velocity in blood. The absolute change in blood volume can differ dramatically between patients. This method of circulatory volume management has largely been an unreliable predictor of hypotension and more severe IDH.[85] It is therefore, extremely important to find alternative and more reliable methods of measuring intradialytic hemodynamic instability predictive of circulatory stress.

1.13 Thesis Motivation, Hypothesis, Aims/Objectives

1.13.1 Motivation

As a practicing HD nurse for many years, I was aware of the poor quality of life that HD patients experience however, I was largely unaware that the HD procedure itself is a significant contributor to the adversity seen in this vulnerable population. Upon transitioning to a research focus under the supervision of Dr. McIntyre, I began to more fully acknowledge and appreciate the phenomenon of HD-induced circulatory stress and the disease/treatment dyad. HD is a requirement to sustain life for patients with ESRD – I personally could not imagine living life knowing that the very treatment that keeps me alive makes me feel so unwell and induces additional harm. It is therefore my passion to find methods of improving the treatments that we delivery to the patients we serve.

1.13.2 Hypothesis

The overarching goal of this work is to study methods to identify and ameliorate HD-induced circulatory stress through intradialytic monitoring and intervention. We therefore hypothesize that intradialytic non-invasive microcirculatory monitoring of the cutaneous vascular bed is indicative of HD-induced circulatory stress (myocardial stunning) and is reflective of vital organ perfusion, and that we can ameliorate HD-induced myocardial injury by incorporating IDE into the HD regime. To address this overarching hypothesis, this thesis has been divided into three projects with individual aims/objectives.

1.13.3 Aims/Objectives

1. To determine if intradialytic monitoring at the microcirculatory level (cutaneous vascular bed) using PPG technology would be predictive of HD-induced circulatory stress.
    a) Assess the intradialytic utility of cutaneous microcirculatory monitoring using PPG technology during HD.
    b) Assess HD-induced circulatory stress by determining the development of RWMA (myocardial stunning) using serial echocardiography.
    c) Explore the relationship between changes in cutaneous microcirculatory monitoring (using PPG technology) and HD-induced circulatory stress.

2. To determine if intradialytic microcirculatory monitoring of the cutaneous circulation using PPG technology was reflective of vital organ perfusion (myocardium) during HD and how both relate to the development of HD-induced circulatory stress.
    a) Explore the relationship between changes in cutaneous microcirculation using PPG technology and changes in direct measures of myocardial perfusion using CT imaging.
    b) Explore the relationship between changes in cutaneous microcirculation (PPG), and HD-induced circulatory stress and the development of RWMA (myocardial stunning) using serial echocardiography.

3. To determine if IDE would be effective intervention to ameliorate HD-induced circulatory stress.
    a) Assess HD-induced circulatory stress by determining the development of RWMA (myocardial stunning) using serial echocardiography during HD without IDE.
    b) Assess HD-induced circulatory stress by determining the development of RWMA (myocardial stunning) using serial echocardiography during HD incorporating IDE.
    c) Assess the effectiveness of IDE as an intervention to ameliorate HD-induced circulatory stress by determining if there was a difference in the development of RWMA between the two visits.

1.14 Research Approach

1.14.1 Challenges to Clinical Research

Clinical research is extremely challenging with experiment design difficult due to a variety of barriers and limitations. Challenges are heightened in the HD population as well as the clinical HD setting. The lives of HD patients are burdened by a multitude of practical barriers and physiological factors. The chronic nature of the disease process, co-morbid conditions and treatment expectations create a life full of demands; including- tight schedules, numerous appointments, negative symptoms and emergent conditions, all of which impact the ability to lead a 'normal' life. As a result, the thought of research can be perceived as yet another 'ask' or burden is an already challenging existence. Additionally, regardless of the commonality of CKD requiring dialysis, patients tend to be extremely heterogenous with varying ages, co-morbid conditions, ESRD etiology, nutritional status, pharmacological requirements, socio-economic status and support systems. These differences cause uncontrolled variability which can be difficult to understand/explain. Furthermore, the clinical setting and HD environment is extremely constrained and chaotic with many moving parts. The logistics of data acquisition during HD must be carefully balanced within the constraints of clinical needs and expectations. Sample size is often a limitation to HD research however, given the multitude of challenges, the ability to carry out research in this population and environment is a commendable achievement. When designing HD studies, the patient experience must be the primary consideration – study design/interventions must not impact too heavily on an already demanding life. Therefore, the projects within this thesis were short in duration (one-two visits) and occurred during the patients regularly scheduled HD sessions. In my experience, this approach/design is generally well accepted by this patient population.

1.14.2 Choices of Technologies/Interventions

Considering the challenges listed above, the following section provides rationale for the technologies and interventions chosen to complete this work.

Echocardiography – Serial echocardiography is the gold standard technology used to non-invasively assess the development of HD-induced RWMA. This methodology has been used in multiple studies to describe the significant detrimental effects of HD-induced circulatory stress in the form of myocardial stunning[23,25,30]. From a patient perspective, most patients are either aware of/or have had a clinical echocardiogram. Therefore, intradialytic echocardiography is widely accepted with minimal discomfort to patients, and no additional requirements asked of the patient.

Photoplethysmography – PPG is extremely common in most clinical environments. This technology is commonly used to acquire information on a patient's oxygen saturation. PPG is widely accepted and non-invasive. It has been used as a method of assessing a patient's CV status however, arbitrary units of measure make some technologies difficult to apply for continuous, real-time assessment. Therefore, we chose to implement the CVInsight ® device to studies described in Chapters 2 and 3. This device has been used intra-dialytically and was shown to predict episodes of IDH with 80% sensitivity with a lead time of approximately 59 minutes prior to the development of symptoms (unpublished data from two studies). Another study demonstrated that the technology was used to drive HD therapy using proprietary algorithms and intervention alerts. As a result of the alert system and prompted interventions, volume control was optimized with reflective target (ideal) weights and systolic BPs reductions. Additionally, reactivity to symptoms and adversity (IDH) was avoided; including- fluid boluses, stopping UF and premature discontinuation of treatment (also unpublished). From a patient perspective, there are no additional requirements necessary, there is no additional time commitment, and the forehead sensor is comfortable to wear for the duration of treatment.

Intradialytic Exercise – IDE has been shown to be effective in improving physical functioning, quality of life, muscle wasting, nutritional status and dialysis adequacy.[119,120,125] From these studies, IDE offers numerous health benefits and is a fairly

well accepted intervention requiring no extra time commitment from a patients perspective. However, from a healthcare perspective, there are numerous challenges and barriers to the implementation of IDE into routine care.[116,118] These challenges are currently being addressed, however in order to answer our research question, we took advantage of partnering with one of the few well established pre-existing intradialytic exercise programs in the country in order to gain an understanding on IDE as an additional strategy to ameliorate HD-induced circulatory stress.

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Chapter 2

2 Percutaneous Perfusion Monitoring for the Detection of Hemodialysis Induced Cardiovascular Injury

2.1 Co-authorship Statement

The content of this chapter was published in *Hemodialysis International,* July 2018, 22(3):351-358. doi: 10.1111/hdi.12632, co-authored by Jarrin D. Penny, Clair Grant, Fabio R. Salerno, Anne Brumfield, Marcus Mianulli, Lori Poole and Christopher W. McIntyre.

Penny *(100%)* administered the hemodialysis treatment, Penny *(80%),* Grant & Poole collected the data. The data were analyzed by Penny *(50%),* Grant, Salerno, Brumfield & Mianulli. The data were interpreted by Penny *(50%),* Grant, Mianulli, McIntyre. Each author contributed important intellectual content during the drafting and revising of the manuscript and accept accountability for the overall work by ensuring that questions pertaining to the accuracy and integrity of any portion of the work are appropriately investigated and resolved.

Research ethics board approval is provided in Appendix B. The permission to reproduce this manuscript is provided in Appendix C.

2.2 Introduction

It has been well established that HD patients have significantly elevated rates of CV mortality, which are not driven by the same risk factors or pathophysiological processes that are evident in the general population.[1,2] Atherosclerotic coronary artery disease is not the predominant mode of death in patients receiving HD. Records from the US Renal Data System have shown that HD is an independent risk factor for the development of both de novo and recurrent heart failure, with a 2-year mortality risk after a diagnosis of congestive heart failure as high as 51%.[3] Furthermore, a significant percentage of cardiac mortality is due to sudden death, which has been shown to be temporarily related to the dialysis procedure itself.[4] Additionally, HD patients are more susceptible to demand myocardial ischemia because of LV hypertrophy, reduced peripheral arterial compliance, impaired microcirculation and ineffective vasoregulation during HD and UF.[5]

Several studies have described the phenomenon of HD-induced myocardial stunning [4,6] commonly encountered in HD patients and associated with reductions in myocardial contractile function and patient survival.[7] Measurement of myocardial blood flow during dialysis demonstrated that HD can precipitate myocardial ischemia.[8] Ongoing and recurrent episodes of ischemia precipitated by HD have negative consequences, leading to further myocardial injury and development of eventually non-viable myocardium. Echocardiography can be used to detect myocardial stunning by identifying reductions in segmental and global systolic contractile function. Cardiac injury/stunning is associated with loss of cardiac function, increased cardiac events and increased morbidity and mortality.[7] Currently, the detection of myocardial stunning requires the use of serial imaging during dialysis to recognize the segmental reduction in systolic function. This is typically performed only for research purposes and is not a realistic diagnostic tool that can be utilized for individual patient care delivery. Furthermore, currently the identification of stunning using echocardiography implies established myocardial ischemic challenge and is not useful to allow dynamic prevention of organ hypo-perfusion within the HD treatment being studied. Currently, there are no viable means to identify myocardial stunning resulting from HD-induced systemic circulatory stress early enough to allow timely intervention and modification of the dialysis session to allow safer delivery of HD

treatment.

Recently however, a non-invasive, continuous hemodynamic monitoring system has been introduced. CVInsight® (CVI) (InteloMed Inc., Warrendale, PA), has been developed as an easy-to-use device available for real-time intradialytic monitoring. The CVI monitoring system assesses cardiovascular status via a commercially available peripheral PPG. The system consists of a patient sensor, control unit and a medical grade tablet pictured in *Figure 2-1*.

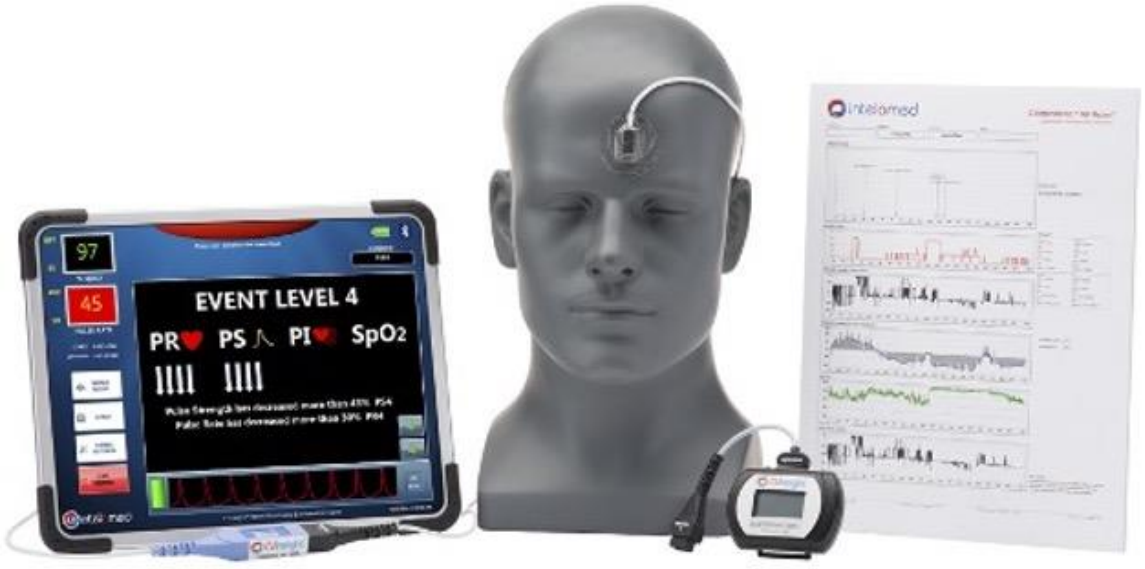

Figure 2-1: CVInsight ® Monitoring System

The sensor emits a specific wavelength of infrared light, which is absorbed by oxyhemoglobin proportionally to blood volume. The portion of light that is not absorbed, is reflected back to the sensor and is then converted to a displayed waveform. The waveform has been shown to correlate with invasive hemodynamic measures in animal experiments which can be seen in *Figure 2-2* (unpublished data).

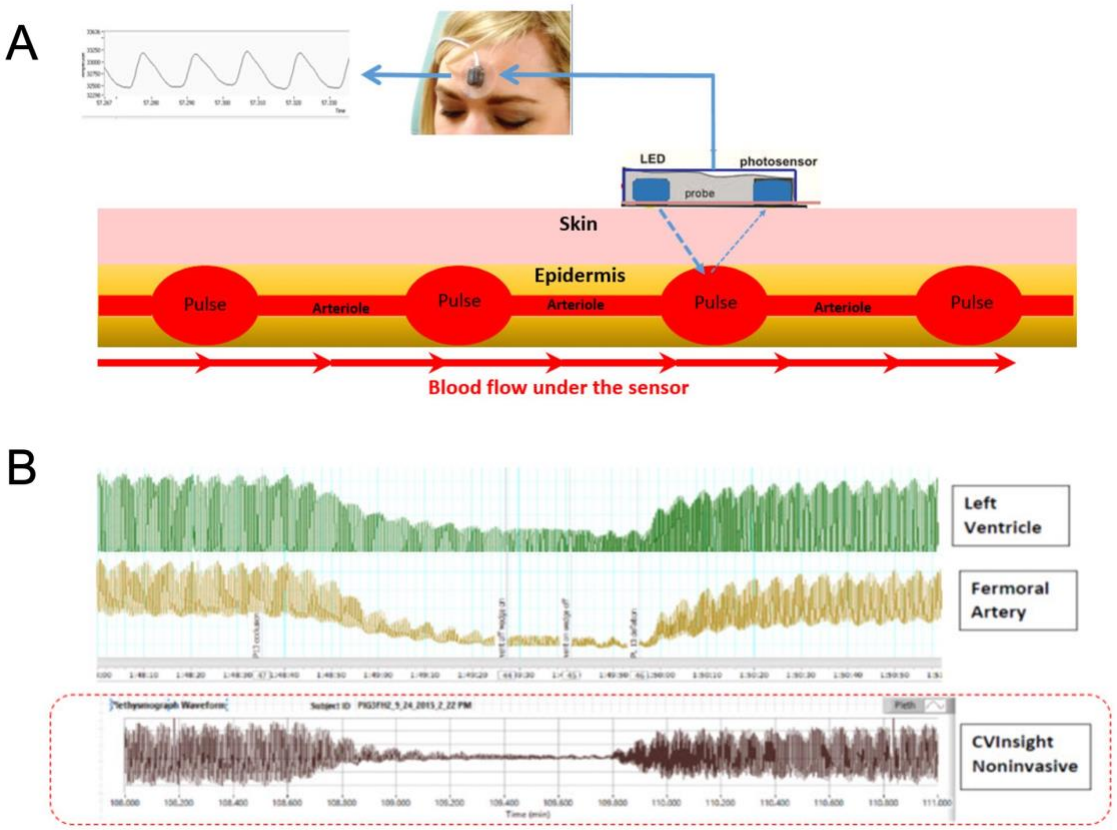

Figure 2-2: CVInsight ® Sensor Operation and Physiological Correlates. Infrared light is absorbed by the blood proportionally to and the blood volume, with the remainder reflected from the arteriole bed back to the sensor. This signal is processed and displayed as a waveform (A). The CVInsight® waveform has been shown in animal studies to closely mirror invasive hemodynamic measurements. This recording was made during mechanical manipulation of preload with a balloon catheter placed in the superior vena cava (B).

The device continuously analyzes the pulse waveform with proprietary algorithms and displays information for numerous key physiologic parameters including Pulse Strength (PS), Pulse Rate, Pulse Irregularity, Oxygen Saturation and SpO_2 Variability. SpO_2 Variability is the cyclic waxing and waning of the SpO_2 waveform that has been shown by previous studies to reflect respiratory disturbances.[9–11] The PS is the volume of blood delivered within the capillaries with each heart beat which is an indicator of tissue perfusion and reflective of stroke volume.

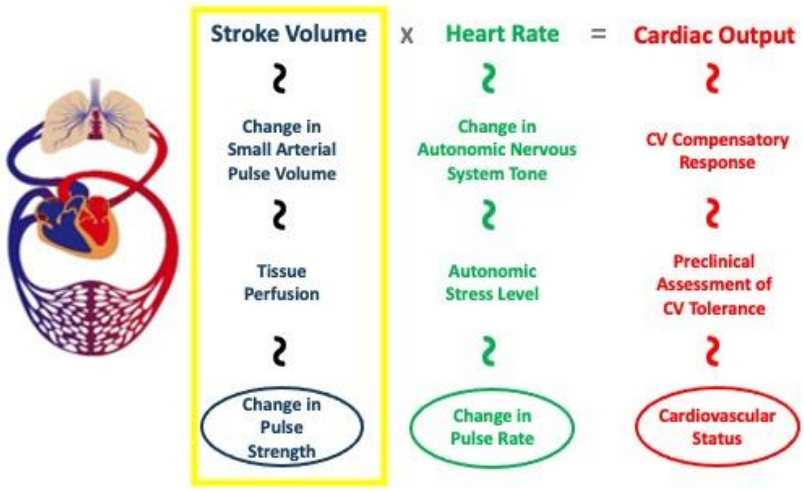

Figure 2-3: Changes in Pulse Strength are Representative of Tissue Perfusion/Stroke Volume.

This monitoring system provides patient-specific assessment of CV stability monitoring the relative changes in a patient's CV compensatory capacity and HD tolerance. This differs from other CV monitors that provide absolute numerical values which must be interpreted against a standard measurement, and often do not reflect a given patient's unique compensatory status.

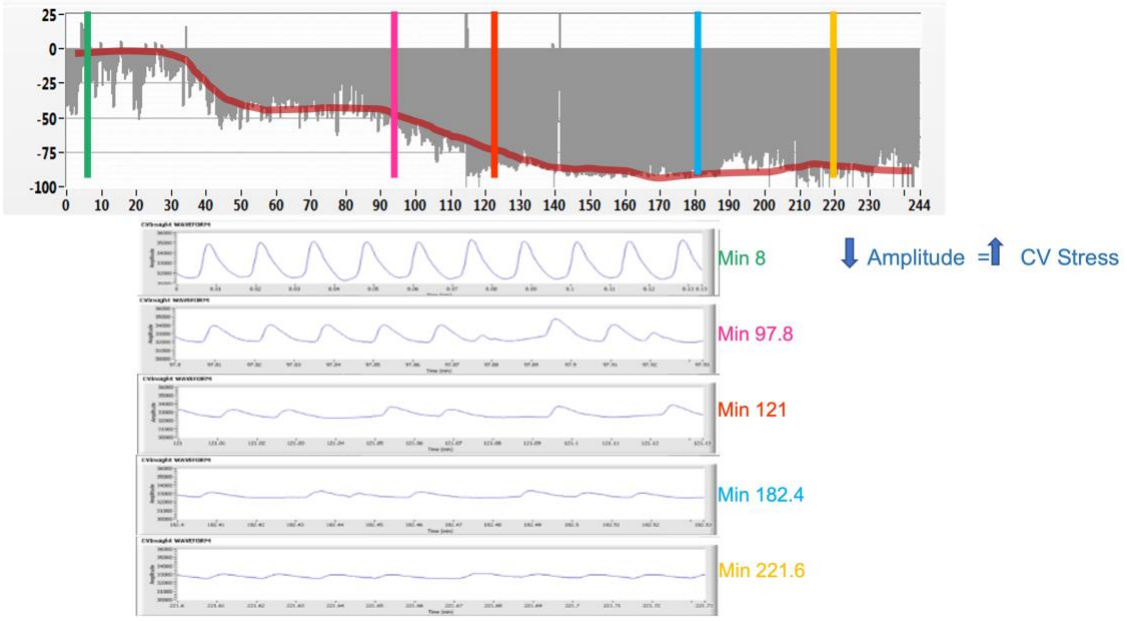

Figure 2-4: Graphic of CVInsight ® Outputs. Percent change in pulse strength (top graph) is represented as a pulse amplitude waveform (bottom graphs). As pulse strength decrease there is a flattening of the amplitude waveform. Flattened amplitude waveform is indicative of increasing CV stress.

The aim of this study was to evaluate the utility of this non-invasive, real-time percutaneous monitoring device to identify HD-induced circulatory stress and the development of RWMA (myocardial stunning). We compared CVI response to cardiac echocardiographic assessment of myocardial function during and nearing the end of HD, and compared the degree and duration of change in CVI measurements with change in echocardiographic indices of myocardial stunning during HD.

2.3 Methods

This study was conducted according to GCP/ICH guidelines and the principles of the Declaration of Helsinki, with appropriate ethics committee approval. All patients gave their written, informed consent before participating in the study.

2.3.1 Study Population

Eight patients were recruited/consented to participate in study from the prevalent adult HD population in the London Health Sciences Centre Renal Program. Patients were included if they were >18 years of age and received chronic thrice weekly HD therapy for >3 months.

2.3.2 Study Design

This single-centred exploratory pilot study aimed to compare the intradialytic percentage of change in PS to the number of LV RWMA observed by echocardiography during one HD session.

2.3.3 Dialysis Treatments

Dialysis treatments were delivered in a single centre by a single operator (JP). HD was delivered using a Fresenius 5008 system using high-flux polysulfone dialyzers as per the patient's usual prescription. Treatment times were either three and one half hours or four hours (usual treatment time). Dialysate was programmed according to each patient's individual prescriptions; sodium of 140mmol/L for all patients except one who was 138mmol/L, four patients had 1.5mmol/L potassium dialysate and four had 3.0mmol/L, all patients had a dialysate calcium of 1.25mmol/L and bicarbonate ranged from 34-40mmol/L. Anticoagulation was achieved using low-molecular weight heparin (Dalteparin) except for one patient who received unfractionated Heparin. Dialysate flow was 500mL/min and dialysate temperature were set at 36.5ºC. For each session, net ultrafiltration was set on an individual basis according to ideal dry weight. Blood pump speed varied between 320 and 400 ml/min. Dialysis access was via arteriovenous fistula in five patients and via central venous catheter in the remaining three patients. All studies were conducted mid-week after a 48 hour interdialytic period. For this study, IDH was

defined as a fall in systolic BP ≥20mgHg and/or ≤100mg/Hg in association with typical symptoms of hypotension including, nausea, light-headedness or cramping requiring intervention.

2.3.4 Continuous Cutaneous Perfusion Monitoring

The CVI sensor was placed to the right of the patient's forehead midline, approximately 2.5 cm above the level of the nose. The sensor consists of a reusable pulse oximetry sensor and a disposable adhesive CVI SensorCircle™ Calibrated Cap. Once attached, a baseline recording was captured to ensure proper sensor placement and adequate PPG signal prior to initiating HD. Hemodynamic data were continuously captured from 20 minutes prior to the HD treatment until 30 minutes after the end of dialysis. CVI data were recorded, but not reviewed until after the treatment had concluded. All acquired CVI data was analyzed post hoc using LabVIEW software (AB, MM). Intradialytic events were annotated on the monitoring device for each individual patient, including: initiation and completion of echocardiogram, initiation and completion of HD treatment, any symptoms experienced by the patient including dizziness, lightheadedness, cramping, nausea, headache, pain/discomfort, decrease in blood pressure or any interventions delivered by the care provider such as adaptions to UF rate, dialysis chair position changes and/or fluid resuscitation requirements.

2.3.5 Echocardiogram Image Acquisition

Echocardiography was performed and images acquired by a trained investigator (CG) prior to commencing HD and repeated approximately 15 minutes prior to the end of HD (known as peak HD-stress) using commercially available equipment (1.5-3.6MHz M4S probe, Vivid-q, GE Medical Systems, Soningen, Germany). Standard parasternal apical two-chamber and four-chamber views with three cardiac cycles were recorded for each time point and analysis post hoc with a semi-automated computer program (EchoPac, GE Healthcare) using 2D speckle tracking software.

2.3.5.1 Speckle-tracking

2D speckle-tracking echocardiography is used for the quantification of global, regional and segmental LV mechanics using standard two-dimensional grey scale images.[12] 2D speckle-tracking is angle independent and can analyze deformation in the longitudinal, radial and circumferential components.[13,14] Speckle-tracking estimates motion by tracking the speckles in the image[14]. The speckles appear as a result of interference generated when ultrasound waves scatter in tissue, resulting in a pattern of bright and dark pixels. In the myocardium, the tissue structures cause interference and stationary within the tissue and randomly distributed. This produces a speckle pattern that is a stable and a unique 'fingerprint' of the region that moves with the tissue. Previous studies have validated its accuracy against the reference standard of cardiac magnetic resonance.[15,16] Using the two and four chamber views the endocardial border is traced manually, the speckle-tracking software then divides the LV chamber into segments [12 in total (six in the four-chamber view, six in the two-chamber view)] and uses speckle tracking to calculate strain values for each of the segments.

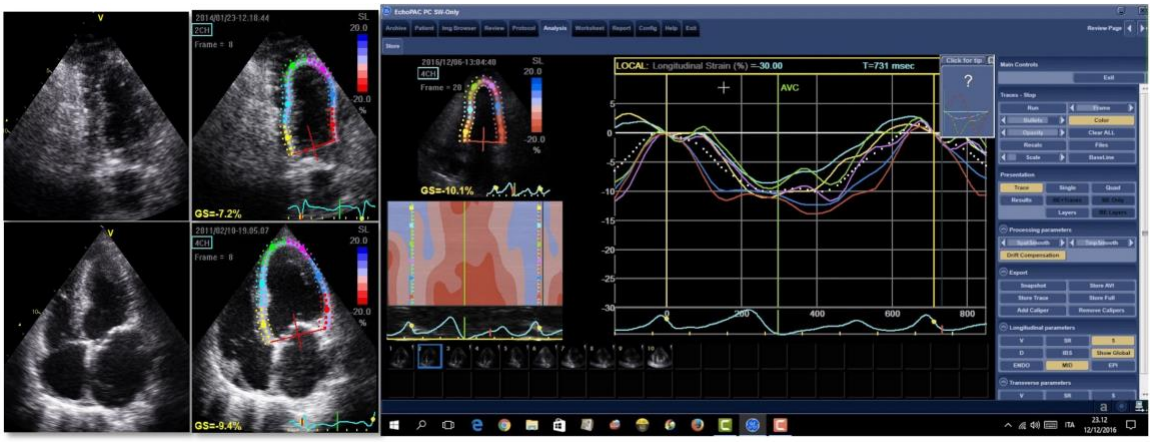

Figure 2-5: Speckle-tracking Analysis - apical 2 chamber, apical 4 chamber

2.3.5.2 Echocardiogram Analysis

Images were anonymized and analyzed in random order by the same investigator (CG). A random sample of these images were then analyzed in random order by a second appropriately trained investigator to determine estimates of inter-observer reliability. Three cardiac cycles were analyzed for each time-point and values derived for segmental (12-left ventricular segments) and global LS recorded. If a myocardial segment underwent a reduction in LS $\geq$ 20%, it was defined as a RWMA. This cut-off was chosen by analogy with previous studies employing a 20% reduction in shortening fraction.[6,7,17] The presence of myocardial stunning was defined as the presence of two or more LV RWMA, in accordance with previously published methods[6,7,17].

2.3.6 Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 23 (IBM, Chicago). Continuous variables are expressed as mean $\pm$ standard deviation. All data were tested for normality using the Shapiro-Wilk test. Comparison of continuous outcomes between two groups was performed using the independent t-test for parametric data and Mann Whitney U test for non-parametric data. Comparisons of related outcomes at two different time points were performed using the paired t-test for parametric data and the Wilcoxon signed-rank test for non-parametric data. Bivariate correlation was assessed using Pearson's correlation coefficient for parametric data and Spearman's coefficient for non-parametric data. An alpha error of less than 5% ($p<0.05$) was statistically significant.

2.4 Results

2.4.1 Baseline Characteristics

The mean age of participants was 59.1 ± 13.3 years. Six patients were on a thrice weekly dialysis regimen, the other two participants typically dialyzed six days per week, however their treatment schedule was adapted for the week of study (all patients had 48 hours between previous HD treatment and study visit). Two participants were female and six were male. Dialysis vintage mean was 72 ± 66.8 months ranging from 10-180 months. HD vintage mean of 60 ± 61.7 months ranging from 5-158 months. The most common causes of end stage renal disease (ESRD) were hypertension (25%) and diabetes (25%). Other causes included lithium toxicity, Thrombotic Thrombocytopenic Purpura (TTP), obstruction and IgA Nephropathy. Comorbidities included hypertension (88%), diabetes (50%), coronary artery disease (38%) and congestive heart failure (25%). Demographics can be seen in the *Table 2-1* below.

Table 2-1: Demographic Information and Medical History

Age (years)	59.1 ± 13.3
Gender (M/F)	6/2
Diabetes (Y/N)	4/4
History of CHF (Y/N)	2/6
History of CAD (Y/N)	3/5
ACE/ARB (Y/N)	4/4
Beta-blocker (Y/N)	5/3
Statin (Y/N)	3/5
HD Vintage (months)	72 ± 66.8
Previous transplant (Y/N)	3/5
Systolic BP (mm/Hg)	151 ± 16.3
Diastolic BP 9 (mm/Hg)	71.1 ± 30.4
Hemoglobin (g/L)	110.6 ± 26.2
Thrombocyte count	175.9 ± 81.6
Urea (mmol/L)	19.8 ± 3.69
Creatinine (mmol/L)	778 ± 95.2
Sodium (mmol/L)	135 ± 4.64
Albumin (g/L)	38.2 ± 2.7

M=male, F=female, ACE/ARB=Angiotensin converting enzyme inhibitors/angiotensin receptor blockers, HD=hemodialysis.

Total UF was 1827.5 ± 823.7 ml, with one patient having no fluid removed due to hypotension preceding treatment, max UF rate range was 0-858 mL/min. All patients were taking either monotherapy or combination antihypertensive/cardiac medication. Intradialytic symptoms, yet not necessarily associated with IDH included cramping (two patients, without IDH), nausea (two patients, with IDH), headache (one patient, without IDH). Details of HD can be seen in *Table 2-2.*

Table 2-2: Hemodialysis and Symptoms Information

Study ID	Total UF removed (ml)	Mean UF rate (ml/hour)	Min RBV (%)	Nadir SBP (mm/Hg)	IDH	Cramping	Headache	Nausea
1	2000	522	91.6	148	no	no	no	no
2	2070	650	88.9	94	yes	no	no	yes
3	1950	600	89	111	no	no	no	no
4	0	181	89.9	100	yes	no	no	yes
5	2500	321	87.8	143	no	yes	no	no
6	2100	627	83.7	126	no	no	yes	no
7	1400	400	91.4	123	no	no	no	no
8	2600	650	86.8	120	no	yes	no	no

2.4.2 Perfusion Monitoring

All but one patient displayed a reduction in PS of up to 20%. This lasted for, 157.9 ± 69.5 minutes (range 40.5-235.3), which corresponded to, 69.8% ± 30.1% (range 16.9-99.6) of the HD session, with onset at <1-43.3 minutes. Six patients had a reduction if PS of ≥40% which lasted for an average of 107.5 ± 86.7 minutes, or 47.8% ± 38.1% of the total HD session, this reduction was observed 11.4 ± 10 minutes into HD. PS improved in one symptomatic patient throughout HD after fluid resuscitation (bolus) and without UF (*it is worth noting that this patient's baseline was atypical as he had taken his prescribed antihypertensive medication prior to the commencement of HD due to dialysis time change*

for this study).

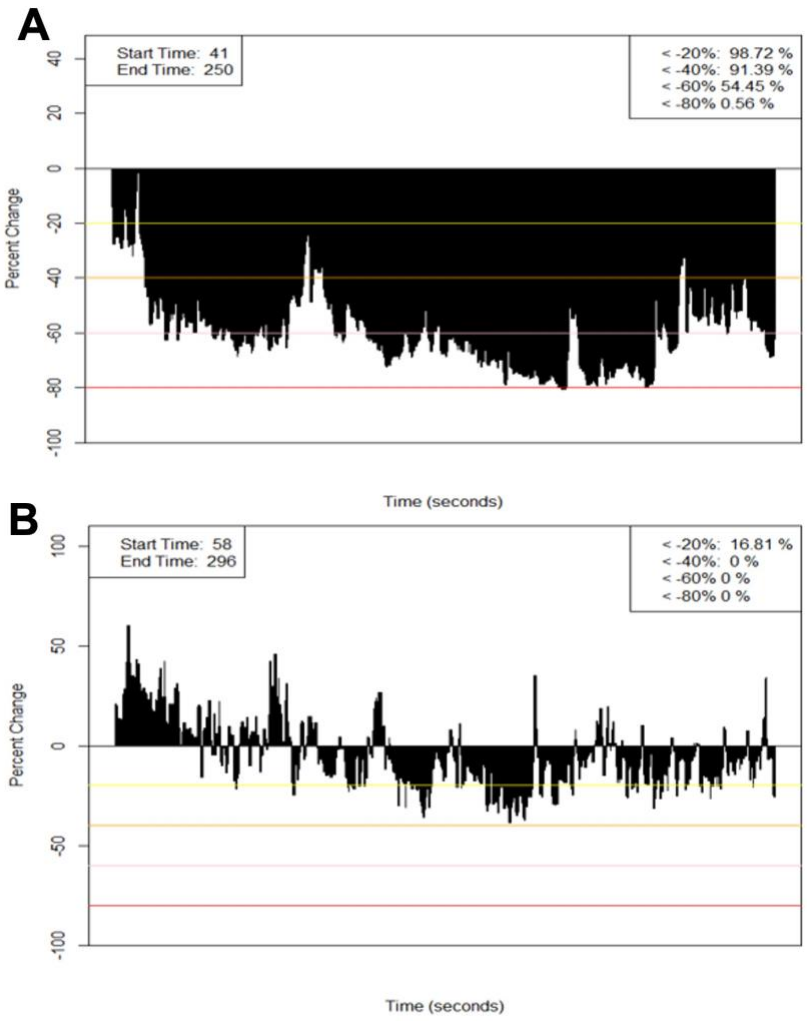

Figure 2-6: Representative Pulse Strength Response. Patient that showed echocardiographic evidence of myocardial stunning with extreme pulse strength reduction (A). Patient that did not show echocardiographic evidence of myocardial stunning had much less extreme pulse strength reduction (B).

2.4.3 Relationship of Pulse Strength to Cardiac Injury

Six out of eight patients exhibited myocardial stunning. the number of segments affected ranged between two and seven (median 5). Routine measures of intradialytic stability included systolic BP monitoring and relative blood volume measurements (mean 88.6% ± 2.58). Two patients had a systolic BP ≤100mmHg with symptoms of IDH requiring intervention, of which myocardial stunning was evident in one. Five patients had a systolic BP reduction of 20mmHg, three of which showed evidence of myocardial stunning. One patient had a further reduction of systolic BP of 40mmHg and developed myocardial stunning *(note that this patient is also captured in the previous two categories)*. There was no consistent relationship between BP reduction and myocardial stunning, nor BP reduction and reductions in PS. All patients that demonstrated a reduction in cutaneous PS ≥40% also exhibited myocardial cardiac stunning (p 0.005), whereas the two patients that did not exhibit myocardial stunning showed no such reduction of PS.

All patients that demonstrated myocardial stunning spent at least half of their HD session with a PS reduction of at least 20%, although no significant relationship was seen (p 0.08, r 0.64).

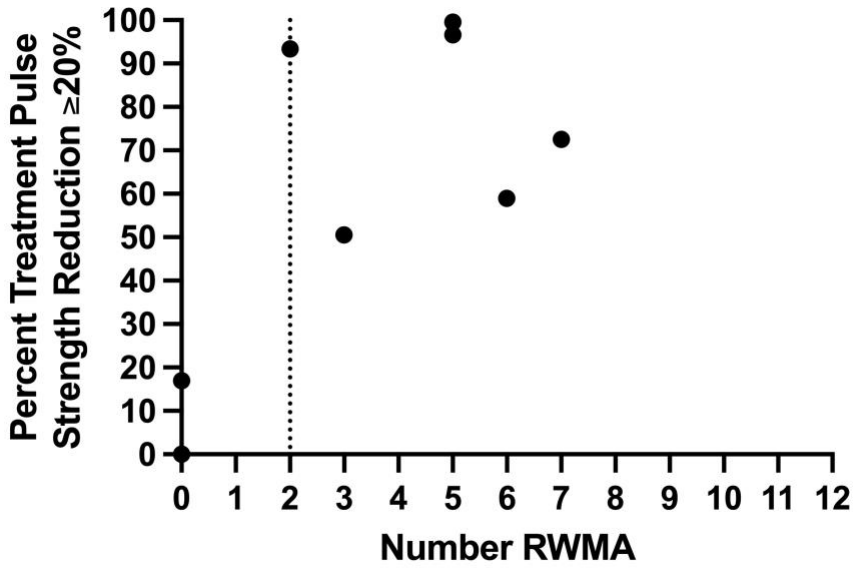

Figure 2-7: Association between time spent with pulse strength reduction ≥20% and number RWMA *(p 0.08, r 0.64).* Vertical dotted line indicates myocardial stunning (2+RWMA).

Based on previous unpublished clinical evaluation of this device (discussed in Section 1.14.2), a significant drop in PS was defined as a PS reduction of ≥40% for at least 20% of the HD treatment. Current study demonstrated that all participants that developed myocardial stunning spent at least 10% of their HD treatment with a PS reduction of ≥40% from baseline (p 0.40, r 0.35).

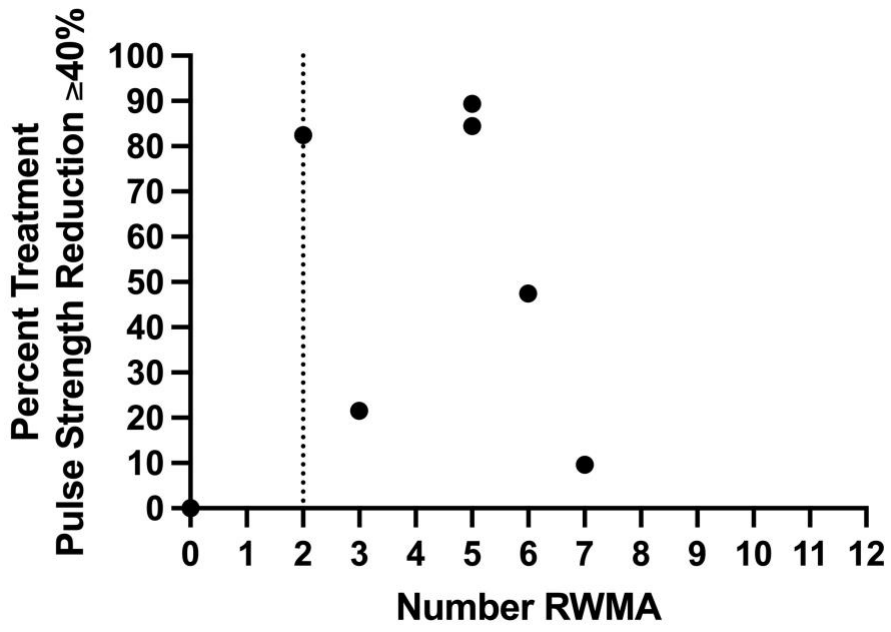

Figure 2-8: Association between time spent with pulse strength reduction ≥40% and number of RWMA *(p 0.40, r 0.35).* Vertical dotted line indicates myocardial stunning (2+RWMA).

A reduction in PS was observed in all subjects who developed signs and symptoms of IDH during their treatment, furthermore PS changes were noted to rapidly reflect the hemodynamic effects from clinical interventions for these episodes [(fluid bolus, patient positioning, changes to ultrafiltration rate *(refer to Figure 2-9)]*.

2.4.4 Relationship to Standard HD Stress Indicators

There was no correlation between reduction in PS and age (p 0.56, r -0.695). There was also no correlation between PS reduction ≥40% and systolic BP <100mmHg (p 0.60, r 0.218), symptoms of IDH (p=0.73, r=-0.149), relative blood volume (p=0.87, r=0.069), total UF volume (p 0.33, r 0.395), nor HD vintage (p 0.50, r 0.281). Details can be found in *Table 2-2.*

Graphical PS response during an episode of symptomatic IDH can be seen in *Figure 2-9,* in which the subject's PS reduced quickly at the beginning of dialysis which were associated with the development of IDH symptoms (nausea, dizziness), systolic BP decreased by 25mmHg (to 100/53) within 15 minutes of treatment initiation. At that time, UF rate was reduced, patient was placed in Trendelenburg position and a 100ml fluid resuscitation was administered increasing cardiac preload. As you can see in *Figure 2-9,* PS responded rapidly to intervention, real-time outputs are a valuable feature of this devise.

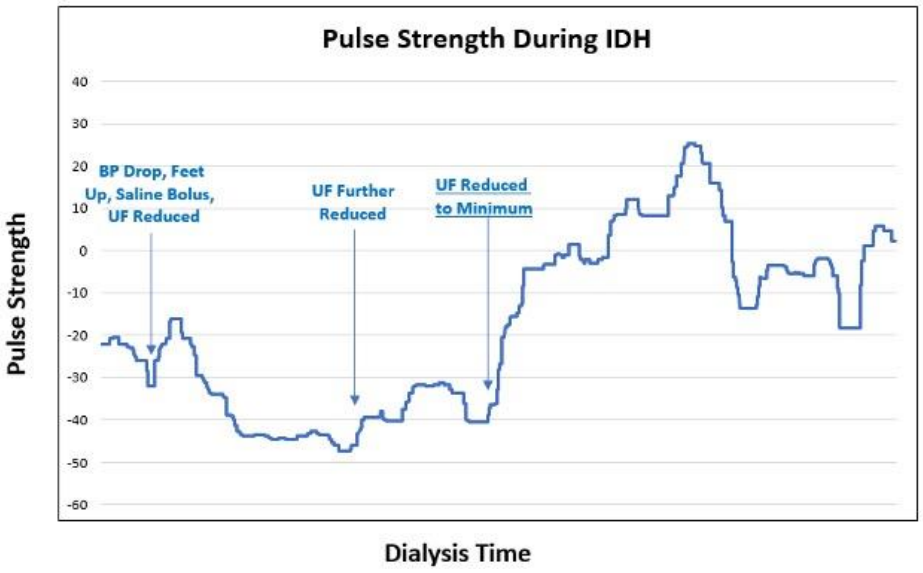

Figure 2-9: Pulse strength response during an episode of intradialytic hypotension with clinical intervention.

2.5 Discussion

This pilot study demonstrated that CVI effectively identified HD patients with HD-associated myocardial stunning, potentially enabling interventions aimed at preventing myocardial injury. This is particularly relevant as there were no relationships demonstrated between myocardial stunning and conventionally utilized indices of intradialytic hemodynamic stability such as BP reduction, symptoms of IDH nor reduction in blood volume.

Myocardial stunning is indicative of compromised myocardial perfusion.[4–6,8,18] The presence of myocardial stunning is associated with increased mortality, as its recurrent injury pattern during chronic HD has a cumulative effect on overall cardiac function.[4–8,18–22] Thus, it is important to intervene to prevent the progression of cardiac dysfunction. Cutaneous perfusion by CVI appears to mirror changes in visceral perfusion (seen in animal models). It has been demonstrated that currently used indicators of dialysis-related circulatory stress are not adequate for predicting myocardial stunning, and often occur at a point that is too late to intervene/prevent injury. Therefore, having a device that sensitively detects the propensity for cardiac injury and does so within a temporal window for dialysis-based intervention is potentially valuable to improve patient outcomes.

Importantly, commonly used methods for the monitoring of intradialytic hemodynamic stability failed to identify those patients with either myocardial stunning or a significant reduction in PS. This is likely because the development of IDH and related symptoms occur late during CV stress, when the patients' compensatory responses are no longer able to maintain cardiovascular stability.

This study supports the necessity for individualized care and the inquiry into individual pathophysiology of HD induced cardiovascular stress. Because PS reduction occurred early into HD treatment, there is a need to acquire more specific information in order to identify possible interventions for the reduction of such significant decline in PS, reducing the cardiovascular effects that conventional treatment regimens can cause. Modifications to the HD process to improve the hemodynamic tolerability have been shown to reduce the

evidence of dialysis-induced cardiac injury lowering the rates of CV morbidity and mortality in the dialysis population. A variety of innovative approaches both dialysis based (dialysate cooling, HD biofeedback, longer and or more frequent treatment times, individual care planning – positioning during treatment, UF modifications) and non-dialysis based (review of antihypertensive medications, intensive glycemic control, dietary sodium management to reduced interdialytic fluid gains) have proven effective in the reduction of myocardial stunning, CV stress, IDH and treatment outcomes. Although trial interventions to reduce the risk/rate of PS decline were beyond the scope of this study, it is reasonable to consider these therapeutic techniques to better understand individual pathophysiological processes warranting further examination with the use of CVI.

2.5.1 Limitations

Firstly, this was a study with a small sample size. Despite this, statistical significance was found in correlations of PS with cardiac stunning and with the number of stunned segments. Secondly, echocardiography was performed at two time points: pre-dialysis and peak HD stress (20-13 minutes before the end of treatment), limiting our ability to determine the exact time point that stunning occurred relative to PS reduction.

2.5.2 Conclusion

In conclusion, this pilot study demonstrated in a small number of patients that PS via percutaneous perfusion monitoring correlated with echocardiographic evidence of myocardial stunning. Therefore, CVI has the potential to identify cardiovascular stress earlier than traditional markers of hemodynamic stability during HD and can provide a window of opportunity for intervention prior to the occurrence of cardiac injury. These initial results are encouraging and the utility of CVI monitoring for the prevention of dialysis-associated CV stress warrants further study.

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Chapter 3

3 Non-invasive Intradialytic Percutaneous Perfusion Monitoring: a view to the heart through the skin

3.1 Co-authorship Statement

The content of this chapter has been accepted for publication by *Frontiers in Nephrology & Hypertension,* 2023, and currently in press. The title of the manuscript is "Non-invasive Intradialytic Percutaneous Perfusion Monitoring: a view to the heart through the skin: by Penny, Hur, Salerno, Wong, Jan, McIntyre.

Penny *(100%)* administered the hemodialysis treatments. Penny *(90%)* collected the data PPG perfusion data. Hur collected and analyzed the CT perfusion data. The PPG perfusion data were analyzed by Penny *(25%)*, Salerno, Wong & Jan. The data were interpreted by Penny *(90%)* & McIntyre. Each author contributed important intellectual content during the drafting and revising of the manuscript and accept accountability for the overall work by ensuring that questions pertaining to the accuracy and integrity of any portion of the work are appropriately investigated and resolved.

Research ethics board approval is provided in Appendix D

3.2 Introduction

To recap, CKD is often diagnosed when approximately 50% of kidney function has been lost and a uremic environment has been well established.[1–5] Patients with CKD are at significant risk for CV morbidity/mortality – a risk 15-times greater than the general population.[4,6] Mortality rates are driven by pathophysiological processes shared by both the small and large vasculature.[7,8] A state of uremia, and associated co-morbid conditions (hypertension, diabetes) trigger a cascade of microcirculatory conditions deteriorating the vascular circulation.[1,9,10] The continuous activation of the vascular endothelium creates an environment of chronic inflammation, thrombosis and compromised vascular response,[4] with biomarkers shown to progressively increase as kidney function declines.[11] Consequently, structural and functional changes occur within the circulatory system resulting in permanent damage and loss of compensatory mechanisms, leaving patients vulnerable to hemodynamic instability.[4,12] At the microcirculatory level, poor tissue oxygenation and nutrient exchange occur within the tissues as capillary density and viability is lost - a precursor to the development of multiorgan vascular damage (skeletal muscle, kidney, heart, brain, gut).[1,9]

The introduction of HD adds additional insult to this pre-existing state adding to extremes in morbidity/mortality.[13–16] HD patients are exposed to repetitive insults of demand myocardial ischemic-reperfusion injury as a result of HD and UF causing hypoperfusion.[17] Recurrent episodes of ischemia precipitated by intermittent HD have negative consequences, leading to progressive myocardial damage and the development of non-viable myocardium and irreversible damage within months of starting HD. Many studies have described the phenomenon of HD-induced myocardial stunning – a common consequence of intermittent HD, directly associated with myocardial contractile dysfunction and patient survival.[16–24] HD has been shown to be associated with reductions in global and segmental myocardial blood flow and the development of LV-RWMA.[19,23–27] The identification of myocardial stunning provides value for research purposes however due to serial echocardiography/post-hoc analysis, clinical application is not viable. However, the results seen in Chapter 2 of this thesis describes the utility of a non-invasive percutaneous perfusion monitoring system which continually assesses an individual's

unique CV status and response to HD using peripheral PPG *(Pictured in Figure 2-1)*. HD treatments are currently driven by parameters specific to macro-vasculature monitoring techniques where subtleties of hemodynamic change either go without notice or are extremely latent responses.

The aim of our study was to further evaluate the utility of PPG as a predictor of HD-induced circulatory stress and the development of RWMA. Furthermore, it was our intent to compare microcirculatory changes in skin perfusion (an accessible vascular bed) to direct measures of global myocardial perfusion changes during HD using intravenous contrast and CT imaging.

3.3 Methods

This study was conducted according to GCP/ICH guidelines and the principles of the Declaration of Helsinki, with appropriate ethics committee approval. All patients gave their written, informed consent before participating in the study.

3.3.1 Study Population

Twelve participants from the prevalent chronic HD population – London Health Sciences Centre Renal Program, London, Ontario, Canada were evaluated. Patients were included if they were >18 years of age, receiving chronic thrice weekly HD therapy for >3 months and had minimal to no urine output (<250ml/24hours – for CT purposes).

3.3.2 Study Design

This single-centred exploratory study aimed to compare changes in PPG – PS to the number of LV-RWMA observed by echocardiography during HD and to changes in global myocardial perfusion observed by CT perfusion imaging.

3.3.3 Dialysis Treatments

Dialysis treatments were delivered in a single centre (St. Joseph's Hospital, London, Ontario, Canada) by a single operator (JP). HD was administered using the Fresenius 5008 system, with high-flux polysulfone dialyzer and according to the participants routine HD prescription. Treatments were delivered mid-week (Wednesday/Thursday) during the short interdialytic period. Majority of treatments were four hours in length (10/12), however two patients received slightly shorter treatments. Dialysate parameters were programmed according to patient's individual prescriptions; dialysate sodium range 137-140mmol/L, dialysate potassium was either 1.5 or 3mmol/L, all patients had a dialysate calcium of 1.25mmol/L and bicarbonate ranged from 35-40mmol/L. Anticoagulation was achieved using low-molecular weight heparin (Dalteparin) with doses between 2,500–5,000 units. Dialysate flow was 500mL/min and temperature was set at 36.5ºC for all treatments. For each session, net ultrafiltration was set on an individual basis according to the patients' achievable ideal dry weight. Blood pump speed varied between 330 and 400ml/minute. Four participants dialyzed via arteriovenous fistula, one via arteriovenous loop graft and the remaining seven participants via central venous catheter. Interdialytic weight gain ranged from 1.1-2.8kg, see *Table 3-1* for details. Dialysis monitoring parameters were obtained in accordance with program policy with intradialytic measures documented every 30 minutes and more often as required. IDH was defined as a reduction in systolic BP ≥20mmHg and/or ≤100mm/Hg in association with typical symptoms of hypotension such as, nausea, light-headedness or cramping requiring intervention by care provider.

3.3.4 Continuous Cutaneous Perfusion Monitoring

The forehead area of interest was cleansed using 70% isopropyl alcohol. The optical oximetry sensor was placed on the patient's forehead midline, approximately 2.5 cm above the level of the nose. Once securely attached, the patient was asked to sit comfortably in their typical dialysis position (e.g. feet elevated, chair reclined) for approximately five minutes to establish a resting state at which point a baseline PPG measurement was captured. Baseline measures are taken to: a) ensuring proper sensor placement and adequate PPG signal, and b) as the basis for individualized hemodynamic comparison of variations throughout HD. Continuous hemodynamic data were then captured throughout

the entire HD treatment. Any HD events/interventions were annotated on the monitoring device for each participant including: initiation and completion of HD, timing of echocardiogram and CT, symptoms experienced by participant (dizziness, lightheadedness, cramping, nausea, headache, pain/discomfort, decrease in blood pressure or any interventions delivered by the care provider such as ultrafiltration changes, position change or fluid resuscitation requirements). Monitoring system can be seen in Chapter 2 *Figure 2-1*. CVI-derived variables were extracted from the CVI-generated output files on a case-by-case basis using a customized semi-automated pipeline designed using R Studio (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: http://www.R-project.org/ and RStudio Team (2022). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/) using the *tidyverse* package[29]. All acquired data were analyzer post hoc (FS, MHJ, DW, JP).

3.3.5 CT Perfusion

Dynamic CT images of the heart were acquired at baseline and peak HD treatment timepoints. Participants were aligned on a CT bed in supine position and scans were performed between 75%-75% R-R interval, prospectively ECG-gated while the participants were free breathing. For the quantification of myocardial blood flow, iodinated contrast agent (Isovue 370) was delivered intravenously during the image acquisition and the delivery of contrast was traced with 32 scans every 1-2 heartbeats. The scanner setting for all dynamic CT images are as listed: display field of view = 45.0 cm, tube voltage = 100 – 120 kV; tube current = 100 mA; detector coverage = 160 mm; gantry period = 0.28 s; slice thickness = 2.5 mm. Following the end of the imaging visit, the dynamic images were post processed by (L.H.) utilizing the proprietary ASiR algorithm (Resolution CT console, GE Healthcare) to alter the slice thickness to 2.5mm with the intent to increase signal to noise ration. The reconstructed images were corrected for residual cardiac and respiratory motion using a 3D non-rigid registration algorithm on a proprietary workstation (GE proprietary software, advantage workstation, GE Healthcare). Myocardial blood flow maps of the dynamic images were generated with the application of the Johnson-Wilson-Lee model of tracer kinetics for each HD timepoint. Severn slices of the left ventricle

myocardium were selected and delineated for absolute measures of global myocardial blood flow. For each timepoint, the seven slices were averaged, and the mean global myocardial blood flow measures were recorded for analysis. All CT details and analysis were completed by co-author (LH).

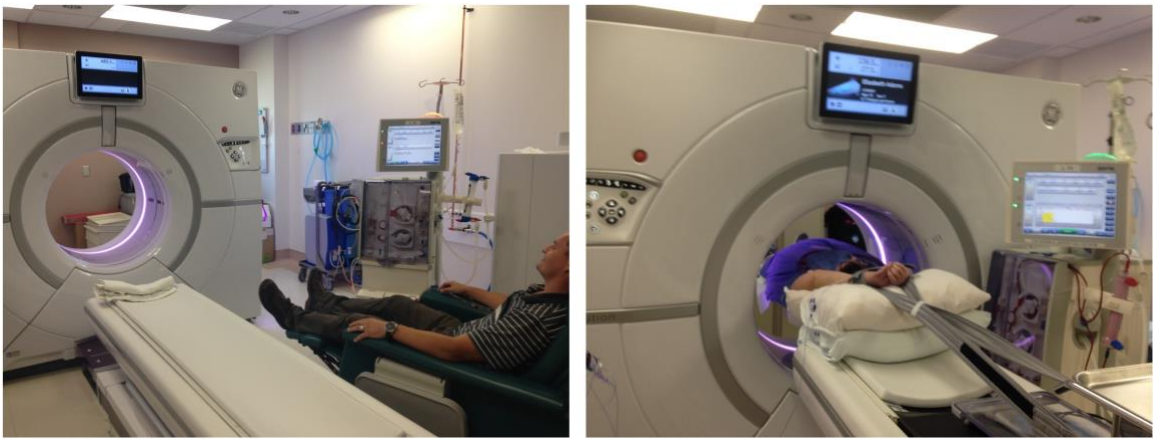

Figure 3-1: Picture of HD taking place during CT

3.3.6 Echocardiography

Echocardiography was performed by a trained investigator (LH) prior to commencing HD and again at peak-HD stress (approximately 15 minutes prior to the end of HD) using commercially available equipment (1.5-3.6MHz M4S probe, Vivid-q, GE Medical Systems, Soningen, Germany). Standard apical two and four chamber views of the LV were recorded for off-line analysis with a semi-automated software (EchoPac, GE Healthcare) using 2D speckle tracking software. Images were anonymized and analyzed in a random order by a trained investigator (JP) and a random sample of these images were analyzed in random order by a second appropriately trained investigator (LH) to determine estimates of inter-observer reliability. Three cardiac cycles were analyzed for each time point and values derived for segmental strain (12-left ventricular segments). Myocardial segments with a ≥20% reduction in longitudinal strain (between pre and peak-HD stress) were determined to have developed a HD-induced RWMA. Two or more RWMA has been

defined as myocardial stunning in accordance with previously published methods.[19,24] Poor quality images were removed from analysis and any segment not visible or in which the software was not able to track appropriately were not counted as RWMA.

3.3.7 Statistical Analysis

Statistical analysis was performed using JASP [Netherlands (version 0.14.1)]. Descriptive statistics are expressed as mean ± standard deviation, median or percent. All data were tested for normality using the Shapiro-Wilk test. Comparisons of related outcomes at two different time points were performed using the paired t-test for parametric data and the Wilcoxon signed-rank test for non-parametric data. Bivariate correlation was assessed using Pearson's correlation coefficient for parametric data and Spearman's coefficient for non-parametric data. An alpha error of less than 5% ($p<0.05$) was statistically significant. Graphs were created using Prism GraphPad (version 9.4.0).

3.4 Results

3.4.1 Baseline Characteristics

All participants received conventional thrice weekly chronic HD. All participants were anuric. Mean age of this population was 67.2 ± 13.4 years, mean dialysis vintage was 54.8 ± 40.7 months, nine participants were male. Causes of renal failure included hypertension (58%) and diabetes (33%). Other causes included IgA Nephropathy, hepatorenal syndrome, toxicity. Other comorbidities included coronary artery disease (50%) and congestive heart failure (25%). All patients were taking either monotherapy or combination antihypertensive/cardiac medication. Mean systolic BP prior to the initiation of HD was 143.3mmHg ± 22.3, diastolic BP 64mmHg ± 13.7 and intradialytic nadir systolic BP 101.3mmHg ± 15.9. Average interdialytic weight gain was 1.8kg ± 0.66, mean UF rate 735.6ml/hour ± 174.8 and mean UF ml/kg/hour was 8.5 ± 2.9. One participant had intradialytic symptoms due to vasal vagal response to choking/coughing (pre-existing issue) – this was not related to intradialytic hypotension, however a 200ml bolus of fluid was delivered due to brief unresponsiveness. Seven treatments required reductions to UF rate related to non-symptomatic reductions in BP. There were no treatments that met our

definition of IDH. The average intradialytic reduction in systolic BP was 41.7mmHg ± 14.5 in the absence of symptoms. Mean relative blood volume reduction was 41.7% ± 14.5. Demographic details can be found in the following *Table 3-1*.

Table 3-1: Patient Demographics and Dialysis Treatment Details

	Mean ± SD
Age (years)	67.2 ± 13.4
Hemodialysis Vintage (months)	54.8 ± 40.7
3-6 RWMA	48 ± 39
7-12 RWMA	77.6 ± 17.7
Gender (M/F)	9/3
Diabetes (Y/N)	6/6
History CHF (Y/N)	3/9
History CAD (Y/N)	6/3
ACE/ARB (Y/N)	4/8
Beta blocker (Y/N)	7/5
Statin (Y/N)	9/3
Hemoglobin (g/L)	98.8 ± 9.9
Urea (mmol/L)	18.3 ± 5.9
Creatinine (mmol/L)	765.7 ± 209.9
Sodium (mmol/L)	134.2 ± 2.8
Potassium (mmol/L)	4.4 ± 0.7
Albumin (g/L)	37.8 ± 2.5
Treatment time (minutes)	232.5 ± 16.4
Pre-HD Systolic BP (mmHg)	143.3 ± 22.3
Pre-HD Diastolic BP (mmHg)	64 ± 13.7
Nadir Systolic BP (mmHg)	101.3 ± 15.9
IDWG (kg)	1.8 ± 0.66
UF Rate (ml/hr)	735.6 ± 174.8
UF (ml/kg/hr)	8.5 ± 2.9
Minimum RBV (%)	84.7 ± 4.6
Intradialytic symptoms (Y/N)	1/11
Intradialytic interventions (Y/N)	8/4
IDH (Y/N)	0/0
Intradialytic Systolic BP reduction (mmHg)	41.7 ± 14.5
Age (years)	67.2 ± 13.4
Hemodialysis Vintage (months)	54.8 ± 40.7
3-6 RWMA	48 ± 39
7-12 RWMA	77.6 ± 17.7
Gender (M/F)	9/3
Diabetes (Y/N)	6/6
History CHF (Y/N)	3/9
History CAD (Y/N)	6/3
ACE/ARB (Y/N)	4/8
Beta blocker (Y/N)	7/5
Statin (Y/N)	9/3
Hemoglobin (g/L)	98.8 ± 9.9
Urea (mmol/L)	18.3 ± 5.9
Creatinine (mmol/L)	765.7 ± 209.9
Sodium (mmol/L)	134.2 ± 2.8
Potassium (mmol/L)	4.4 ± 0.7
Albumin (g/L)	37.8 ± 2.5
Treatment time (minutes)	232.5 ± 16.4
Pre-HD Systolic BP (mmHg)	143.3 ± 22.3
Pre-HD Diastolic BP (mmHg)	64 ± 13.7
Nadir Systolic BP (mmHg)	101.3 ± 15.9
IDWG (kg)	1.8 ± 0.66
UF Rate (ml/hr)	735.6 ± 174.8
UF (ml/kg/hr)	8.5 ± 2.9
Minimum RBV (%)	84.7 ± 4.6
Intradialytic symptoms (Y/N)	1/11
Intradialytic interventions (Y/N)	8/4
IDH (Y/N)	0/0
Intradialytic Systolic BP reduction (mmHg)	41.7 ± 14.5

SD=standard deviation, RWMA=regional wall motion abnormalities, M=male, F=female, Y=yes, N=no

The PPG waveform produced an embedded raw PS measurement at baseline. From this baseline measurement, the mean intradialytic PS change was -10.9% ± 33.8, while the lowest PS reduction from baseline was found to be -57.5% ± 22.2. On average, it took 119.7 minutes ± 53.5 for the population to reach their lowest PS threshold. Participants spent on average 61.6 ± 34.4% of HD treatment with PS reduction of 10% from baseline, which represents the entire population. Ten participants had a further reduction in PS of 20% from baseline spending 53.5% ± 32 of HD treatment at that threshold. The same participants displayed a further reduction in PS of 30% and 40% for 40.6% ± 29.6 and 28.3% ± 24.6 of HD respectively. A further PS reduction of 50% was seen in nine participants who spent 15.2% ± 18.2 of HD at this threshold.

3.4.2 HD-Induced Myocardial Ischemic Injury and Relationship to Percutaneous Perfusion

All 12 participants exhibited treatment induced myocardial ischemic injury, defined as myocardial stunning. The number of left ventricular segments that underwent a ≥20% reduction in LS ranged between three and 12, mean 6.1 ± 2.9. Details can be found in *Table 3-2*.

Table 3-2: Descriptive Statistics for Measures of Hemodialysis-induced Circulatory Stress

	Mean ± SD	Median	Range
Change in PS (%)	-10.9 ± 33.8	-24.7	-46.5-62.9
Number of RWMA	6 ± 2.9	6.5	3-12
Lowest PS Reduction (%) 3-6 RWMA 7-12 RWMA	-57.5 ± 22.2 -47 ± 25.9 -67.9 ± 12.5	-52.7 -60.5 -70.2	-10- -83 -10.5- -70 -46.4- -83
Time to Lowest PS (minutes)	119.7 ± 53.7	130.2	5.5-200.6
Time spent PS Below -10 (%) 3-6 RWMA (%) 7-12 RWMA (%)	61.6 ± 34.4 48.4 ± 38.5 78.8 ± 26.6	73.5 62.8 85.7	0.1-98.4 0.1-87.1 37.2-98.4
Time spent PS Below -20 (%) 3-6 RWMA (%) 7-12 RWMA (%)	53.5 ± 32 40 ± 32.8 65.1 ±28.8	60.1 48.9 75.7	0-91.3 0-76 29.6-91.3
Time spent PS Below -30 (%) 3-6 RWMA (%) 7-12 RWMA (%)	40.6 ± 29.6 30 ± 26.3 51.3 ±31.2	42.9 32.2 59	0–81.7 0-64.5 6.5-81.7
Time spent PS Below -40 (%) 3-6 RWMA (%) 7-12 RWMA (%)	28.3 ± 24.6 19.1 ± 19.1 37.5 ± 27.7	23.1 16.1 37.8	0– 3.5 0-48.2 0.5-75.5
Time spent PS Below -50 (%) 3-6 RWMA (%) 7-12 RWMA (%)	12.2 ± 18.2 6.5 ± 7.5 23.9 ± 22.2	73.9 3.6 22.1	0-57.2 0-17.5 0-57.2
Change in GP (%) 3-6 RWMA (%) 7-12 RWMA (%)	-17.1 ± 16.9 -12 ± 15.2 -21.5 ± 17.7	-15.1 -14 -16	-52.4– .2 -23.5-3.6 -6.8- -52.4
GP Pre-HD (ml/min/100g)	93.9 ± 28.5	83.8	59.8- 41.2
GP Peak HD-stress (ml/min/100g)	74.2 ± 13.3	70.9	57.8-1 01.8

PS=pulse strength, RWMA=regional wall motion abnormalities, GP=global perfusion, HD=hemodialysis

We found an association between the lowest PS reduction in percutaneous perfusion during HD and the development of RWMA (p 0.03, r -0.63), pictured in *Figure 3-1*.

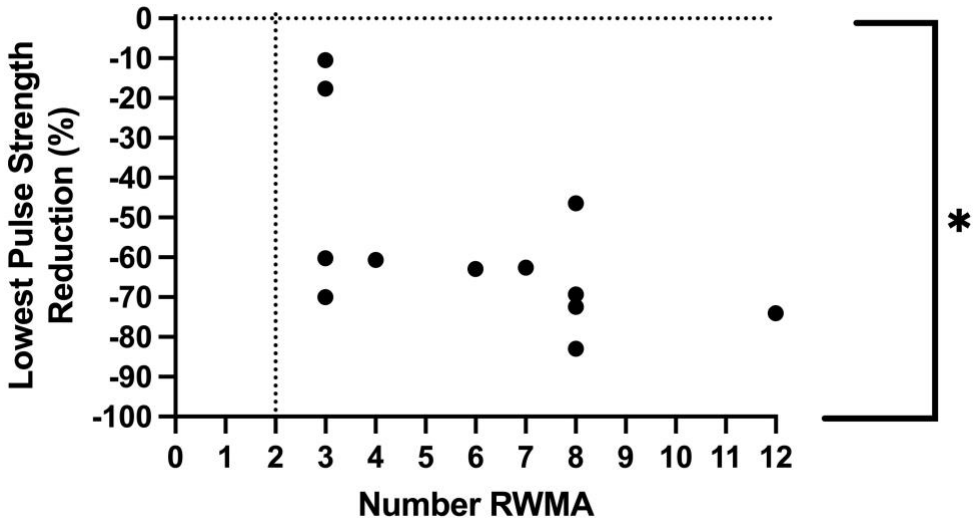

Figure 3-2: Lowest pulse strength reduction during hemodialysis was associated with the number of RWMA developed. **Denotes p 0.03, r -0.63.*

In addition, patterns trended toward an association between the duration of time spent at reduced PS thresholds and the number of RWMA developed. Statistical significance was reached once there was a 50% reduction in PS from baseline [(p 0.048, r 0.58), see details in *Tables 3-2, 3-3*].

Table 3-3: Table of Relationships/Correlations

			P value	Correlation
A	Percent change GP	Lowest PS reduction	0.048*	0.58
	Percent change GP	Pre HD Systolic BP	0.144	0.45
	Percent change GP	Systolic BP reduction	0.451	0.24
	Percent change GP	Nadir BP	0.151	0.44
	Percent change GP	Minimum RBV	0.049*	0.58
	% treatment PS -20%	Number RWMA	0.055	0.59
	% treatment PS -30%	Number RWMA	0.058	0.56
	% treatment PS -40%	Number RWMA	0.052	0.57
	% treatment PS -50%	Number RWMA	0.048*	0.58
	UF ml/kg/hr	Percent change GP	0.001***	-0.83
	UF ml/kg/hr	Number RWMA	0.026*	0.64
	UF ml/kg/hr	Time spent PS -10%	0.032*	0.63
	UF ml/kg/hr	Time spent PS -20%	0.033*	0.61
	UF ml/kg/hr	Time spent PS -30%	0.066	0.55
	UF ml/kg/hr	Time spent PS -40%	0.144	0.45
	UF ml/kg/hr	Lowest PS reduction	0.003**	-0.78
	Mean UFR	Percent change GP	0.028*	-0.64
	Lowest PS reduction	Number RWMA	0.030	-0.63
	Lowest PS reduction	Pre HD Systolic BP	0.560	0.19
	Lowest PS reduction	Nadir BP	0.974	0.01
	Lowest PS reduction	Systolic BP reduction	0.564	0.19
	Lowest PS reduction	Minimum RBV	0.534	0.20
B	GP Pre-HD	GP Peak HD-stress	0.002**	

GP=global perfusion, RWMA=regional wall motion abnormalities, UF=ultrafiltration, PS=pulse strength, HD=hemodialysis

When participants were stratified by severity of myocardial stunning using the mean number of developed RWMA, it was found that patients that developed more RWMAs had a substantially lower (but not statistically significant) PS reduction (3-6 RWMA PS-47.4 ± 25.9, 7-12 RWMA PS-67.9 ± 12.5, p 0.09) and also spent more time at each PS threshold (*Table 3-2, Figure 3-2*).

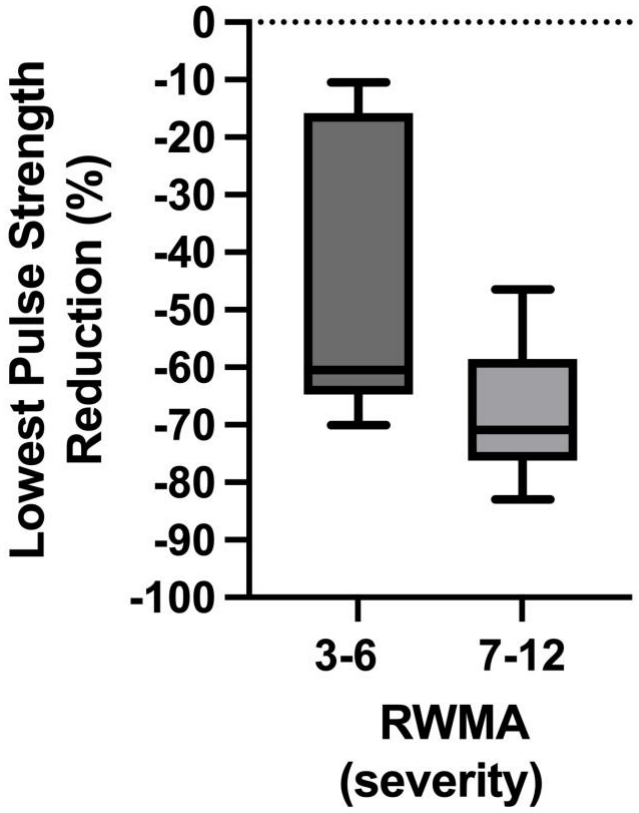

Figure 3-3: Number of RWMA stratified into severity. Those with mores severe myocardial stunning (7-12 segments) had a lower pulse strength reduction *(p 0.09)*. Boxes represent median and spread of data, error bars represent maximum/minimum values.

Additionally, there was a greater reduction in global myocardial perfusion in those with more severe HD-induced myocardial stunning. Furthermore, increasing numbers of RWMA was associated with longer HD vintage [7-12 RWMA = 77.6 ± 17.7 months, whereas 3-6 RWMA = 48 ± 39 months (*Table 3-1*)].

3.4.3 Direct Measures of Cardiac Perfusion and Relationship to Percutaneous Perfusion

Mean global perfusion before HD was 93.9ml/min/100g ± 28.5 while the mean global perfusion at peak HD-stress was reduced to 74.2ml/min/100g ± 13.3 [(p 0.002), *Figure 3-3, Tables 3-2, 3-3]*.

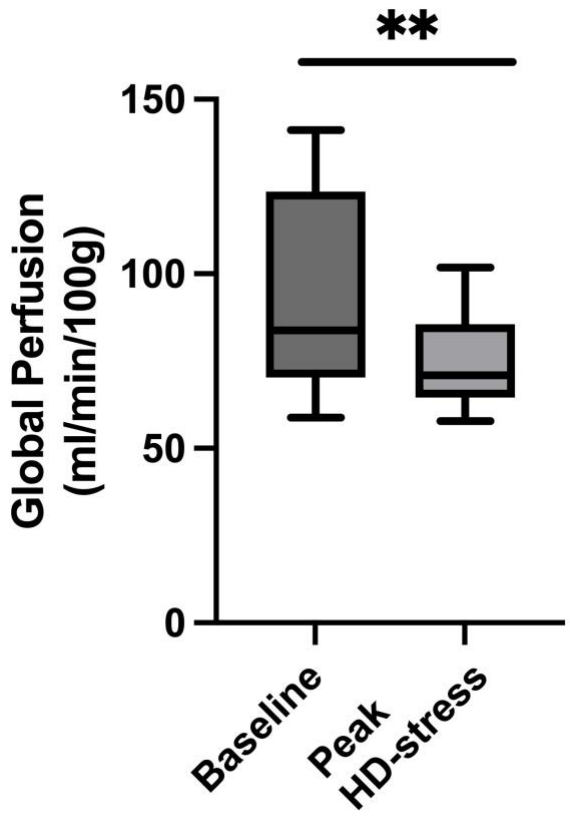

Figure 3-4: Changes in global perfusion during hemodialysis. ***Denotes p 0.002.* Boxes represent median and spread of data, error bars represent maximum/minimum values.

The average change in global perfusing between the two timepoints was a reduction of 17.1% ± 16.9 (*Table 3-2*). Ten participants followed this trend, with a reduction in global cardiac perfusion at peak HD-stress, however two participants exhibited a very slight increase in global perfusion between the two timepoints (3.6ml/min/100g, 4.2ml/min/100g), this was associated, in one participant with an extremely low UF rate. Direct changes in intradialytic global perfusion were associated with lowest PS reduction [p 0.048, r 0.58 (*Table 3-3*, *Figure 3-4*)].

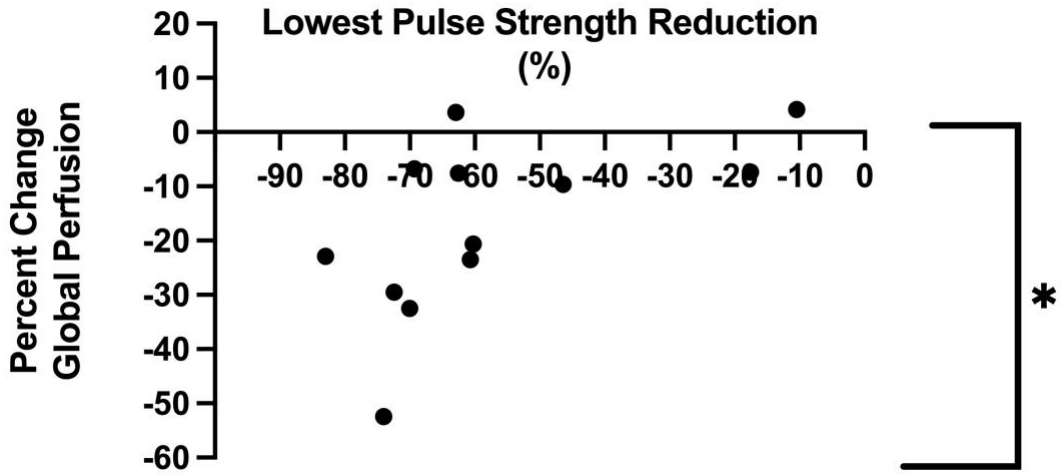

Figure 3-5: Association between changes in global perfusion and lowest pulse strength reduction. **Denotes p 0.048, r 0.58.*

Although not statistically significant, participants that developed more RWMA (severity of myocardial stunning) during HD trended toward a greater reduction in global perfusion in the myocardium [3-6 RWMA global perfusion -12 ± 15.2, 7-12 RWMA global perfusion -21.5 ± 17.7, p 0.48 (*Table 3-2, Figure 3-5*).

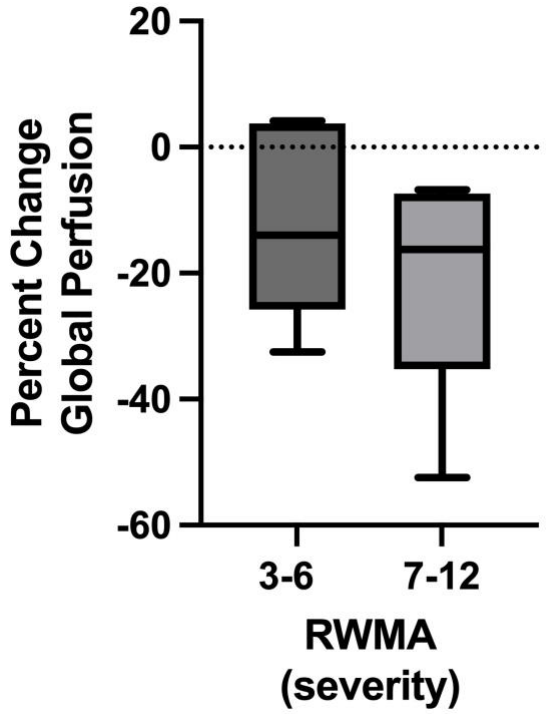

Figure 3-6: Number of RWMA stratified into severity by median. Those with more severe myocardial stunning (7-12 segments) had a more severe reduction in global perfusion *(p 0.48)*. Boxes represent median and spread of data, error bars represent maximum/minimum.

3.4.4 Relationship to Ultrafiltration

UF rates were set using the patients achievable prescribed ideal body weight. Mean UF rate was 735.6 ± 174.8 ml/hour equating to 8.5 ± 2.9 ml/kg of body weight per hour (ml/kg/hour), which was used for the following correlations seen in Table 3-3. Rate of fluid removal was associated with percutaneous perfusion measures of lowest PS reduction [p 0.003, r -0.78 (*Figure 3-6*)], time spent at 10% reduction threshold (p 0.032, r 0.63) and time spent at 20% reduction threshold [(p 0.033, r 0.63), *Table 3-3*].

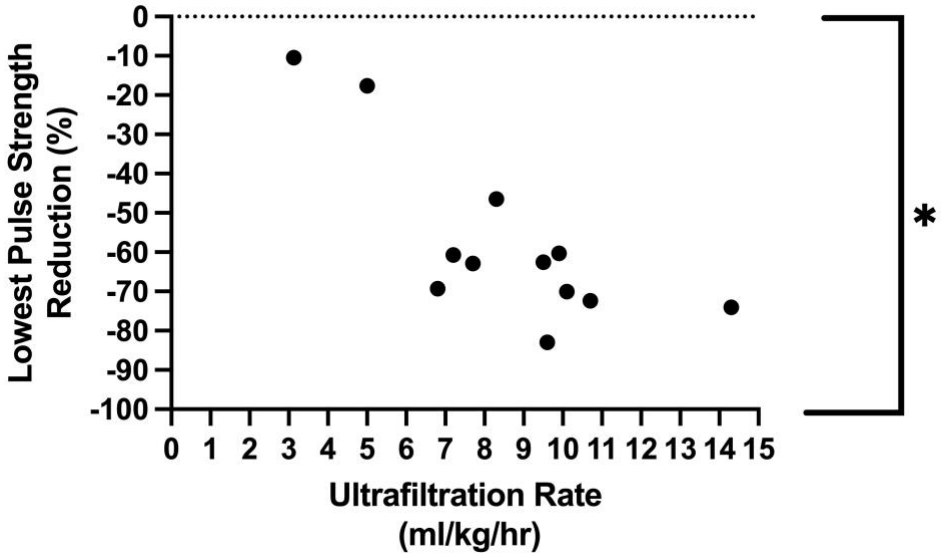

Figure 3-7: Rate of ultrafiltration was associated with lowest pulse strength reduction. **Denotes p 0.003, r -0.78.*

UF rate was also associated with the development of HD-induced RWMA [p 0.026, r 0.64 (*Figure 3-7*)], as well as direct changes in myocardial perfusion [p 0.001, r -0.83 (*Figure 3-8*)].

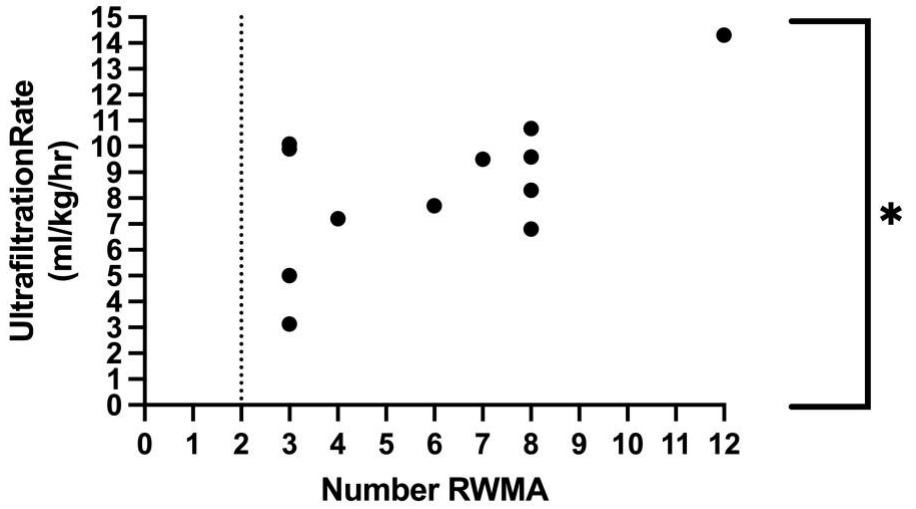

Figure 3-8: Rate of ultrafiltration was associated with the number of RWMA. **Denotes p 0.026, r 0.64*

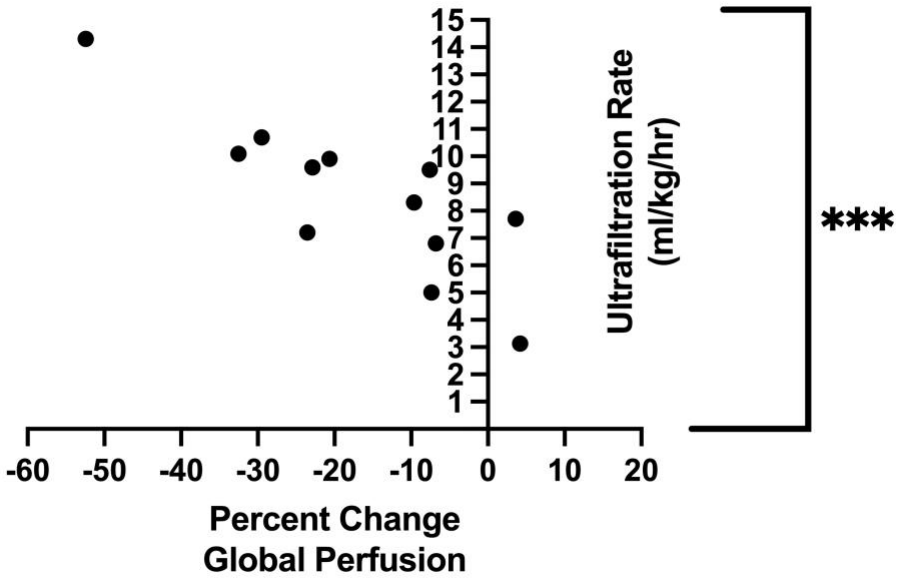

Figure 3-9: Rate of ultrafiltration was associated with changes in global perfusion. ***Denotes p 0.001, r -0.83*

3.4.5 Standard HD Parameters

There were no relationships found between population demographics and lowest PS reduction nor between demographics and changes in global perfusion - including age (p 0.174, p 0.313 respectively) and HD vintage (p 1.0, p 0.543 respectively). There were also no associations between traditional macrovascular measures of intradialytic HD associated stability and reductions in PS – including pre-HD systolic BP (p 0.560), intradialytic systolic BP reduction (p 0.564), nadir BP (p 0.974) or minimum RBV (p 0.534). Additionally, we found no relationship between pre-HD systolic BP, intradialytic systolic BP reduction, nadir BP and changes in global perfusion (p 0.144, p 0.451, p 0.151 respectively), there was however a slight association between changes in global perfusion and relative blood volume [RBV (p 0.049, r 0.58)]. Details can be found in *Table 3-3.*

3.5 Discussion

This study further confirms that percutaneous perfusion monitoring (using PPG) is a useful method of assessing intradialytic hemodynamic stability and HD-induced circulatory stress. Additionally, the information generated at the microcirculatory level of the skin is reflective of direct measures of myocardial perfusion and the development of HD-induced myocardial stunning.

Current results confirm previous findings (using the same technology) identifying the variable PS, as a key PPG parameter signaling the development of HD-induced circulatory stress and myocardial stunning at the microcirculatory level.[28] The PS parameter represents the delivered pulsatile blood volume to the capillaries of the skin with each heartbeat and is reflective of stroke volume and microcirculatory tissue perfusion. In the critical care setting, accessible vascular beds (sublingual mucosa) were used as surrogates for vital organ perfusion (gut),[30–32] indicating that microcirculatory resuscitation was directly associated with clinical outcomes - whereby survivors had a restoration of microcirculatory perfusion, and non-survivors did not (independent to large vessel indices).[31,33–37] During HD, extracorporeal redistribution, UF and reduced circulatory volume reflect a negative PPG waveform whereby PS reduction from baseline (before the initiation of HD) progress over the course of HD as volume is removed (alternatively, a positive waveform is reflective of overhydration/vascular refill – all of which are displayed in real-time).

In this study, all participants had a PS reduction of at least -10% from baseline. The majority (83%)

of the population spent half of treatment with a PS -20% which progressed on to a further reduction of -40% (consistent with previous findings seen in Chapter 2). Various studies have described the impact of changing circulating volume (due to HD/UF) on reductions in myocardial blood flow and the development of ischemic injury during HD[23–26,38] - broadly described as occurring at the end of HD – a time of heightened circulatory stress and volume depletion.[23–26] However, current findings indicate that at the microcirculatory level the lowest PS reduction was reached after only two hours of HD when approximately 50% of target volume removal was achieved. This early signal may be a warning of pending circulatory stress and supports literature describing microcirculatory response precedes that of the microvasculature.[7,8] This mid-treatment threshold may be a key timepoint worth further consideration/evaluation in the future. Additionally, although statistical significance was not reached due to our small sample size, participants with more severe myocardial stunning (7-12 RWMA developed) had a lower PS reduction than those with fewer RWMA. They also spent more time at each PS threshold, had a lower reduction in global myocardial perfusion and were on dialysis longer (HD vintage). Since there were no associations (in this study or the precious pilot study) between the development of HD-induced circulatory stress and routinely measured intradialytic monitoring parameters nor symptoms of hemodynamic instability, our study suggests a benefit of incorporating microcirculatory monitoring into routine HD care. This alternative perspective may provide valuable insight into a patient's individual response to treatment.

3.5.1 Limitations

Intradialytic imaging is extremely difficult to incorporate into research and although our study cohort was small, the results (indirect vs. direct perfusion) are impactful. PPG technology does have some limitations. Since the skin is thermally regulated, it is unknown if ambient room temperature or comfort measures (warm blankets) had any impact on the PPG waveforms. Changes in patient positioning play a role in PPG outputs – reclined position (increasing pre-load) and standing position (reducing pre-load).

3.5.2 Conclusion

In conclusion, our study shows that the skin (an accessible microcirculatory vascular bed) is a surrogate for direct measures of organ perfusion. PPG technology is a well-accepted option for enhanced intradialytic monitoring at the microcirculatory level providing a window of opportunity to preemptively adapt therapy and individualizing treatment. This proactive approach may result in safer HD delivery with improved clinical outcomes - where current methods fail.

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Chapter 4

4 Intradialytic Exercise Preconditioning: an observational study on the effect on myocardial stunning

4.1 Co-authorship Statement

The contents of this chapter were adapted from an original research manuscript entitled "Intradialytic Exercise Preconditioning: an observational study on the effects on myocardial stunning", which was published in *Nephrology Dialysis Transplant* in 2019 and co-authored by Jarrin D. Penny, Fabio R. Salerno, Ranveer Brar, Eric Garcia, Krista Rossum, Christopher W. McIntyre and Clara J. Bohm.

Penny *(50%),* McIntyre & Bohm planned the trial. Penny *(80%),* McIntyre & Bohm wrote protocol. Penny *(80%),* Garcia, Rossum & Bohm collected the data. The data were analyzed by Penny *(80%),* Brar & Bohm. The data were interpreted by Penny *(80%),* McIntyre & Bohm. Each author contributed important intellectual content during the drafting and revising of the manuscript and accept accountability for the overall work by ensuring that questions pertaining to the accuracy and integrity of any portion of the work are appropriately investigated and resolved.

Research ethics board approval is provided in Appendix E. The permission to reproduce this manuscript are provided in Appendix F

4.2 Introduction

The phenomenon of transient myocardial ischemia leading to permanent LV dysfunction is known as *myocardial stunning*. Myocardial stunning results from repetitive circulatory stress and is often precipitated by the rapid removal of fluid during conventional intermittent HD, which results in segmental ischemia.[5] Over time, this leads to changes in ventricular structure and function.[6,7] In the research setting echocardiography has been used to detect myocardial stunning during HD by identifying reductions in segmental RWMA. These effects of HD on the heart have been confirmed by additional studies utilizing a range of imaging modalities, including PET and intradialytic cardiac MRI.[5,8,9] Direct measurement of myocardial blood flow during dialysis has also demonstrated that HD commonly precipitates myocardial ischemia.[9] Furthermore, studies of the effect of HD on vulnerable vascular beds such as the heart, brain and gut have revealed that HD is capable of inducing acute injury with demonstrable longer-term chronic injury.[10–12] HD-induced myocardial stunning is common, resulting in cumulative injury, development of heart failure, cardiac events and reduced survival.[4,7,13–15] Modifications to the dialysis procedure, such as cooling dialysis fluid to reduce episodic IDH have been shown in robust randomized control trials to mitigate both cardiac and brain injury. However, there is an urgent need for additional low cost, well tolerated interventions to further abrogate HD-induced ischemic based injury.

Ischemic pre-conditioning refers to the application of small repetitive ischemic insults to improve the ability of the heart to cope with larger ischemic insults such as acute myocardial infarction. Acutely, exercise provides cardio-protective effects similar to those described with ischemic pre-conditioning. This protection occurs immediately and persists for several days as evidenced in humans and pre-clinical animal models.[16,17] IDE has been a topic of investigation for some time. Benefits identified include improved oxygenation, aerobic capacity, physical function, dialysis efficacy, reduction in arterial stiffness and in some studies reduced incidence of IDH.[18–22] We hypothesize that IDE (through exercise preconditioning and/or reduction in IDH) might provide immediate protection against HD associated ischemic cardiac injury. We therefore performed an exploratory study to evaluate the potential of a cycling-based IDE intervention to reduce the severity of HD-

induced myocardial stunning.

4.3 Methods

This study was conducted according to the principles of the Declaration of Helsinki, with appropriate ethics committee approval. All patients gave their written, informed consent before participating in the study.

4.3.1 Study Design

This single-centre cross-sectional study aimed to compare the number of left ventricular RWMA observed by echocardiography during a HD session including intradialytic exercise with the number of RWMA observed in the same individuals during a HD session with no intradialytic exercise in individuals already established in a pre-existing intradialytic exercise program.

4.3.2 Study Population

All patients were from a prevalent adult HD population in the Manitoba Renal Program, Canada. The eligible population included adults (≥18 years), who were receiving chronic, thrice weekly HD at Sherbrook Centre Dialysis Unit (SCDU). Participants were able to understand English and provide consent. All individuals included in the study were established in the Manitoba Renal Program's clinical intradialytic cycling program and already regularly participating in a clinical intradialytic cycling program once-thrice weekly. No new intervention was applied as part of this observational study.

4.3.3 Exposure to Exercise

The Manitoba Renal Program's intradialytic cycling program is a pre-existing clinical program. As part of this program, participants are assessed by the unit Nephrologist who will identify any absolute contraindications and assess relative contraindications to exercise before providing clearance to participate in the program.

Table 4-1: Inclusion/Exclusion to Intradialytic Exercise Program

Inclusion Criteria	Exclusion criteria	
	Absolute contraindication	Relative contraindications (physician to determine)
Adult (>18 years)	Acute myocardial infarction, crescendo or unstable angina within past 3 months	Hemoglobin <85g/L
>12 weeks post-HD start	Unstable arrhythmia	Physical limitations affecting ability to use ergometer
	Symptomatic hypoglycemia >2 times/week in previous month	Severe musculoskeletal injury or pain precluding exercise participation
	Shortness of breath at rest	Unstable hemoglobin with frequent hypotension (SBP <90mmHg or drop in BP by >20mmHg with symptoms prior to enrollment)
	Home oxygen use	HD access issues
	Potassium consistently >6.5 pre-HD	

Once cleared, participants cycle on a stationary TherapyCycle^{TM} (Greely, CO) during their regular HD sessions under the supervision of a kinesiologist. Moderate intensity exercise is prescribed (3-4/10 on the Borg Rating of Perceived Exertion). Participants cycle in the first half of their HD session for 30-60 minutes. In addition to routine HD monitoring, participants had BP, pulse and glucose (diabetics) measured before and after completion of IDE.

The clinical exercise program is voluntary, and participants choose not to cycle during some HD sessions. In general, participants cycle one-two times, out of a total of three weekly IDE sessions. No change in how the exercise program was delivered was made as part of this study protocol. Exercise sessions were identical to individuals' usual clinical programming. Participants were asked to align their non-exercise days to make it more convenient to collect echocardiogram data without exercise.

As part of their ongoing participation in the clinical exercise program, each study participant had 2 study visits over the same week: a) the HD session during which they did not exercise served as the *Control Visit*; and b) HD session in the same week during which patients participated in their usual IDE regime served as the *Exposure Visit*. In this manner, participants served as their own controls. Echocardiography was performed 3 times during each study session.

4.3.4 Outcomes

The primary outcome was the change in the number of RWMA from baseline to post-exercise and from baseline to peak HD stress (20-30 minutes before the end of HD). RWMA were assessed using echocardiography and defined as a reduction in longitudinal strain of 20% or greater. This cut-off was chosen by reference to previous studies.[9,14,15,23] Secondary outcomes included the number of episodes of IDH over the HD session which is defined by a 20mmHg decrease in BP from HD start, global longitudinal strain and left ventricular ejection fraction.

4.3.5 Dialysis Treatments

Dialysis treatments were delivered using Fresenius 5008 dialysis monitors and high flux polysulfone dialyzers. Treatment times ranged from 3.5-4.5 hours. Dialysate was programmed according to patient's individual prescription; sodium range 135-141 mmol/L, potassium 2.0-3.0 mmol/L, calcium of 1.25-1.5 mmol/L and bicarbonate 35 mmol/L for all patients. Anticoagulation was achieved using unfractionated heparin. Dialysate flow ranged from 500-800 mL/min and mean dialysate temperature 36.3 ± 0.9 ^{o}C. Seven patients had fluid profiling during treatment, two had sodium profiling and one patient used both fluid and sodium profiling. For each session, net ultrafiltration (UF) was calculated on an individual basis according to ideal dry weight. UF requirements were effectively identical, the mean UF volume removed during HD was 2.85 ± 0.86 litres in the control visit and 2.8 ± 0.9 litres in the exposure visit. Blood pump speed ranged between 280 and 400 ml/minute with 15 patients using an arteriovenous fistula and four dialyzing with a central venous catheter. BP and pulse were measured as per unit protocol (every 30 min or more frequently as required). All dialysis conditions remained identical for each of

the treatment sessions evaluated with echocardiography. All control study visits were conducted mid-week and exposure visits at week's end, both of which were after a 48 hour inter-dialytic period.

Table 4-2: Hemodialysis Treatment Details

	Control Visit N=19	Exposure Visit N=19
HD treatment duration (min)	227.6 ± 20.9	226.1 ± 17.9
UF rate (L/hour)	0.0125± 0.0036	0.0123 ± 0.0038
Net UF volume (L)	2.85 ± 0.86	2.80 ± 0.90
Pre-HD SBP (mm/Hg)	148.4 ± 21.9	141.8 ± 17.9
Pre-HD DBP (mm/Hg)	71.5 ± 10.7	67.4 ± 12.9
Intradialytic SBP (mm/Hg)	140.9 ± 22.3	131.3 ± 20
Intradialytic DBP (mm/Hg)	69.6 ± 13.8	67 ± 12.6
Post-HD SBP (mm/Hg)	144.1 ± 25.8	136.5 ± 23.4
Post-HD DBP (mm/Hg)	71.1 ± 15.7	65.3 ± 15.5

HD=hemodialysis, UF=ultrafiltration, SBP=systolic blood pressure, DBP=diastolic blood pressure

4.3.6 Image Acquisition

Baseline echocardiograms were acquired (JP) before HD commenced, a second echocardiogram was performed immediately after exercise completion in exposure visit and at the same time point in the control visit. A final echocardiogram was performed at peak HD stress, 15 minutes prior to the end of each HD treatment.[15,23–25]

Echocardiography was performed using commercially available equipment (1.5-3.6MHz M4S probe, Vivid-q, GE Medical Systems, Soningen, Germany). Standard parasternal 2 and 4 chamber views were recorded for off-line digital analysis with a semi-automated computer program (EchoPac®, GE Healthcare) using 2D speckle tracking software. Images were anonymized and analyzed in a random order by the same investigator (JP). A random sample of these images was analyzed in random order by a second appropriately trained investigator to determine estimates of inter-observer reliability. Three cardiac cycles were analyzed for each image to derive values for segmental (12 left ventricular segments) and global longitudinal strain.

4.3.7 Definition of HD-induced Cardiac Stunning and Strain Analysis

Segmental values of LV longitudinal myocardial strain were analyzed and reported (JP) LS describes the fractional change in the length of a myocardial segment (12 in total) and is expressed as a percentage change (either positive or negative depending on lengthening or shortening). The values obtained for baseline, to post-exercise, and baseline to peak HD-stress were calculated for each segment as well as globally (average of all segments). If a segment underwent a ≥ 20% reduction in LS, it was considered to have a RWMA and subject to HD induced cardiac injury. The presence of myocardial stunning was defined as the presence of two or more segments with RWMA. This level of abnormality is considered clinically significant as it is associated with the development of fixed reductions in systolic function and increased mortality.[9,15] Any ventricular segments that were not able to be tracked by the software were described as < 20% change in LS or no RWMA.

4.3.8 Sample Size

Sample size determination was for a primary outcome of change in number of RWMA. We have previously demonstrated a difference in this variable using a similar protocol to this study when investigating the effects of other HD based interventions (biofeedback dialysis and dialysate cooling).[26–29] A sample size of 10 patients would appear to be sufficient to detect a difference of at least 20% (less than observed in previous studies) in the number of effected segments based upon a previously observed standard deviation of 14%, significance level of 0.05 and 80% power. We planned to study 24 patients (patients serving as own controls) to allow for patient drop out and to provide a range of exercise intensities; allowing preliminary evaluation of the effect of exercise dose on cardio-protection.

4.3.9 Statistical Analysis

Descriptive statistics were reported as mean ± standard deviation or median (interquartile range) for continuous variables and as frequency and percentages for categorical variables. Mean differences between control and exercise groups of the number of stunning segments were analyzed using the paired t-test. All analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC, USA).

4.4 Results

All 51 patients participating in the clinical intradialytic cycling program at SCDU at the time of recruitment were approached to participate in this study, of which, 27 consented to participate. However, three participants were unable to perform their usual cycling exercise due to illness and, one individual was admitted to hospital during the week of the study. Although a total of 24 individuals participated in at least one study visit, 19 patients were included in final analysis.

4.4.1 Baseline Characteristics

Mean age was 57.2 ± 11.8 years. Mean HD treatment was 227.6 ± 20.9 minutes in the control visit and 226.1 ± 17.9 minutes in the exposure visit. Forty two percent of participants were female. Mean body mass index was 28.5 ± 4.2 and mean dry weight was 84 ± 20.5 kg. Dialysis vintage was 4.3 ± 2.3 years. Documented causes of kidney disease included diabetes (31.5%), hypertension (5.3%), glomerulonephritis (5.3%), multifactorial (10.4%) and other causes (47.4%). Comorbidities included hypertension (79%), diabetes (42.1%), congestive heart failure (10.5%), stroke (10.5%), ischemic heart disease (15.8%), peripheral vascular disease (21.1%), cancer (15.8%) and arthritis (15.8%).

Table 4-3: Baseline Demographics

Age (years)	**57.2 ± 11.8**
Gender (M/F)	11/8
BMI	28.5 ± 4.2
Dry weight (kg)	84 ± 20.5
Dialysis Vintage (years)	4.3 ± 2.3
Hemoglobin (g/L)	106.1 ± 6.7
Albumin (g/L)	33.2 ± 3.6
Calcium (mmol/L)	2.3 ± 0.2
Potassium (mmol/L)	4.9 ± 0.6
Creatinine (umol/L)	874 ± 217.1
Phosphate (mmol/L)	1.7 ± 0.4
Kt/V	1.5 ± 0.2
ACE (%)	26.3% (5)
Beta Blocker (%)	57.9% (11)
Statin (%)	15.8% (3)
Hypertension (%)	79% (15)
Diabetes (%)	42.1% (8)
CHF (%)	10.5% (2)
Stroke (%)	10.5% (2)
IHD (%)	15.8 % (3)
PVD (%)	21.1% (4)
Cancer (%)	15.8% (3)
Arthritis (%)	15.8% (3)

M=male, F=female, BMI=body mass index, ACE=angiotensin converting enzyme, CHF=congestive heart failure, IHD=ischemic heart disease, PVD=peripheral vascular disease

BP findings were similar during both control and exposure visits (details in *Table 4-2*). Thirteen patients were being treated for hypertension with either monotherapy or combination antihypertensive/cardiac medications. Mean hemoglobin was 106.1 g/L ± 6.7; albumin 33.2 g/L ± 3.6, serum calcium 2.3 mmol/L ± 0.2, and serum potassium 4.9 mmol/L ± 0.6. All blood values were obtained from most recent monthly bloodwork and were drawn pre HD. Mean Kt/V for all study sessions was 1.5 ± 0.2 obtained from machine output and calculated by ionic dialysance at the end of each HD session. Details can be found in *Table 4-3*.

Participants began to exercise 33.7 ± 36.1 minutes (range 6-108) into their HD treatment and cycled for a duration of 39.2 ± 0.01 minutes (range 25-60), at a moderate level of intensity. The post-exercise echocardiogram occurred at a 77.6 ± 36.6 minutes (range 38-155) into treatment, and the peak HD-stress echocardiograms occurred at 206.4 ± 20.2 minutes (range 185-260) into treatment.

4.4.2 Relationship of Exercise to Myocardial Stunning

In the control visit, at the post-exercise timepoint, 17/19 patients had evidence of myocardial stunning with a cumulative total of 86 RWMA, mean 4.5 ± 2.6 (range 2-10). At the peak HD-stress timepoint , the total number of RWMA increased to 110, mean 5.8 ± 2.7 (range 2-12). However, when patients were exposed to exercise, 14/19 patients developed myocardial stunning at the post-exercise timepoint, 68 RWMA mean 3.6 ± 2.7 (range 2-10). At peak HD-stress, the total RWMA developed was 76, mean 4 ± 1.8 (range 2-8). See *Table 4-4.*

Table 4-4: Myocardial Stunning in Control and Exposure Visits

	Control Post-exercise	Control Peak Stress	Exposure Post-exercise	Exposure Peak Stress
Number stunning patients	17	18	14	18
Number stunned segments	86	110	68	76
Stunned segments (mean, SD)	4.5 ± 2.6	5.8 ± 2.7	3.6 ± 2.7	4 ± 1.8
GLS (%)	-14.3 ± 3.6	-13.0 ± 4.2	-14.5 ± 3.1	-13.9 ± 2.8
LVEF (%)	62.5 ± 8.8	61.3 ± 7.6	61.6 ± 5.8	61.1 ± 9.8

SD=standard deviation, GLS=global longitudinal strain, LVEF=left ventricular ejection fraction

The change in the number of RWMA between *Control* and *Exposure* visits at post-exercise was -0.95 ± 2.9 (p=0.17), while at peak HD-stress, the difference in the number of RWMA was -1.8 ± 2.8; p = 0.01 (*Figure 4-1).*

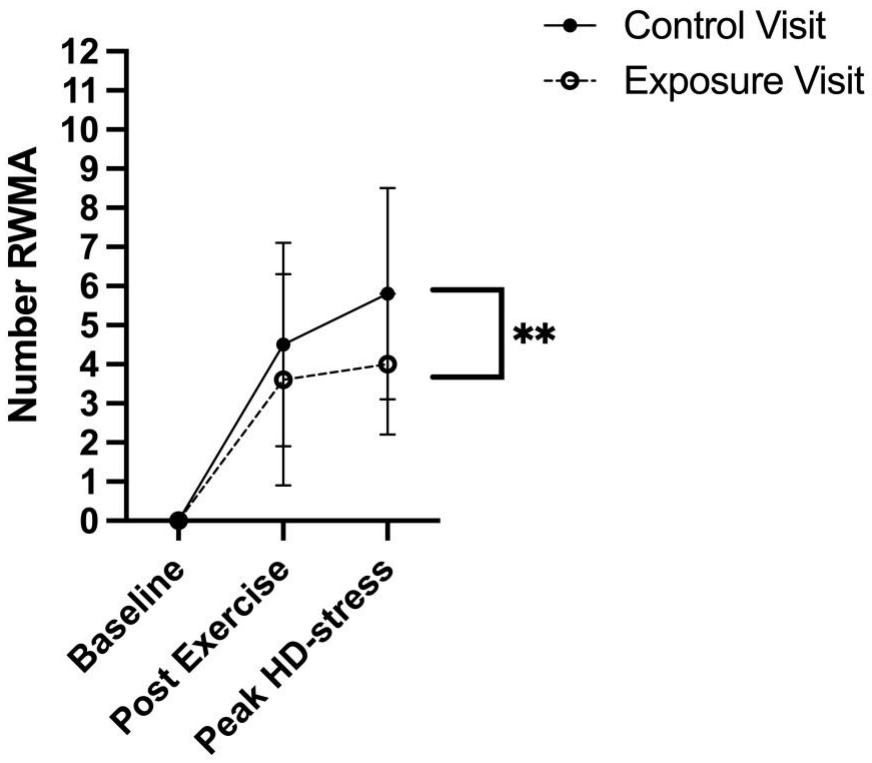

Figure 4-1: Mean number of RWMA at each echocardiogram timepoint. Control visit (solid line) and exposure visit (dotted line). Error bars represent standard deviation of the mean. *****Denotes p 0.01.*

We found no significant difference in the number of developed RWMA at peak HD-stress related to the dose of exercise. Exercise dose was described as *Low Dose* (30 minutes or less) vs. *High Dose* (>30 minutes). Patients who participated in lower dose exercise (12 patients) developed 3.8 ± 2.0 RWMA (range 1-8), whereas higher dose participants (7 patients) developed 4.4 ± 1.4 (range 3-7) RWMA.

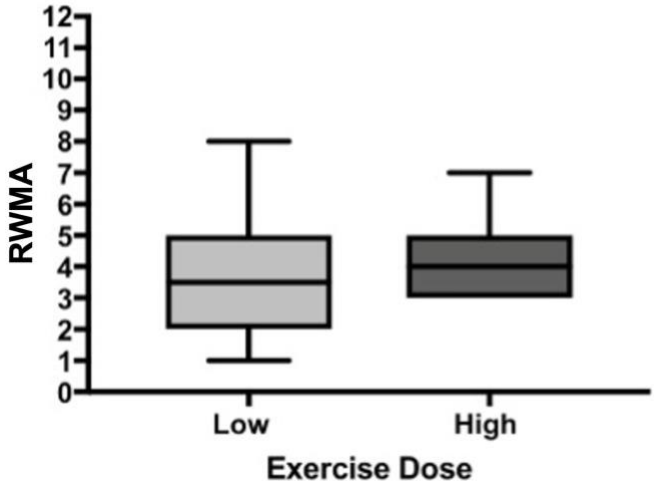

Figure 4-2: Median number RWMA in relation to exercise dose. Low ≤30 minutes, High ≥30 minutes. Error bars represent minimum/maximum values.

4.4.3 Relationship of Exercise to other Cardiac Measures

There were no significant differences found in global longitudinal strain (GLS). Post-exercise, GLS was -14.3 ± 3.6% in the *Control Visit* and -14.5 ± 3.1% in the *Exposure Visit* (p = 0.86). At peak HD-stress, GLS was -13.0 ± 4.2% (*Control Visit*), and 13.9 ± 2.8% [*Exposure Visit* (p = 0.25)]. There were also no significant changes in LV ejection fraction (EF). Mean LV-EF at post-exercise 62.5 ± 8.8% (*Control Visit*) and 61.6 ± 5.8% (*Exposure Visit*), p = 0.71. Similarly, at peak HD-stress, LVEF was 61.3 ± 7.6% (*Control*) and 61.1 ± 9.8% (*Exposure*), p = 0.94.

4.4.4 Relationship of Exercise to Intradialytic Hypotension

There were five episodes of IDH during the *Control Visit*, whereas, in the *Exposure Visit* there were six. Two of these patients had more than one episode of IDH. However, all BP measurements, including mean pre, post and intradialytic were similar in both visits.

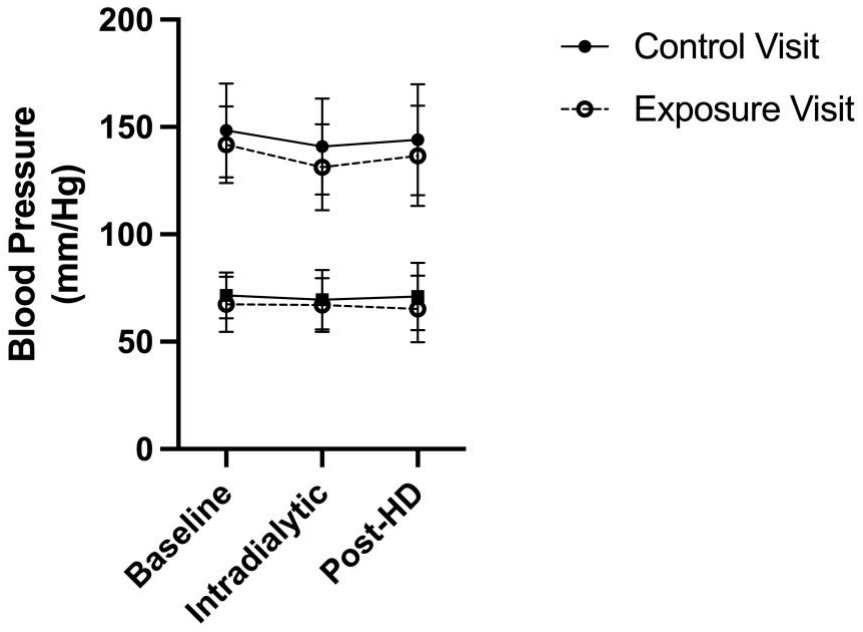

Figure 4-3: Mean blood pressure response (upper lines represent systolic BP, lower lines represent diastolic BP at control visit (solid line) and exposure visit (dotted line). Error bars represent standard deviation of the mean.

4.5 Discussion

We have shown that IDE was associated with a significant reduction in myocardial stunning in patients receiving maintenance HD. This cardio-protective effect was most evident at reducing RWMA at peak HD stress. Additionally, this effect did not appear to be associated with changes in hemodynamic stability, as indicated by frequency of IDH.

This novel finding suggests that the application of IDE (in addition to its other previously identified benefits) appears to be associated with effective immediate preconditioning of the heart against HD-induced ischemic injury. Both ischemic and exercise preconditioning activate signaling pathways in the mitochondria and lead to improved HD-induced cardiovascular outcomes.[16,30] In animals models there is a bi-phasic response to exercise, including an immediate benefit, which lapses and then returns between 12-24 hours and lasts for several days.[17] One episode of exercise has been found to provide up to five days of cardio-protection in both animals and humans.[17] Moreover, subsequent and cumulative doses of exercise have been found to have a compounding effect, abrogating the decline in protection.[17] We have found previously that remote ischemic preconditioning (using a leg cuff based intervention) results in a cardio-protective effect that lasts for up to 28 days in HD dependent individuals.[16,30] Our observation of the apparent lack of dose dependency in protective response to exercise has also been noted in animal studies, but has not been previously assessed in humans.[17]

Exercise, as delivered within this study, did not change the global performance of the myocardium and had no association to commonly prescribed HD parameters or changes made to the HD prescription. Likewise, exercise has been reported to modify the hypotensive response to HD in some patients, which is significantly associated with HD-induced acute cardiac injury, however typically this occurs at the threshold of a profound and symptomatic IDH episode, which did not occur in participants in the current study.

In this study, there was a significant reduction in myocardial stunning at peak HD stress, which is associated with repetitive and cumulative CV injury and increased mortality. The minimal clinically significant difference in number of stunned segments is unknown. In

this small exploratory study, the observed reduction in myocardial stunning with exercise was not associated with change in blood pressure or symptom burden over the course of the HD treatment. We did not investigate effect on time required to recover post HD. However, prior studies have shown that myocardial stunning during HD is associated with repetitive and cumulative CV injury and increased mortality.[4,15,24,25] As such, larger studies of longer duration are necessary to further delineate the clinical effects of IDE-related reductions in myocardial stunning and to determine if there is a desirable length, intensity and frequency of IDE for the greatest protective effect. Further work is needed to define and refine the intervention of IDE for maximum benefit.

4.5.1 Limitations

This study was designed as an initial scoping exercise to detect a possible signal of exercise related cardio-protective benefit. Limitations include small sample size and single center. However, the HD population studied was highly representative of typical HD patients, with similar age and chronic kidney disease etiology. Because participants were established exercise participants, there was no randomization to the exercise dose, which may have affected cardiovascular response to exercise. As all participants were exposed to exercise prior to the study, we were only able to study subjects who had already evidenced their ability to perform the intervention, leading to selection bias. As well, the biphasic nature of the preconditioning response may have confounded some of the observed benefit. However, this would likely act to lessen the magnitude of cardiovascular effect observed compared to an exercise naïve cohort. Finally, due to the study's cross-sectional nature, we were unable to assess long-term outcomes. However, in previous studies we have demonstrated that a reduction in recurrent short term injury does translate to longer term maintenance of cardiac function. Exercise may also provide protection to other vulnerable vascular beds in other organ systems during HD (as we have previously demonstrated with alternative intradialytic interventions). However, this was beyond the scope of this initial study.

4.5.2 Conclusion

Intradialytic exercise was associated with a decrease in myocardial stunning. IDE appears to provide safe and effective preconditioning against HD-induced acute ischemic cardiac injury. Given that even lower doses of moderate intensity exercise seem capable of providing cardio-protection; this therapy has exciting potential to be widely applied within the characteristically elderly and highly co-morbid HD population. Optimum dose and timing of exercise requires further clarification.

4.6 References

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Chapter 5

5 Thesis Summary and Future Work

The importance of the knowledge and understanding gained from this work is fundamental to my goal of improving the delivery of HD and has led to an Advanced Practice Fellowship supporting the development of a *'Patient Optimization Program'* (currently in development). The aim of this program is to improve HD tolerability by individualizing HD delivery based on physiological requirements (which will include methodologies described in this thesis – echocardiography, PPG, IDE).

5.1 Project Summary and Conclusion

The purpose of this thesis was to study methods that could identify and ameliorate HD-induced circulatory stress through intradialytic monitoring and intervention. The investigations that were conducted to address this overarching goal are summarized below.

5.1.1 Percutaneous Perfusion Monitoring for the Detection of Hemodialysis-induced Cardiovascular Injury

The safe delivery of HD faces dual challenges; the accurate detection of systemic circulatory stress producing CV injury, and the ability to enable effective pre-emptive intervention for such injury.

In Chapter 1, we performed a pilot study to examine the capability of a non-invasive, real-time monitoring system to detect the deleterious effects of HD on CV stability. Eight chronic HD patients were evaluated with cardiac echocardiography prior to the initiation of HD and again at peak HD stress. Continuous CV physiologic monitoring was obtained throughout HD using an oximeter-based pulse waveform monitoring device (PPG). LS values for 12 left ventricular segments were generated using speckle-tracking software, to assess the development of HD-induced RWMA, indicative of myocardial stunning.

We found that patients that developed treatment induced myocardial stunning (two or more RWMA) also had significant reductions in PS which occurred quite early in the HD

treatment. Changes were not associated with standard-of-care measures of hemodynamic stability/instability including changes in BP, symptoms of IDH nor relative blood volume changes. Additionally, this technology was able to capture the individual response patterns to treatment, modifications made to treatment delivery (UF reductions) and/or interventions administered (positioning, fluid resuscitation) during HD.

We found that percutaneous perfusion monitoring, using PPG appears to be useful in identifying circulatory stress during HD and was predictive of the development of HD-induced myocardial stunning with a lead time long enough to consider timely intervention.

5.1.2 Non-invasive Intradialytic Percutaneous Perfusion Monitoring: a view to the heart through the skin

HD is known to induce recurrent episodes of systemic circulatory stress which accumulate over time and lead to the development of permanent myocardial dysfunction. Injury is largely a consequence of challenged microcirculatory blood flow within the myocardium as a result of demand ischemia caused by HD and UF challenges. Currently HD stability monitoring is measured by methods focused on macrovascular parameters and not via the microcirculation where deficiencies are known to originate.

As indicated in Chapter 2, non-invasive intradialytic percutaneous perfusion monitoring has been shown in a small number of patients to be predictive of HD-induced myocardial stunning. In Chapter 3, we expanded this initial observation in a larger cohort of patients. In addition to assessing HD-induced changes in percutaneous perfusion in relation to myocardial contractile function using echocardiography, we aimed to compare changes in skin perfusion to direct measures of myocardial perfusion (using CT imaging). Intradialytic microcirculatory response was assessed in 12 patients, receiving conventional intermittent HD. Continuous measures of cutaneous perfusion were obtained throughout HD (using pulse-oximeter based PPG), cardiac echocardiography was performed prior to the initiation of HD and again at peak HD-stress to assess the development of RWMA. Myocardial perfusion CT imaging was also obtained at the same timepoints (pre-HD & peak-HD stress). Intradialytic changes in cutaneous perfusion (using the output of PS) during HD

were compared to the direct measures of myocardial perfusion, as well as to the development of RWMA.

We found there to be an association between intradialytic PS reductions – to the lowest threshold (PPG) and changes in global myocardial perfusion, as well as to the development of RWMA. These changes were again not associated with standard-of-care measures of HD stability/instability (BP, relative blood volume). However, UF rate (ml/kg/hour) was consistently found to be the significant driver of HD-induced circulatory stress (associated with microcirculatory PS reductions, reduction in global myocardial perfusion, as well as the development of RWMA), consistent with previous literature.[1–3]

Intradialytic percutaneous perfusion monitoring using PPG is seemingly a useful method of assessing intradialytic hemodynamic stability and HD-induced circulatory stress. The information generated at the microcirculatory level of the skin is reflective of direct measures of myocardial perfusion and the development of HD-induced myocardial stunning.

5.1.3 Intradialytic Exercise Preconditioning: the effects on myocardial stunning

Exercise preconditioning provides immediate protection against cardiac ischemia in clinical/pre-clinical studies in subjects without chronic kidney disease. In individuals requiring HD remote ischemic preconditioning has been shown to be protective against HD induced myocardial injury [4,5] however, at the time of study, no study had been conducted regarding the effectiveness of IDE as a preconditioning treatment against HD-induced circulatory stress and the development of RWMA.

To address this gap in knowledge, in Chapter 4 we explored the role of IDE as a preconditioning intervention and assessed its' effect on HD-induced myocardial stunning. This observational study was performed in 19 adult chronic HD patients, who were participating in an existing clinical IDE program. HD-induced cardiac stunning was evaluated over two HD sessions within the same week: a *control visit* (no exercise) and an *exposure visit* (incorporating patient's usual intradialytic cycling regime). Echocardiography was performed at the same three time points for each visit [baseline,

post exercise (at the same timepoint in treatment for control visit) and again at peak HD-stress]. LS values for 12 left ventricular segments were generated and evaluated using speckle-tracking software to assess the presence of HD-induced RWMA.

We found there to be a reduction in the number of HD-induced RWMA when exercise was incorporated into HD. There was a response immediately after exercise, however the greatest reduction in RWMA was noted at peak HD-stress. Additionally, the response did not seem to be dose dependent and therefore minimal duration (30 minutes) was as effective as longer periods of exercise. This study demonstrated for the first time that IDE has a pre-conditioning effect against HD-induced myocardial injury.

5.2 Significance of this Work

The work completed for this thesis generates new knowledge highlighting the value and practical application of novel intradialytic therapeutics. Using a commercially available PPG technology (a non-invasive real-time monitoring system), intradialytic reductions in cutaneous perfusion at the microcirculatory level were found to be reflective of changes in perfusion within the myocardium during HD. Therefore, the skin of the forehead can be used as a surrogate vascular bed for vital organ perfusion. Furthermore, reductions in PS were predictive of HD-induced circulatory stress and the development of HD-induced RWMA. The lowest PS threshold was consistently found to be (in projects one and two), a reduction of approximately 50% from baseline which occurred two hours into HD. As clinicians, we often treat the latter portion of the HD procedure as the most crucial time for instability –however, new insight reveals that two hours into the HD procedure is a timepoint predictive of circulatory stress and therefore as a preventative measure the first half of HD becomes the window of opportunity and optimal time for tailored care planning and/or intradialytic interventions to take place. Additionally, this research has proven the efficacy of incorporating IDE as an optional intradialytic intervention to ameliorate the development of HD-induced myocardial ischemia. An viable intervention requiring minimal training and low cost attachments.

5.3 Future Work

5.3.1 Non-invasive Percutaneous Monitoring

In Chapters 2 and 3 of this thesis, although the sample size was small, we were able to consistently demonstrate the clinical significance of intradialytic microcirculatory monitoring as a predictor of HD induced circulatory stress as it relates to the development of LV contractile dysfunction. Because there is no published literature related to microcirculatory methodology to drive HD therapy, a larger scale study is in order to further interrogate the clinical benefit of intradialytic PPG monitoring. The device used in our research currently enables an embedded proprietary alert threshold system, however, because of the observational nature of our study design, these thresholds were not utilized. Future work would focus on sensitizing the alert system thresholds with outcome measures consistent with previous projects (HD-induced RWMA). A randomized control trial design with a control arm (standard-of-care) and an intervention arm (alert system to drive HD). Based on the findings from Chapters 2 and 3, the alert system would prompt clinical interventions at each threshold (for example Alert Level One = pulse strength reduction of 10% for 20% of session would prompt the user to elevate patients legs and/or recline the chair position – for blood redistribution, increasing pre-load, Alert Level Two = pulse strength reduction 20% for 20% of session would prompt further intervention such as UF rate changes, further positioning). The intent of this design would be to refine the alert system to improve HD stability thereby reducing the intensity of HD-induced circulatory stress (reducing IDH and myocardial stunning). As evident in Figure 5-1 (below), both the severity of reduction and the time spent at thresholds are important indicators of myocardial stunning and should be considered when refining algorithmic alerts and parameters to drive HD.

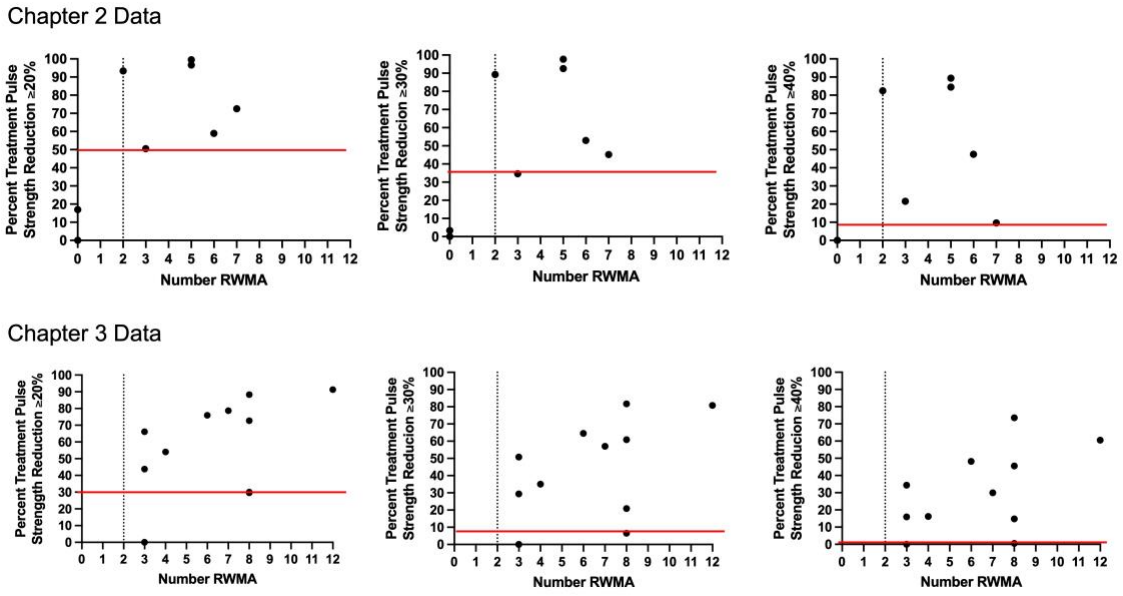

Figure 5-1: Percent hemodialysis spent at pulse strength thresholds and the development of RWMA in Chapters 2,3 (Projects 1,2).

5.3.2 Intradialytic Exercise

This study was designed as an initial scoping exercise to detect a possible signal of exercise related cardio-protective benefit. Limitations of this study include small sample size and single center design. Because participants were established exercisers, there was no randomization to the exercise dose, which may have affected cardiovascular response to exercise, however, I suspect if anything our findings may have been minimized as the population was already pre-conditioned in comparison to an exercise naïve cohort. Additionally study participants had already evidenced their ability to perform the intervention, leading to selection bias. Finally, due to the study's cross-sectional nature, we were unable to assess long-term outcomes. Regardless of these limitations however, the insight gained from this initial IDE study is clearly a topic of interest. Chapter 4 of this thesis has led to subsequent research focusing on the cardio-protective benefits of IDE in the HD population. Using similar methodology, a recent study demonstrated consistent findings in an exercise naïve patient population[6,7]. Additionally, the results described in Chapter 4 have subsequently led to a federally funded multi-centre international (Canada,

US, Australia) randomized control trial (ClinicalTrials.gov – NCT04877041), which is slated to begin in early 2023 using identical methodology. My supervisor and I are co-investigator for this trial, London Health Sciences Centre is a participating site and the Kidney Clinical Research Unit (Dr. C. McIntyre) is the core laboratory for the analysis of all serial echocardiography and the determination of RWMA (myocardial stunning) which is the primary end-point of this trial.

5.3.3 Other Intradialytic Interventions to Ameliorate HD-induced Circulatory Stress

Based on findings in this thesis as well as existing literature[1–3,8], we know that the intensity of fluid removal (UF) during HD is a driver of hypoperfusion and myocardial ischemic injury. Therefore, a study looking at maximum UF rate thresholds related to the development of RWMA would be beneficial. Again, a randomized design comparing standard-of-care to tailored/maximum UF rate thresholds would be advantageous. Furthermore, the pre-clinical development of a wearable ultrafiltration device is underway with human safety testing slated to begin early in 2023. Based on this initial testing, a study utilizing the wearable devise as an adjunct ultrafiltration device would be interesting. The goal would be to drive safer HD therapy with guided UF thresholds, any unattained ultrafiltration needs could be achieved between HD sessions at a slow continuous rate.

Ultimately, my goal would be to investigate viable intradialytic methods of tailoring treatment delivery to improve clinical outcomes for HD patients.

5.4 References

1. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol*. 2009;4(5):914-920. doi:10.2215/CJN.03900808

2. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol*. 2009;4(12):1925-1931. doi:10.2215/CJN.04470709

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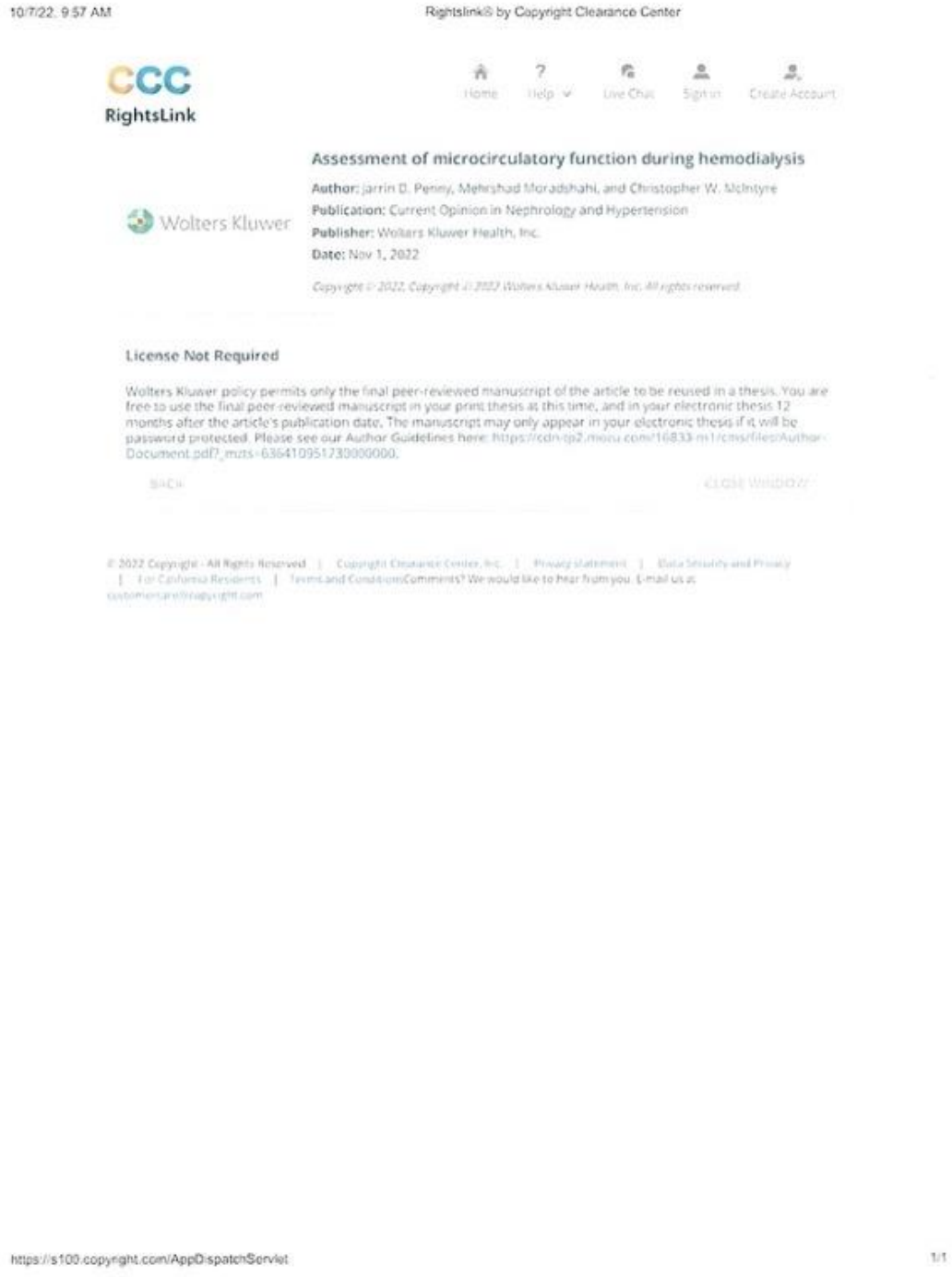
5. Crowley LE, Odudu A MC. *Remote Ischaemic Preconditioning Protects against Dialysis-Induced Cardiac Injury*.; 2015.

6. Mcguire S, Horton EJ, Renshaw D, Jimenez A, Krishnan N, Mcgregor G. Hemodynamic Instability during Dialysis: The Potential Role of Intradialytic Exercise. *Biomed Res Int*. 2018;2018. doi:10.1155/2018/8276912

7. McGuire S, Horton EJ, Renshaw D, et al. Cardiac stunning during haemodialysis: the therapeutic effect of intra-dialytic exercise. *Clin Kidney J*. 2021;14(5):1335-1344. doi:10.1093/ckj/sfz159

8. Dasselaar JJ, Slart RHJA, Knip M, et al. Haemodialysis is associated with a pronounced fall in myocardial perfusion. *Nephrol Dial Transplant*. 2009;24(2):604-610. doi:10.1093/ndt/gfn501

Appendices



Appendix A: Copyright permission "Assessment of microcirculatory function during hemodialysis", ***Current Opinions in Nephrology and Hypertension.***

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Full Board Initial Approval Notice

Principal Investigator: Dr. Christopher McIntyre
Department & Institution: Schulich School of Medicine and Dentistry\Medicine-Dept of,London Health Sciences Centre

Review Type: Full Board
HSREB File Number: 106879
Study Title: Evaluation of the effects of hemodialysis and eating on liver perfusion, endotoxemia and uremic toxin handling in the hemodialysis patient
Sponsor:

HSREB Initial Approval Date: August 11, 2015
HSREB Expiry Date: August 11, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Western University Protocol	v2	2015/07/13
Letter of Information & Consent	v2	2015/07/13
Data Collection Form/Case Report Form	v2	2015/07/13
Instruments	Study Questionnaire: Pruritus	2015/07/13
Instruments	Study Questionnaire: SF-36	2015/07/13
Instruments	Study Questionnaire: HADS	2015/07/13
Instruments	Study Questionnaire: SNAQ	2015/07/13
Female Partner Pregnancy Letter/Consent	v1	2015/07/13

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

This is an official document. Please retain the original in your files.

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6G 1G9 t. 519.661.3036 f. 519.850.2466 www.uwo.ca/research/ethics

Appendix B: Research Ethics Board Approval for Project 1.

CCC Marketplace™

Order Number: 1219446
Order Date: 09 May 2022

Payment Information

Jarrin Penny | **Billing Address:** | **Customer Location:**

Order Details

1. HEMODIALYSIS INTERNATIONAL

Billing Status: Open

Article: Percutaneous perfusion monitoring for the detection of hemodialysis induced cardiovascular injury.

Order License ID	1219446-1	**Type of use**	Republish in a thesis/dissertation
Order detail status	Completed		
ISSN	1492-7535	**Publisher**	BLACKWELL PUBLISHING, INC.
		Portion	Chapter/article

0.00 CAD
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LICENSED CONTENT

Publication Title	HEMODIALYSIS INTERNATIONAL	**Publication Type**	Journal
		Start Page	351
Article Title	Percutaneous perfusion monitoring for the detection of hemodialysis induced cardiovascular injury.	**End Page**	358
		Issue	3
		Volume	22
		URL	http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1542-4758
Author/Editor	International Society for Hemodialysis,, International Symposium on Home Hemodialysis., Dialysis Conference.		
Date	01/01/1999		
Language	English		

Appendix C: Copywrite approval "Percutaneous perfusion monitoring for the detection of hemodialysis induced cardiovascular injury", *Hemodialysis International.*

Western Research

Date: 6 August 2019

To: Dr. Christopher McIntyre

Project ID: 113905

Study Title: Investigation of Electrophysiological Substrate of Arrhythmia in Hemodialysis patients

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: August 20, 2019

Date Approval Issued: 06/Aug/2019

REB Approval Expiry Date: 06/Aug/2020

Dear Dr. Christopher McIntyre

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
AR_LOI_July31	Written Consent/Assent	31/Jul/2019	1
ArrhythmiaProtocol_July31	Protocol	31/Jul/2019	1
CRF_June13	Other Data Collection Instruments	13/Jun/2019	1

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

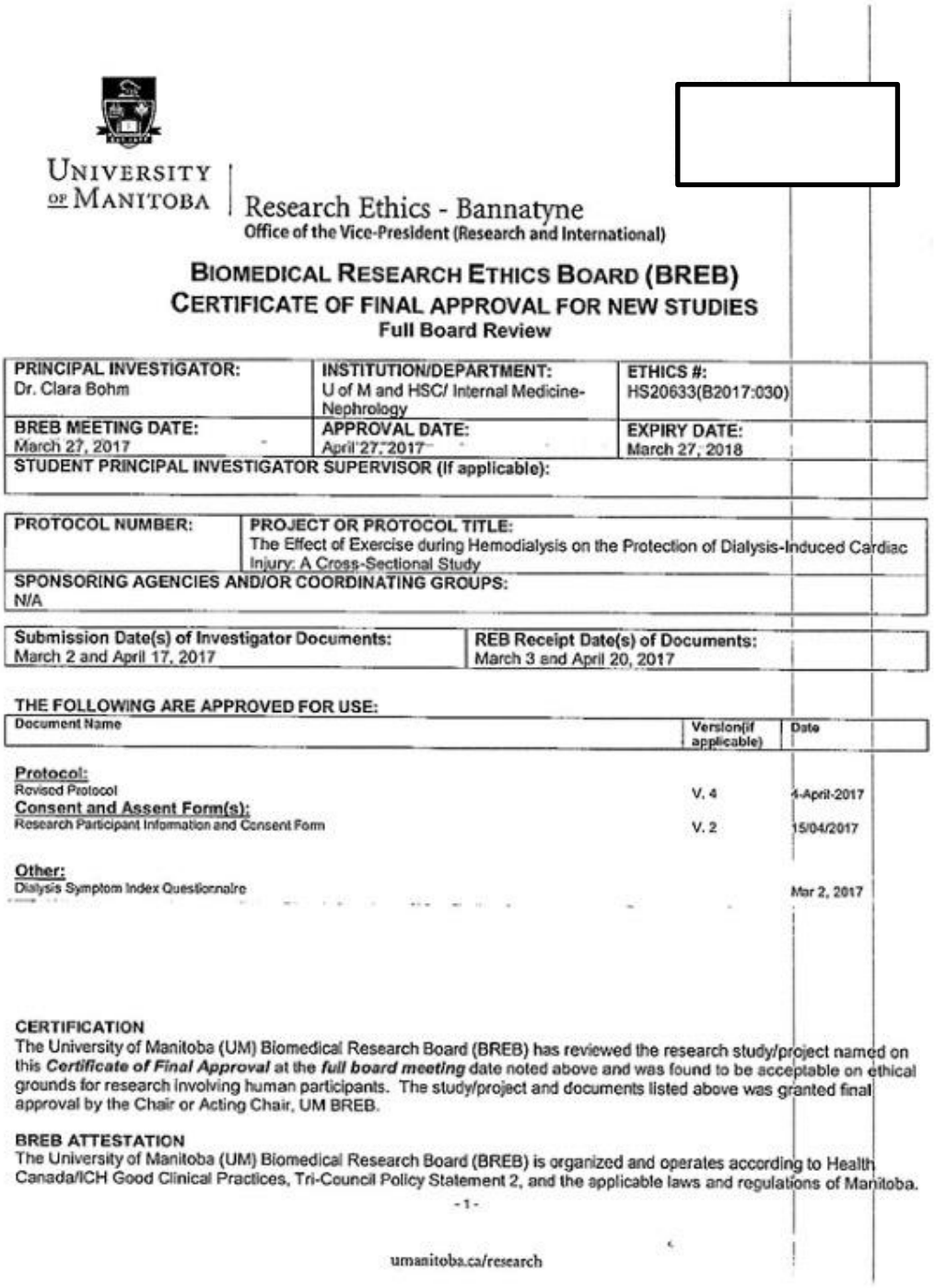
Please do not hesitate to contact us if you have any questions.

Sincerely,

Karen Gopaul, Ethics Officer on behalf of Dr. Philip Jones, HSREB Vice-Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix D: Research Ethics Board Permissions for Project 2.



UNIVERSITY OF MANITOBA | Research Ethics - Bannatyne
Office of the Vice-President (Research and International)

BIOMEDICAL RESEARCH ETHICS BOARD (BREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Full Board Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Dr. Clara Bohm	U of M and HSC/ Internal Medicine-Nephrology	HS20633(B2017:030)
BREB MEETING DATE: March 27, 2017	**APPROVAL DATE:** April 27, 2017	**EXPIRY DATE:** March 27, 2018
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (if applicable):		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE: The Effect of Exercise during Hemodialysis on the Protection of Dialysis-Induced Cardiac Injury: A Cross-Sectional Study
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: N/A	

Submission Date(s) of Investigator Documents:	REB Receipt Date(s) of Documents:
March 2 and April 17, 2017	March 3 and April 20, 2017

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol: Revised Protocol	V. 4	4-April-2017
Consent and Assent Form(s): Research Participant Information and Consent Form	V. 2	15/04/2017
Other: Dialysis Symptom Index Questionnaire		Mar 2, 2017

CERTIFICATION
The University of Manitoba (UM) Biomedical Research Board (BREB) has reviewed the research study/project named on this ***Certificate of Final Approval*** at the ***full board meeting*** date noted above and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM BREB.

BREB ATTESTATION
The University of Manitoba (UM) Biomedical Research Board (BREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba.

Appendix E: Research Ethics Board Approval for Project 3.

CCC Marketplace™

Order Number: 1089980
Order Date: 06 May 2022

Payment Information

Jarrin Penny | **Billing Address:** | **Customer Location:**

Order Details

1. Nephrology, dialysis, transplantation

Billing Status: Open

Article: Intradialytic exercise preconditioning: an exploratory study on the effect on myocardial stunning.

Order License ID	1089980-2	**Type of use**	Republish in a thesis/dissertation
Order detail status	Completed		
ISSN	0931-0509	**Publisher**	OXFORD UNIVERSITY PRESS
		Portion	Chapter/article

0.00 CAD
Republication Permission

LICENSED CONTENT

Publication Title	Nephrology, dialysis, transplantation	**Rightsholder**	Oxford University Press - Journals
Article Title	Intradialytic exercise preconditioning: an exploratory study on the effect on myocardial stunning.	**Publication Type**	Journal
		Start Page	1917
		End Page	1923
		Issue	11
Author/Editor	EUROPEAN DIALYSIS AND TRANSPLANT ASSOCIATION - EUR	**Volume**	34
Date	01/01/1986		
Language	English		
Country	United Kingdom of Great Britain and Northern Ireland		

Appendix F: Copyright approval "Intradialytic exercise preconditioning: an exploratory study on the effect on myocardial stunning". *Nephrology, Dialysis, Transplantation.*

Curriculum Vitae

Name: Jarrin D. Penny RN, BSN, C.Neph(C)

Post-secondary Education and Degrees:

Fanshawe College, School of Nursing
London, Ontario, Canada
1991-1994 Nursing Diploma

The University of Victoria
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2008-2012 Bachelors Science Nursing (BSN)

The University of Western Ontario
London, Ontario, Canada
2016 Department of Medical Biophysics MSC
2017 Department of Medical Biophysics (reclassification PhD)

Honours and Awards:

Province of Ontario Graduate Scholarship,, 2016-2022
LHSC Academic Realignment Fellowship, 2022-2024
Mitacs Research Accelerated Internship, 2021-2023
Kidney Foundation of Canada Allied Health Fellowship, 2021/22
Young Investigator Award (Baxter Healthcare), 2021
Best Abstract – Nephro-cardiology Conference, 2019
Satellite Healthcare Collaborative Research Grant, 2016
Canadian Nephrology Novice Research Grant (CANNT), 2016
Best Peritoneal Dialysis Abstract, Annual Dialysis Conf, 2014

Certifications:

College of Nurses Ontario – Registered Nurse, in good standing since 1994
Canadian Nurses Association – Certificate Nephrology, in good standing since 2008
Diabetes Educator Certification Board – Diabetes Nurse Educatory, 2011-2016

Professional Affiliations:

Registered Nurses Association of Ontario
Canadian Nurses Association
Canadian Association Nephrology Nurses/Technologists

Research Interests:

Nephrology, Dialysis, Hemodialysis, Chronic Kidney Disease, Diabetes, Myocardial Stunning, Dialysis Optimization/tolerability, Education, Nursing, Simulation-based Training, Patient Safety, Quality Improvement, Quality-of-life

Work related experience:

- 2015-present – **Research Associate/RN** – Kidney Clinical Research Unit, Lawson Health Research Institute, London Health Sciences Centre, London ON
- 2015-2016 – **Renal Project Consultant** – London Health Sciences Centre – Renal Program, London ON
- 2012-2016 – **Charge RN** – Westmount Hemodialysis Unit, Kidney Care Centre, London Health Sciences Centre – Renal Program, London ON
- 2011-2012 **– Hemodialysis RN** – Adam Linton Dialysis Unit, London Health Sciences Centre – Renal Program, London ON
- 2011-2012 – **Diabetes Nurse Educator** – Tillsonburg & District Memorial Hospital, Tillsonburg ON
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- 2003-2011 **- Hemodialysis RN** – St. Joseph's Healthcare Hamilton Satellite Dialysis Unit Brant Community Health-systems, Brantford ON
- 1997-2003 – **Hemodialysis RN** – London Health Sciences Centre Regional Renal Program – Satellite Dialysis Unit Woodstock General Hospital, Woodstock ON
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- 1994-1997 – **Staff RN** – Nephrology, Renal Transplant, Peritoneal Dialysis, Urology, St. Joseph's Healthcare, Hamilton ON

Publications:

1. **Penny JD,** Grant C, Salerno F, Brumfield A, Mianulli M, Poole L, McIntyre CW. *Percutaneous perfusion monitoring for the detection of hemodialysis induced cardiovascular injury*. Hemodialysis Int. 2018 Jul;22(3):351-358. doi: 10.1111/hdi.12632. Epub 2018 Jan 23. PMID: 29360287.

2. **Penny JD,** Salerno FR, Brar R, Garcia E, Rossum K, McIntyre CW, Bohm CJ. *Intradialytic exercise preconditioning: an exploratory study on the effect on myocardial stunning*. Nephrol Dial Transplant. 2019 Nov 1;34(11):1917-1923. doi: 10.1093/ndt/gfy376. PMID: 30590580.

3. Qirjazi E, Salerno FR, Akbari A, Hur L, **Penny J,** Scholl T, McIntyre CW. *Tissue sodium concentrations in chronic kidney disease and dialysis patients by lower leg sodium-23 magnetic resonance imaging*. Nephrol Dial Transplant. 2020 Apr 6:gfaa036. doi: 10.1093/ndt/gfaa036. Epub ahead of print. PMID: 32252091.

4. **Penny JD,** Salerno FR, Akbari A, McIntyre CW. *Pruritus: Is there a grain of salty truth?* Hemodialysis Int. 2021 Jan;25(1):E10-E14. doi: 10.1111/hdi.12885. Epub 2020 Sep 29. PMID: 32996258.

5. **Penny JD,** Jarosz P, Salerno FR, Lemoine S, McIntyre CW; *Impact of expanded hemodialysis using medium cut-off dialyzer on quality of life: application of dynamic patient-reported outcome measurement tool*. Kidney Medicine. 2021. doi: https://doi.org/10.1016/j.xkme.2021.05.010. PMID: 34939008.

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7. Lemoine S, **Penny JD,** Salerno FR, House A, Slessarev M, McIntyre CW. *Novel extracorporeal treatment to modulate hyperinflammation in COVID-19 patients*. Scientific Reports. 2022.

8. Anazodo U, Wong D, Theberge J, Dacey M, Gomes J, **Penny JD,** Van Ginkel M, McIntyre CW; *Application of intradialytic magnetic resonance imaging and spectroscopy demonstrates hemodialysis-related acute brain injury***.** Journal of the American Society of Nephrology. 2022. (In Press)

9. **Penny JD,** Hur L, Salerno FR, Wong D, Jan MH, McIntyre CW. *No-invasive intradialytic percutaneous perfusion monitoring: a view to the heart through the skin.* Frontiers Nephrology/Hypertension. Invited 2022 (Submitted).