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Symptomatic Hypotension, Venous Oximetry and Outpatient Hemodialysis

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Symptomatic Hypotension, Venous Oximetry and Outpatient Hemodialysis

by

H. Paul Smith

Dissertation

Submitted in partial satisfaction of the requirements for the degree of

Doctor of Philosophy

in

Nursing

in the

Graduate Division

of the

University of California, San Francisco
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by

H. Paul Smith
ACKNOWLEDGEMENTS AND DEDICATION

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I’d like to dedicate this to the memory of my mother Betty A. Smith. I hope you are proud and know how much I miss you.
ABSTRACT
Symptomatic Hypotension, Venous Oximetry and Outpatient Hemodialysis
H. Paul Smith

Problem Statement: Symptomatic hypotension is the most common complication during hemodialysis. It can induce cardiac arrhythmias and predisposes patients to coronary, splanchnic, and/or cerebral ischemic events. Non-invasive intermittent blood pressure measurement is used to identify hypotension during dialysis, yet it is a post-facto indicator of intravascular hypovolemia. Continuous monitoring of central venous oxygen saturation (ScvO2) may offer an innovative approach to early detection of symptomatic hypotension during outpatient hemodialysis.

Aims: The overall aim of this study is to determine whether ScvO2 is related to changes in systolic blood pressure (SBP) and acute signs and symptoms in outpatients undergoing hemodialysis. The specific aims of this study are to determine the: 1.) change in ScvO2 as fluid is removed during outpatient hemodialysis; 2) relationship between ScvO2 and changes in systolic blood pressure during hemodialysis; 3.) association between percent change in ScvO2 and acute signs and symptoms during hemodialysis; 4.) association between the percent change in SBP and acute signs and symptoms during hemodialysis; and 5.) change in ScvO2 in patients without symptomatic hypotension compared to those with symptomatic hypotension.

Methods: In this prospective observational study, data were collected from adult hemodialysis outpatients with a central line dialysis catheter. ScvO2, blood pressure, blood volume change, total fluid removed and acute signs and symptoms were recorded during one week of consecutive hemodialysis treatments. Descriptive statistics, multi-
level regression and multi-level negative binomial regression models were utilized to analyze data.

**Findings:** Subjects (n=39) were mostly African American (49%) and White (28%) with a mean age of 60 ±17 years. There was a statistically significant linear and quadratic change in ScvO2 during hemodialysis and the change trajectory was significantly greater in those patients with symptomatic hypotension. ScvO2 was significantly associated with SBP and acute signs and symptoms. Acute symptoms associated with hypotension occurred in 38% of patients and 24% of dialysis treatments.

**Conclusion:** ScvO2 may be used by dialysis nurses to guide therapeutic interventions to avoid symptomatic hypotension in the outpatient setting. Further research is warranted to replicate these findings and broaden our understanding of strategies to mitigate hypotensive symptoms.
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CHAPTER 1
INTRODUCTION

There are over 341,000 people in the United States with end-stage renal disease (ESRD) who are dependent on dialysis for survival (United States Renal Data Systems, 2009). Hemodialysis is performed three to four times per week to remove wastes that cannot be excreted due to end-organ kidney disease. Basically, hemodialysis involves exposing patient blood to a semi-permeable membrane to allow wastes and fluid to be removed from the body. The rate of fluid removal is preset by the dialysis prescription and nurses monitor patient responses to fluid removal using blood pressure (BP), heart rate (HR) and subjective complaints. These parameters reflect intravascular hypovolemia and associated end-organ ischemia.

The number of people requiring dialysis continues to increase annually. Between 2005 and 2006, the greatest increase in number of these patients occurred among those age 45 – 64 and 65 – 74, at 6.1, and 3.5 percent respectively (United States Renal Data Systems, 2009). The emergence of the baby boomers into a senior population will contribute to the rapid growth of the overall dialysis population, with projections exceeding 600,000 dialysis dependent patients by the year 2020 (United States Renal Data Systems, 2009).

The most common causes of ESRD are diabetes and hypertension, significantly increasing the risk of cardiovascular complications and mortality (National Kidney Foundation Kidney Early Evaluation Program, 2006). Patients with kidney disease experience symptoms associated with both their comorbid conditions and dialysis treatment. Hemodialysis is associated with physiologic responses and symptoms which
negatively impact patients’ health and quality of life (Al-Arabi, 2006). Consequently, most patients on dialysis are vulnerable to ischemia related to cardiovascular instability and symptomatic hypotension (Santoro, 2006).

Statement of the Problem and Significance

Hypovolemia of the intravascular compartment through ultrafiltration is the most common complication of hemodialysis and results in the occurrence of symptomatic hypotension in 10 to 50 percent of dialysis treatments (Henrich, 1999; Hossie, 2005; Schreiber, 2001). In a survey of 422 registered nurses working in hemodialysis units across the country, more than two-thirds (69%) stated that dialysis hypotension occurs several times a week to daily (Thomas-Hawkins, Flynn, & Clarke, 2008). Symptomatic hypotension during hemodialysis is a well-documented cause of patient discomfort as well as early termination of dialysis therapy (DeOreo, 1997; Rocco & Burkart, 1993). Hypotension that occurs during dialysis treatments can induce cardiac arrhythmias, predispose patients to coronary, splanchnic, and/or cerebral ischemic events, and is associated with end-organ damage and increased mortality (Jakob, Ruokonen, Vuolteenaho, Lampainen, & Takala, 2001; National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2005b; Shoji, Tsubakiha, Fujii, & Imai, 2004).

Recent clinical practice guidelines established by the National Kidney Foundation (2005a) define symptomatic hypotension as a decrease in systolic blood pressure (SBP) of 20 mm Hg or a decrease in mean arterial pressure (MAP) of 10 mm Hg associated with symptoms. These acute symptoms include muscle cramps, nausea, vomiting, dizziness or fainting, abdominal discomfort, yawning, sighing, restlessness, and anxiety (National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2005a). In
addition to these acute symptoms, dialysis patients experience a plethora of chronic, often co-occurring signs and symptoms during and in between dialysis sessions. Common chronic symptoms include fatigue, pain, itching and thirst (Janssen, Spruit, Wouters, & Schols, 2008; Murtagh, Addington-Hall, & Higginson, 2007).

The primary monitoring parameters during dialysis are limited to intermittent BP and HR measurements and the patient’s subjective complaints (National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2005a, 2005b, 2006b). While often used to monitor circulatory competence, changes in BP and HR reflect the later stages of circulatory failure and not the adequacy of the circulation to meet the metabolic demands of the tissues (Cordtz, Olde, Solem, & Ladefoged, 2008; Shoemaker, 1996). The primary purpose of the circulatory system is to deliver oxygen to the tissues to maintain viability, yet the movement and utilization of oxygen in patients experiencing symptomatic hypotension during hemodialysis has not been well investigated. Recent advances in hemodialysis technology allow continuous measurement of blood oxygen saturation during a dialysis session. Monitoring of venous blood oxygen saturation is utilized routinely in critical care as an early indicator of hemodynamic instability, including impending hypotension, but has not been fully explored in patients undergoing outpatient hemodialysis.

Study Aims

The overall aim of this study is to determine whether central venous oxygen saturation (ScvO2) is related to changes in SBP and acute signs and symptoms in outpatients undergoing hemodialysis.
The specific aims of this study are to determine:

1. the change in ScvO2 as fluid is removed during hemodialysis;
2. the relationship between ScvO2 and changes in SBP during hemodialysis;
3. the association between percent change in ScvO2 and acute signs and symptoms during hemodialysis;
4. the association between the percent change in SBP and acute signs and symptoms during hemodialysis;
5. the change in ScvO2 among patients with no symptomatic hypotension compared to those with symptomatic hypotension.
CHAPTER 2
CONCEPTUAL FRAMEWORK AND REVIEW OF LITERATURE

Introduction

The reasons for symptomatic hypotension during hemodialysis are multifactoral, but primarily due to intravascular hypovolemia and decreased cardiac output from too rapid of fluid removal during the dialysis procedure (Daugirdas, 1991). Care of the chronic dialysis patient requires an understanding of the physiologic mechanisms and the various treatment and patient related factors associated with symptomatic hypotension. This chapter will discuss circulatory physiology, oxygen delivery and consumption, the process of hemodialysis and the physiologic responses to hemodialysis related to the dialysis patient. A review of the literature pertaining to ischemic signs and symptoms during hemodialysis will also be presented.

Circulatory Physiology: Basic Concepts of Volume, Pressure, and Flow

The primary role of the circulatory system is the delivery of dissolved gases and other molecules for nutrition, growth, and repair (Boron & Boulpaep, 2005). The normal heart, blood, and vessels are highly integrated and during everyday activities are able to adapt or compensate to meet the oxygen requirements of organs and cells. The body’s ability to compensate, however, may be challenged under conditions of advanced age, physiologic stress such as trauma or illness, and cardiovascular disease.

An understanding of basic circulatory physiology is necessary in order to contextualize what occurs in patients undergoing hemodialysis. The most important characteristics of the circulation are volume, pressure, and flow (Smith & Kampine,
1990). These core concepts are interrelated and provide a foundation for understanding one of the primary functions of the circulation: the movement and utilization of oxygen.

**Volume**

The total blood volume is the sum of formed elements which include red cells, white cells, and platelets, in a liquid medium called plasma. The plasma is the non-cellular part of the blood and communicates continuously with the interstitial fluid through the pores of the capillary membranes. The percentage of the blood that is cells is called the hematocrit. Therefore, if a person has a hematocrit of 40, this means that 40 percent of the blood volume is cells and the remainder is plasma. The cells occupy about 40 percent of the total blood volume and the plasma volume occupies about 60 percent of the total blood volume. These percentages can vary considerably in different people, depending on sex, weight, and other factors (Guyton & Hall, 2000).

In healthy individuals, the plasma volume is maintained by a complex balance between fluid intake and urinary and gastrointestinal output. The total blood volume in a normal adult ranges from 70 to 75 ml / kg of body weight. Therefore, a 70 kg adult has a total blood volume of about 5000 ml with 3000 ml of the total as plasma volume and about 2000 ml as red cell mass (Guyton & Hall, 2000). A person’s total blood volume is not uniformly distributed throughout the body. About two-thirds of the total blood volume is normally in the venous system, about one-sixth is in the arteries, and the remaining is in the heart and pulmonary circulation (Boron & Boulpaep, 2005).
Pressure

Blood pressure is the force exerted by the blood against any unit area of the vessel wall, and is measured in millimeters of mercury (mmHg) (Guyton & Hall, 2000). Vascular tone is maintained by smooth muscle cells and is regulated by a complex balance between the cardiopulmonary and pressoreceptor reflexes, the autonomic and sympathetic nervous systems, and vasoactive hormones such as the renin-angiotensin system (Hollenberg, Kavinsky, & Parrillo, 1999; Sato et al., 2001; Smith & Kampine, 1990; Ushioda et al., 1983).

Because of the structure and relative elasticity of the circulatory system, there is an inverse relationship between volume and pressure in the arteries and veins (Smith & Kampine, 1990). Though the venous system normally contains about four times more blood volume than the arterial system, the internal pressure in the large arteries is normally about 120/80 mm Hg in contrast to 10 mm Hg at the venous end of the capillaries (Smith & Kampine, 1990). All blood vessels contain varying proportions of smooth muscle, elastin, and collagen and the arteries are thicker and have large amounts of elastin as compared to veins. The thicker and elastin rich arteries allow them far greater ability to sustain pressure energy in contrast to the thin-walled venous system.

The difference in the volume/pressure characteristics of arteries and veins have been described as their ‘distensibility’, or the percent increase in volume that is necessary to create a unit pressure change (Guyton & Hall, 2000). The distensibility of the circulatory system is influenced not only by the thickness and composition of the vessel wall, but also by the degree of filling of the vessel. The distensibility of a normal artery is reduced under conditions of high pressure, such as volume overload. Veins on the other hand,
have much lower pressures and much greater distensibility which is why they are able to store 25 to 30 times the volume of the arterial system. Distensibility of the circulatory system is altered by age, disease, autonomic stimulation, and various medications (Boron & Boulpaep, 2005; Smith & Kampine, 1990).

Flow

Blood flow is characterized by the moving stream of blood in the circulation, as the term “flow” is the displacement of volume per unit of time (Boron & Boulpaep, 2005). Blood flow through a vessel is determined by the pressure gradient, or the pressure difference of the blood between the two ends of a vessel, and the vascular resistance within that vessel (Guyton & Hall, 2000). The flow of blood in the vascular system can be calculated by the following formula:

\[ \Delta P = F \times R \]

in which \( \Delta P \) is the pressure difference (gradient) between the two ends of the vessel, \( F \) is blood flow, and \( R \) is the resistance. This calculation is based on Ohm’s law, where the pressure difference (\( \Delta P \)) between an upstream point (P1) and a downstream site (P2) is equal to the product of the flow (F) and the resistance (R) (Figure 2-1).
Normal blood flow delivered by the heart is the quantity of blood that passes a given point in the circulation in a given period of time and is expressed in milliliters per minute or liters per minute (Guyton & Hall, 2000). Blood flow in the circulation of an adult person at rest is about 5000 ml/minute and is called the cardiac output, which is the product of the heart rate times the stroke volume (Guyton & Hall, 2000). Blood flow is dependent not only on the degree of vascular resistance from the vessel diameter, but also the viscosity of the blood (Boron & Boulpaep, 2005).

Viscosity is the resistance to flow due to the friction of molecules in a moving stream of liquid (Boron & Boulpaep, 2005). The viscosity of normal blood is about three times as great as the viscosity of water (Guyton & Hall, 2000). The relative viscosity of whole blood depends on the concentration of cells (hematocrit) in relation to the plasma volume. As red cell volume increases (such as after a blood transfusion) or the plasma volume decreases (such as during dehydration), blood becomes more hemoconcentrated. This
results in an increase in viscosity of the blood and as hematocrit increases, the relative viscosity increases disproportionally. For example, an increase of 10 in the hematocrit from the level of 40 will increase the viscosity about 25% and an increase of 20 to the level of 60 will increase viscosity about 60% (Smith & Kampine, 1990).

Normal Oxygen Delivery and Consumption

Oxygen Delivery

More than 98% of oxygen is transported bound to hemoglobin with less than two percent dissolved in plasma (Boron & Boulpaep, 2005). Hemoglobin is normally present in a concentration of 14 to 15 g/dl of whole blood (Smith & Kampine, 1990). If blood is fully saturated with oxygen (100%), one gram of hemoglobin can combine with 1.34 ml of oxygen so that blood with a hemoglobin concentration of 15 g/dl will then have a maximum oxygen carrying capacity of 20.1 ml / dl (Guyton & Hall, 2000). The amount of oxygen that combines with each unit of hemoglobin is dependent primarily on the partial pressure of oxygen, and to a lesser extent, pH, PC02, blood temperature, or the presence of chronic lung disease (Smith & Kampine, 1990). The normal relationship between oxygen and hemoglobin is best depicted using the hemoglobin-oxygen (Hgb-O2) dissociation curve (Figure 2-2).
The Hgb-O2 dissociation curve represents the “S-shaped” relationship between the hemoglobin saturation (%), the partial pressure of O2 (PO2) (mmHg), and the oxygen content in the blood (ml O2/dl of blood). At low PO2 values, increases in PO2 produce small increases in oxygen saturation and reduced oxygen content in the blood. At moderate PO2 values, the amount of bound oxygen increases more steeply with increases in PO2. Lastly, the curve flattens out at high PO2 values as the hemoglobin saturates even more, maximizing the oxygen content in the blood.

Oxygen delivery to the organs and tissues is determined by several factors, including not only the concentration of Hgb in the blood and its oxygen saturation, but also the cardiac output, and the efficiency with which the O2 is “unloaded” to the tissues. Consequently, despite the presence of a normal PO2, a patient’s O2 delivery may be
inadequate if the patient is anemic, hypovolemic, or has a reduced cardiac output (Dudell, Cornish, & Bartlett, 1990; Guyton & Hall, 2000).

**Oxygen Consumption**

Oxygen is consumed in the tissues to maintain cellular metabolism and energy production and can be measured indirectly by the difference between arterial oxygen content and venous oxygen content (Bauer, Reinhart, & Bauer, 2008). Normally, oxygen delivery is four to five times the oxygen consumption (Dudell et al., 1990), and approximately 20 – 25% of the oxygen delivered is utilized, and the rest remains in the venous blood. If the hemoglobin of the arterial blood is 100% saturated, normal venous hemoglobin saturation will be 75% to 80% saturated.

An abrupt decrease in venous oxygen saturation is caused by a decrease in delivery or an increase in consumption. Tissue oxygenation is determined by a balance between the rate of oxygen transport in the blood to the tissues and the rate at which the oxygen is used by the tissues to meet cellular metabolic demand (Guyton & Hall, 2000). Without evidence of venous oxygen saturation, cardio-respiratory monitoring based solely on the measurement of heart rate, blood pressure, and arterial oxygen saturation alone provides little information on tissue and cellular oxygenation (Bauer et al., 2008).

**Oxygen to Assess Flow**

Oxygen can be used to measure blood flow. In 1870, Fick explored the relationship between cardiac output, global oxygen demand and oxygen extraction and discovered the principle that total uptake or release of any substance by an organ is the product of blood flow to the organ by the difference between the arterial content and the venous content of the substance (Fick’s principle) (Vandam & Fox, 1998). For example, according to the
classic Fick equation, cardiac output equals the oxygen consumption (VO2) divided by the difference between the arterial and venous oxygen content (Mahutte et al., 1994):

$$Q(\text{VO2}) = \frac{\text{VO2}}{13.4\text{Hgb} \cdot (\text{SaO2} – \text{SvO2})}$$

where Q(VO2) denotes cardiac output, VO2 the oxygen consumption, Hgb the hemoglobin, SaO2 the arterial oxygen saturation, and SvO2 the venous oxygen saturation. For the whole body circulation, the input flow is the arterial oxygen delivery to the tissues, and the output flow is measured by the venous oxygen return to the heart (Caille & Squara, 2006).

There is extensive evidence that oxygen is the most flow-dependent blood constituent because it has the largest extraction ratio and the net O2 transported is the amount consumed by the tissues and may be easily and repeatedly measured (Shoemaker, 1987). Oxygen transport is strongly related to survival or death, and therefore circulatory function should be evaluated in terms of oxygen consumption and oxygen delivery. To better understand the physiologic concepts associated with oxygen delivery and consumption during illness, it is important to review the research of cardiac and trauma patients using venous oxygen saturation monitoring.

*Venous Oxygen Saturation Monitoring*

Venous oxygen saturation is the balance between arterial oxygen supply and tissue oxygen demand with a normal value between 60 – 80% (Guyton & Hall, 2000). Venous oxygen saturation decreases when systemic oxygen delivery has been compromised or when systemic oxygen demands increase (Rivers, Ander, & Powell, 2001). Venous
oxygen saturation monitoring or venous oximetry allows for a global assessment of oxygen supply and demand, and is used as a prognostic, diagnostic and therapeutic tool in critically ill patients experiencing sepsis, trauma, hemorrhagic shock, and cardiac dysfunction (Reinhart & Bloos, 2005).

The critical care literature makes reference to mixed venous oxygen saturation and central venous oxygen saturation. The differences between them lie in where these measurements are obtained. Mixed venous oxygen saturation (SvO2) is obtained from the pulmonary artery using a pulmonary artery catheter, necessitating an intensive care environment. Central venous oxygen saturation (ScvO2) is obtained at the junction of the superior vena cava and the right atrium using a central venous catheter, which is widely feasible in most clinical settings. Both provide a measure of oxygen returning to the heart and lungs. The relation between mixed and central venous oxygen saturation in animal and human models has been studied and reviewed extensively (Rivers, Ander et al., 2001). These two indices are highly correlated when viewed serially, with r values ranging from .85 to .99 (Dueck, Klimek, Appenrodt, Weigand, & Boerner, 2005; Goldman, Klughaupt, Metcalf, Spivack, & Harrison, 1968).

A large body of literature has been published regarding the use of both mixed (SvO2) and central (ScvO2) venous oxygen saturation as early indicators of hemodynamic instability in multiple critical care settings. In an early study of patients with myocardial infarction (n=31), Goldman, et al. (1968) demonstrated that as myocardial function deteriorates, ScvO2 falls. In this study, they demonstrated that clinical signs of heart failure were usually present when the ScvO2 was <60% ($p < 0.001$) and that when the ScvO2 was <45%, myocardial dysfunction had progressed to a shock state ($p < 0.001$).
In addition, early research in cardiac surgery demonstrated the usefulness of SvO2 as an early marker of cardiac deterioration (de la Rocha, Edmonds, Williams, Poirier, & Trusler, 1978; Muir, Kirby, King, & Miller, 1970).

Jamieson, et al. (1982) evaluated the usefulness of SvO2 monitoring as an index of cardiac output and overall tissue perfusion in high-risk cardiac surgery patients (n= 20). The results indicated that satisfactory mixed venous oxygen saturation (> 65%) correlated with normal hemodynamic measurements including cardiac output and cardiac index (r > .95), and that a fall in SvO2 of more than 10% was noted before a fall in the mean blood pressure, increase in heart rate, or change in other hemodynamic measures (p < 0.05). Their findings also demonstrated however, that a decrease in measured ScvO2 occurs with fever, pain, shivering, increased work of breathing, and interventions or procedures.

Scalea, et al (1988) investigate the use of multiple hemodynamic parameters to identify the earliest and most reliable indicator of blood loss in the canine model (n=16). Using Swan-Ganz catheters and arterial lines, they collected vital signs and full hemodynamic parameters including arterial and mixed venous blood gases. After bleeding the dogs in increments of 3% of their total blood volume, only cardiac index and SvO2 showed linearity as a function of measured blood loss (r = .85, and .99 respectively).

Scalea, et al (1990) then investigated trauma patients (n=26) with an injury mechanism suggesting blood loss, but who were deemed stable after initial evaluation. They found that ScvO2 was more reliable and sensitive to acute blood loss than blood pressure, pulse, pulse pressure, urine output, and central venous pressure (r = 0.436, p <
0.005). The linear coefficients were considerably less for all parameters in the clinical study as opposed to the laboratory model due to the lack of a controlled environment in the trauma setting. Despite this, the investigators found that a decrease in ScvO2 reliably predicted blood loss and severity of injuries.

Rady, et al. (1996) found that 50% of critically ill patients presenting in shock who were resuscitated to normal vital signs continued to have increased lactate and abnormally low ScvO2, indicating anaerobic metabolism and oxygen debt. These patients required further interventions, giving rise to the clinical use of ScvO2 in the early management of cardiac arrest, the postresuscitation period, trauma and hemorrhage, severe heart failure, severe sepsis and septic shock (Rivers, Ander et al., 2001).

These studies are limited by sample size and generalizable only to cardiac and trauma patients. Despite this, however, these findings raise the question of whether venous oximetry would be a useful monitoring tool in complex dialysis patients experiencing large fluid shifts during the dialysis procedure. Of interest is whether ScvO2 monitoring in the dialysis patient could be used to identify physiologic changes that could then be acted upon by nursing staff to prevent symptomatic hypotension.

*The Process of Hemodialysis and the Dialysis Patient*

The Process of Hemodialysis

Hemodialysis is a substitute process for the filtering functions of the kidney and involves the movement of solutes (waste products) and water across a semi-permeable membrane by diffusion and osmosis (Ahmad, 1999). Clinically, this exchange takes place by exposing the patient’s blood to an artificial membrane outside of the body called an “artificial kidney” or dialyzer. Every dialyzer contains two compartments: the blood
compartment and the dialysate compartment. The semi-permeable membrane, made up of thousands of hollow fibers, separates the two compartments. Water molecules and low molecular weight solutes can pass through the membrane pores, but larger solutes (such as proteins) cannot pass through the semi-permeable membrane (Bregman, Daugirdas, & Ing, 2001). The membrane is enclosed in a plastic case that holds the dialyzer together and provides pathways for blood and dialysate to flow in and out of the dialyzer.

Dialysis allows the removal of waste products such as potassium and urea as well as water from the blood. Water is removed through a process called ultrafiltration, and is expressed in ml/hour, or L/hour. Ultrafiltration is the movement of water molecules across a semi-permeable membrane caused by a pressure gradient between the blood and dialysate compartments of an artificial dialyzer (Ahmad, 1999). These pressure gradients are the result of hydrostatic or mechanical pressure, where water molecules are forced through the membrane, or an osmotic pressure, where water moves through a membrane to equalize a concentration gradient.

Ultrafiltration removes water accumulated by ingestion of food and fluids during the interdialytic period. Fluid removal through ultrafiltration can only take place after accessing the patient’s vascular space using dialysis needles or a central catheter. As water volume is removed from the vascular space during ultrafiltration, excess fluid from the tissues shifts from the tissues into the vascular space. This fluid shift is called plasma refilling and is a compensatory response to reductions in plasma volume (Daugirdas, 2001; Schroeder, Sallustio, & Ross, 2004). The ultrafiltration rate needs to be considered with several other patient related factors including advanced age, the presence of cardiovascular disease and/or diabetes, anemia, the patient’s nutritional state, use of
antihypertensive medications, and volume status. These factors also affect the body’s ability to compensate during conditions of volume loss during hemodialysis.

The Dialysis Patient

Patients with end-stage renal disease often have several comorbid conditions including diabetes, hypertension, and/or cardiovascular disease (United States Renal Data Systems, 2008). The consequences of undergoing hemodialysis therapy in the face of these pathophysiologic conditions are far greater than in those patients without comorbidities, as their compensatory responses are inhibited or altogether absent (Bregman et al., 2001). Dialysis-induced hypotension can be explained by no single mechanism, however, the primary factors are hypovolemia resulting in inadequate cardiac filling and cardiac output as well as a defect in the patient’s ability to regulate vascular tone (Daugirdas, 1991).

The blood volume of a typical dialysis patient is approximately 4.5 to 5 liters, with a corresponding plasma volume of approximately 3 liters (Leypoldt, Cheung, Steuer, Harris, & Conis, 1995). With a patient undergoing three-times-a-week dialysis schedules and gaining approximately 1.5 liters per day, the typical therapeutic requirement would be to remove 3 L of fluid per dialysis treatment which is the equivalent of an entire plasma volume (Daugirdas, 2001). When this amount of volume is removed over the course of a few hours, the body attempts to compensate in order to maintain blood volume, pressure and flow. The amount of fluid removed, in the absence of compensatory mechanisms, is the primary treatment related factor associated with the outcome of symptomatic hypotension (Bregman et al., 2001).
Physiologic Responses to Hemodialysis Related to Volume, Pressure, and Flow

Plasma Refilling to Maintain Volume

Plasma refilling is the movement of fluid from the interstitial to the intravascular space and is the initial compensatory mechanism to increase intravascular volume as water is removed during hemodialysis (Daugirdas, 2001). The refilling rate depends on the ultrafiltration rate of the dialysis machine versus the patient’s state of hydration, plasma sodium levels, total protein balance, and capillary permeability (Akcahuseyin et al., 2000; Aukland & Reed, 1993; Bregman et al., 2001; Schneditz et al., 1992). It is not uncommon for the ultrafiltration rate to exceed the plasma refilling rate. For example, both a high fluid gain and a short treatment time result in more aggressive ultrafiltration, creating an imbalance between the rate of fluid removal and the rate of plasma refilling (Bregman et al., 2001). This imbalance contributes to symptomatic hypotension.

Dialysate sodium concentration is an important factor for plasma refill, as a high dialysate sodium will increase the plasma sodium concentration (Passauer, Bussemaker, & Gross, 1998). High plasma sodium creates an osmotic gradient from plasma to the interstitial compartment that improves refill. The plasma refilling rate is also higher in patients with increased plasma protein concentrations, which translates into increased oncotic pressures (Daugirdas, 1991). The amount and rate of plasma refilling is patient specific and regulated by the Starling principles of hydrostatic, osmotic, and oncotic pressure gradients between the capillary and the interstitial space (Guyton & Hall, 2000; Santoro, 2006).
Peripheral Vascular Resistance to Maintain Pressure

Arterial and venous tone of the circulatory system is highly variable in dialysis patients who are older than 65 years of age, have cardiovascular disease, autonomic dysfunction, and/or take medication for hypertension such as nifedipine, diltiazem, hydrochlorothiazide, and clonidine (Cavalcanti et al., 1997; Chesterton & McIntyre, 2005; Flynn, 1996; Kooman et al., 1992; Sato et al., 2001). A decrease in peripheral vascular resistance has been shown to be an important cause of dialysis hypotension; however the mechanisms behind this phenomenon remain controversial (Chaignon, Chen, Tarazi, Nakamoto, & Bravo, 1981; Daugirdas, 2001).

As people age, the arterial walls are infiltrated with less distensible fibrous tissue, which increases their stiffness and decreases their ability to constrict (Smith & Kampine, 1990). The inability of the peripheral vascular system to constrict as a result of autonomic dysfunction occurs in more than half of patients on dialysis and is a significant contributor to symptomatic hypotension (Dumler & McCullough, 2004). Because most of the blood volume resides in the veins, skin and splanchnic organ systems (spleen, liver and pancreas), a decrease in vascular resistance (regardless of the mechanism) during episodes of hypovolemia results in reduced cardiac filling and a decrease in cardiac output (Daugirdas, 2001; Guyton & Hall, 2000).

Cardiac Output to Maintain Flow

Decreased cardiac output plays a central role in the development of symptomatic hypotension. Cardiac output can be reduced from a decrease in blood volume, decreased vascular resistance, and / or cardiac dysfunction (Bos et al., 2000). A reduction in blood
volume decreases the filling pressure of the circulation and, as a consequence, decreases venous return to the heart resulting in a fall in cardiac output (Guyton & Hall, 2000).

Changes in heart rate in response to hypovolemia are often impaired in dialysis patients as a result of medications and/or a blunted sympathetic response (Barnas, Boer, & Koomans, 1999). A number of electrolyte changes that occur during dialysis (decrease in serum potassium, increase in serum bicarbonate, and changes in serum ionized calcium) affect cardiac contractility (Daugirdas, 2001). Echocardiographic studies have shown that the majority of ESRD patients (74%) have left ventricular hypertrophy as a consequence of long-term volume overload (Foley et al., 1998). The resulting diastolic dysfunction has a significant impact on maintaining cardiac output under conditions of decreased filling, such as during excessive ultrafiltration (Ruffmann, Mandelbaum, Bommer, Schmidli, & Ritz, 1990). A hypertrophied ventricle is stiff and requires a higher filling pressure to maintain output during dialysis than a more compliant, nonhypertrophied ventricle.

**Oxygen Delivery and Consumption During Hemodialysis**

Early research demonstrated a fall in the partial pressure of oxygen in arterial blood (PaO2) during dialysis ranging from 5 – 35 mm Hg (Nissenson, Kraut, & Shinaberger, 1984). Several investigators have since confirmed the occurrence of hypoxia during the hemodialysis procedure (Cardoso et al., 1988; Kishimoto et al., 1993; Nielsen, Jensen, Hegbrant, Brinkenfeldt, & Thunedborg, 1995a). Dhakal, et al. (1997) found that oxygen saturation less than 85% can occur up to 30 minutes post-hemodialysis. The actual mechanisms of hypoxemia during dialysis are multifactoral and include pulmonary leukostasis, chronic pulmonary fibrosis, and alveolar hypoventilation due to carbon
dioxide loss through the dialyzer (De Broe & De Backer, 1989; Dhondt et al., 2000; Herrero et al., 2002). Other factors include sleep apnea syndrome, congestive heart failure, pulmonary edema, and COPD (Kosmadakis & Medcalf, 2008). A decrease in PaO2 may be of little importance in patients with normal resting oxygenation, but could be deleterious in anemic hemodialysis patients and those with cardiopulmonary disease.

Healthy individuals are able to maintain their hemoglobin between 14 – 15 gm / dl. Dialysis patients with end-stage kidney disease suffer from anemia as a result of insufficient production of erythropoietin (EPO), a hormone normally produced by the kidney to stimulate red blood cell production. Synthetic replacement of this hormone is readily available and nephrology clinical practice guidelines recommend a dosing matrix to maintain hemoglobin levels between 10 to 12 gm/dl (National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2006a). This equates to an ‘oxygen capacity’ of only 13.4 to 16.1 ml / dl if their blood was 100% saturated, which is over 20% less capacity than a healthy individual.

The problem of anemia is compounded by the comorbid conditions that accompany a diagnosis of end-stage renal disease. The defects in the circulatory dynamics of volume, pressure, and flow brought on by the process of dialysis with ultrafiltration, in addition to patient comorbidities, impact the functional aspect of the circulation which is oxygen delivery. Oxygen delivery represents only one side of a patients overall oxygen status and does not reflect whether it is sufficient to meet cellular oxygen demand. The utilization or consumption of oxygen during hemodialysis should also be considered.

Oxygen consumption has not been measured directly during symptomatic hypotension in routine outpatient hemodialysis; however, hypotension in this population has been
shown to cause cardiac, splanchnic, and/or cerebral ischemia (Daugirdas, 2001; Jakob et al., 2001; Shoji et al., 2004). Ischemia is the reversible cellular injury that occurs when tissue demand for oxygen exceeds the supply and when toxic metabolites accumulate (West & Pelter, 2003). When the body’s compensatory mechanisms are defective and unable to maintain homeostasis during rapid volume loss in the course of hemodialysis, an imbalance between oxygen delivery and consumption can ensue, resulting in ischemia and ischemic symptoms.

Ischemia During Hemodialysis

Cardiac Ischemia

Left ventricular hypertrophy and coronary artery disease make dialysis patients vulnerable to myocardial ischemic events (Parfrey et al., 1996). In addition, there is substantial evidence that the process of dialysis itself can reduce myocardial blood flow (Dasselaar et al., 2009), and induce myocardial ischemia as measured by ST depression, even in the absence of atherosclerosis (Conlon, Krucoff, Minda, Schumm, & Schwab, 1998; Mohi-ud-din, Bali, Banerjee, Sakhuja, & Jha, 2005; Narula, Jha, Bali, Sakhuja, & Sapru, 2000; Selby & McIntyre, 2007).

Hypovolemia during hemodialysis has been shown to trigger cardiac events in already vulnerable HD patients, including muscle damage, heart failure, and cardiac arrhythmias (Bos et al., 2000). Additionally, hypovolemia that occurs from volume loss during dialysis results in an increase in blood viscosity from the increase in red blood cell concentration in the remaining blood, exacerbating vascular resistance and the sluggishness of blood flow (Guyton & Hall, 2000; Secher & Van Lieshout, 2005).
Splanchnic Ischemia

Splanchnic organ systems include the spleen, liver, pancreas, and the intestines. Acute hypovolemia causes a sustained reduction of splanchnic blood flow and as a compensatory response, splanchnic blood volume decreases during hemodialysis ultrafiltration (Edouard et al., 1994; Yu et al., 1997). Vasoconstriction of the mesenteric vessels can occur during the physiologic stress caused by dialysis-induced hypotension resulting in what is termed non-occlusive mesenteric ischemia (NOMI) (Wilcox, Howard, Plaskon, Unthank, & Madura, 1995).

Non-occlusive mesenteric ischemia (NOMI) is a life threatening condition found in dialysis patients who have experienced dialysis-induced hypotension, with mortality rates of 71% to 100% (John, Tuerff, & Kerstein, 2000; Valentine, Whelan, & Meyers, 1990). Mesenteric ischemia has typically been associated with arterial emboli or venous thrombosis, however, vasoconstriction during rapid volume loss during dialysis sessions was found to be an inciting factor (Wilcox et al., 1995). More importantly, Jakob, et al (2001) examined regional blood flows and oxygen transport during acute hemodialysis in critically ill patients (n=9) and found an acute decrease in stroke volume and splanchnic blood flow during hemodialysis, despite normal blood pressures. In addition, volume loss from ultrafiltration with or without hypotension has been found to be a trigger of non-occlusive mesenteric ischemia (Zeier, Wiesel, Rambausek, & Ritz, 1995).

Cerebral Ischemia

Hemodialysis patients are at high risk for cognitive deficits due to their older age and high prevalence of stroke and cardiovascular risk factors (Murray et al., 2006). Cerebrovascular disease has been strongly implicated in ESRD and it is unknown
whether dialysis treatment improves or exacerbates these defects. Previous literature suggests the possibility of deleterious hemodialysis effects on cognition (Gilli & De Bastiani, 1983), stroke (Iseki & Fukiyma, 2000), and cerebral atrophy (Kamata et al., 2000), however, little is known about the mechanism associated with these defects.

In order to understand the cerebrovascular effects of hemodialysis, Prohovnik et al. (2007) investigated the circulatory pathophysiology of ten subjects with ESRD undergoing hemodialysis, and six control subjects. These subjects underwent magnetic resonance imaging (MRI) measurements of cerebral atrophy and cerebral blood flow, carotid Doppler studies, and cerebral oxygen saturation (rSO2) studies. All measurements were conducted pre- and post hemodialysis. Dialysis patients showed significant cerebral atrophy associated with longer hemodialysis duration and cognitive deficits, and their cerebral oxygenation was extremely low before dialysis (rSO2 41 ± 13, compared with 70 ± 2 in controls, \( p < 0.02 \)) and improved only slightly after dialysis. Carotid blood flow was also very low at the start of dialysis (115 ± 28 ml/sec, versus 193 ± 56 in controls, \( p < 0.005 \)) but normalized at the end of the session (181 ml/sec).

This study is limited by a small sample size; however, their findings are important. Coupled with other vascular risk factors, and the low cerebral oxygenation levels observed in this study, ESRD patients undergoing hemodialysis appear to be particularly vulnerable to cerebrovascular defects. Further study to determine cerebral oxygenation during an episode of symptomatic hypotension is warranted.

Ischemic effects are seen across body systems of dialysis patients including the heart, gut and brain. Ischemic events suggest there is a need for monitoring of oxygen saturation in this population. Monitoring patients for ischemia in the outpatient setting
currently is limited to intermittent blood pressure measurements and assessing for the presence of signs and symptoms. It is important to understand the symptom experience of dialysis patients, specifically in the context of fluid removal and hypotension during the hemodialysis treatment.

Signs and Symptoms During Hemodialysis

Early Studies of Symptoms Associated with Hemodialysis

The first patient started hemodialysis therapy for chronic renal failure at the University of Washington Hospital in Seattle in March 1960 (Blagg, 2007). Clinical developments following the introduction of the Teflon shunt by Scribner and Quinton lead to better understanding of the signs and symptoms and complications of dialysis. Uremic signs and symptoms including anorexia, nausea, vomiting, headache, in addition to muscle cramps, hypotension and hypertension were very common and severe when patients began treatment (Rosa, Fryd, & Kjellstrand, 1980).

In 1980, one of the first studies was published that described the frequency of six dialysis-related symptoms. The study described when a patient’s condition became “stable” on dialysis (Rosa et al., 1980). Forty consecutive dialysis treatments in 21 adults who began long-term dialysis were reviewed and the mean frequency of all symptoms was 1.2 symptoms per patient per dialysis.

Three signs and symptoms, hypotension, nausea, and muscle cramps, stabilized after 13 dialysis treatments (approximately one month). Stability was defined as the patient having less than the mean frequency of symptoms for the entire 40 dialyses (<1.2 symptoms per dialysis). Hypertension and vomiting stabilized after 17 and 20 dialyses, respectively. Headache showed little variation per dialysis. Although a patient’s
condition became “stable”, they were by no means free of symptoms. For example, hypotension appeared during every other dialysis. Muscle cramps or vomiting occurred every 15th to 25th dialysis. These problems occurred despite the patients being well dialyzed.

This was the first long-term study to evaluate actual frequency of symptoms over time. This study demonstrated three important findings that guide our thinking about symptoms and hemodialysis today. First, uremic symptoms and response to dialysis therapy should be evaluated in new dialysis patients after the first month on therapy. Second, once patients are stabilized on hemodialysis, at least one symptom will occur on average during each dialysis. Third, long-term hemodialysis is a procedure with considerable morbidity and discomfort for the patient.

Prevalence of Acute Signs and Symptoms During Hemodialysis

During dialysis, patients experience physical signs and symptoms caused by anemia, osmolality and electrolyte changes, and excessive ultrafiltration (Abuelo, 1993). Symptomatic hypotension and the associated ischemic effects result from rapid intravascular volume depletion coupled with inadequate cardiac reserve, defects in patients’ vascular response, various medications and/or hypoxemia (Daugirdas, 2001; Latos, 1996). Inadequate compensatory cardiovascular responses due to these factors impair dialysis patients’ ability to maintain blood pressure in the face of reduced blood volume (Daugirdas, 1991; Henrich, 1999).

Hypovolemia can be manifested by hypotension, muscle cramps, nausea, vomiting, yawning, anxiety, lightheadedness, syncope, and seizures (Abuelo, 1993). These signs and symptoms can create fear, anxiety, and discomfort for many patients and result in
missed treatments or early termination from a dialysis session. In one study, the most common reasons for early termination of a dialysis treatment were cramping (17.9%), followed by ‘feels bad or sick’ (14.2%) (Rocco & Burkart, 1993). In another study, over one-half of the early terminations were the result of problems that could be directly or indirectly related to the dialysis process, such as cramping, low blood pressure, and “feeling bad” (Parker, 1993). The effect of early sign-offs on the delivery of a dialysis treatment can contribute to under-dialysis and lead to chronic volume overload, hypertension, and cardiac compromise (Kobrin & Berns, 2007).

During hemodialysis, the partial pressure of oxygen in the arterial blood drops by 5 – 30 mm Hg., the etiology of which is not fully understood (Bregman et al., 2001). Hypoxemia can be deleterious in patients with preexisting pulmonary or cardiac disease, and contribute to hemodynamic instability and cardiac arrhythmias during hemodialysis (Ahmad, 1999; Dagurdas, Blake, & Ing, 2001; Huang et al., 1998). Acute signs and symptoms have been associated with hypoxemia, including chest pain, hypotension, nausea and dizziness (Bregman et al., 2001; Sloane, Coeytaux, Beck, & Dallara, 2001).

Research to evaluate the effectiveness of various dialysis methods, clinical interventions or pharmacologic agents in dialysis patients often use acute signs and symptoms as evaluation endpoints. Patients with large decreases in blood volume are more likely to experience symptomatic hypotension during dialysis and as a result, intervention studies that are based on changes in or preservation of blood volume dominate the literature (Bogaard, de Vries, & de Vries, 1994; Jain, Smith, Brewer, & Goldstein, 2001; Steuer, Leypoldt, Cheung, Senekjian, & Conis, 1996). Unfortunately, the primary focus in most studies is on the occurrence of hypotension alone. Studies that
report the related signs and symptoms are limited and typically only report the presence or absence of particular symptoms.

Abuelo, Shemin, and Chazan (1993) examined the occurrence of specific signs and symptoms during chronic outpatient hemodialysis treatments in six studies between 1980 and 1990. The findings are shown in Table 2-1. The table lists the frequency of signs and symptoms both as a percentage of dialysis treatments and as a percentage of patients experiencing the symptoms over a period of time. Hypotension, muscle cramps, and nausea affect a majority of patients.
Table 2-1. Frequency of signs and symptoms during chronic hemodialysis 1980 – 1990 (adapted from Abuelo, 1993).

<table>
<thead>
<tr>
<th></th>
<th>Percent of Treatments</th>
<th>Range</th>
<th>Percent of Patients</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>48</td>
<td>22</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Cramps</td>
<td>4</td>
<td>20</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>12</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Tired/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of</td>
<td>21</td>
<td>2518</td>
<td>147</td>
<td>531</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of</td>
<td>850</td>
<td>135321</td>
<td>26502</td>
<td>22554</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Data in Table 2-2 show the occurrence of specific signs and symptoms during chronic outpatient hemodialysis in eight studies between 1996 and 2007. These studies were either intervention or observational studies to examine the use of blood volume monitoring and/or sodium or ultrafiltration profiling as a strategy to prevent symptomatic hypotension. Four studies investigated the use of blood volume monitoring (Agarwal, Kelley, & Light, 2008; Andrulli et al., 2002; Barth et al., 2003; Steuer et al., 1996), and four studies examined the use of sodium and ultrafiltration profiling (Donauer, Kolblin, Bek, Krause, & Bohler, 2000; Meira, Poli de Figueiredo, & Figueiredo, 2007; Oliver, Edwards, & Churchill, 2001; Tang et al., 2006). Table 2-2 shows the frequency of signs and symptoms both as a percentage of dialysis treatments and as a percentage of patients affected over a period of time (one week to six months). Note that not all of the studies evaluated both the percent of hemodialysis treatments and the percent of patients, however, the data are consistent with what others have reported (Bregman et al., 2001; Henning, 2006).

Though the number of studies that measure the occurrence of signs and symptoms is limited and the occurrence of symptoms is highly variable, the percent of patients experiencing acute symptoms appears to have decreased over the past 20 years. Despite this decrease, a significant number of patients continue to suffer from hypotension, muscle cramps, nausea, and dizziness. Further work in this area is warranted to evaluate the timing, severity and distress of the acute symptom experience of dialysis patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Percent of Treatments</th>
<th>Range</th>
<th>Percent of Patients</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 \textsuperscript{*}</td>
<td>2</td>
<td>3</td>
<td>4 \textsuperscript{*}</td>
</tr>
<tr>
<td>Hypotension</td>
<td>13.3</td>
<td>20</td>
<td>66.8</td>
<td>42.3</td>
</tr>
<tr>
<td>Cramps</td>
<td>20</td>
<td>7</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>7.4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>8.2</td>
</tr>
<tr>
<td>Lightheaded</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>4.7</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Tired/Fatigue</td>
<td>6.4</td>
<td>6.4</td>
<td>6.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td># of Patients</td>
<td>5</td>
<td>53</td>
<td>32</td>
<td>60</td>
</tr>
<tr>
<td># of Treatments</td>
<td>106</td>
<td>188</td>
<td>369</td>
<td>585</td>
</tr>
<tr>
<td>Type of Study</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Patients were identified \textit{apriori} as hypotensive prone. \#\#Number, I=Intervention Study, O=Observational Study 1. (Steuer et al., 1996); 2. (Donauer et al., 2000); 3. (Oliver et al., 2001); 4. (Barth et al., 2003); 5. (Meira et al., 2007); 6. (Agarwal et al., 2008); 7. (Andrulli et al., 2002); 8. (Tang et al., 2006).
Hypotension

Hypotension affects 26 to 47% of patients undergoing chronic hemodialysis and is based on five studies of 13 to 150 hemodialysis patients as shown in Table 2-2. The variation in frequency may be attributed to discrepancies in definitions and outcome descriptors. For example, the literature makes reference to outcomes such as dialysis-induced hypotension, hypotensive events, symptomatic hypotension, intradialytic morbid events (IME’s) and dialysis-associated morbidities (DAM) (Andrulli et al., 2002; Barth et al., 2003; Jain et al., 2001; Oliver et al., 2001).

A hypotensive event has been defined using a specific blood pressure, specific symptoms, or both blood pressure and symptoms. In one study, symptomatic hypotension was defined as a reduction in blood pressure associated with “reactions of the patient prompting nursing intervention, such as placing the patient in Trendelenburg’s position, reducing the ultrafiltration rate, or infusing intravenous fluids” (Donauer et al., 2000, p. 118). Oliver, Edwards, & Churchill (2001) defined hypotension as an “event”, i.e., a systolic BP less than 100 mmHg, or the presence of dizziness, cramps, nausea, and/or headache.

Andrulli et al. (2002) defined symptomatic hypotension as a reduction in systolic blood pressure of 30 mm Hg or more associated with hypotensive symptoms requiring an intervention. Tang et al. (2006) defined a hypotensive episode as an abrupt decrease in systolic blood pressure to lower than 100 mm Hg or diastolic blood pressure to lower than 60 mm Hg. Others defined their outcome measure as a drop in systolic blood pressure to less than 100 mm Hg. (Steuer, Germain, Leypoldt, & Cheung, 1998), a drop in systolic blood pressure to less than 90 mm Hg, or a mean arterial pressure of <70 for
greater than 5 min (Tonelli et al., 2002), with or without symptoms. Still other researchers describe intra-dialytic morbid events (IME), or dialysis-associated morbidities (DAM) documented by any nursing intervention in response to hypotension or the patient’s subjective complaints (Barth et al., 2003; Beige, 2000; Jain et al., 2001).

The variability of definitions of hypotension makes comparing the results of intervention studies difficult. Because the symptom experience is what affects treatment adherence, the key outcome descriptor should include the presence or absence of symptoms. The National Kidney Foundation (2005a) defines symptomatic hypotension as a decrease in blood pressure associated with the presence of a symptom. In clinical practice, symptomatic hypotension is often uniquely patient specific and may be defined differently depending on the patient.

The management of symptomatic hypotension is focused on early detection, measures to support or restore blood pressure, and prevention. Early detection is limited to close monitoring of intermittent blood pressures measurements and making patients aware of the signs and symptoms of hypotension that should be reported to the clinical staff. The most common measures to restore blood pressure include placing the patient flat or in the Trendelenberg position, reducing or stopping the ultrafiltration rate of the dialysis machine and administering volume replacement with intravenous normal saline (Bregman et al., 2001).

Muscle Cramps

Muscle cramps remain a common morbidity during hemodialysis and occur in up to 55% of patients (Table 2-2). This is based on three studies of 13 to 150 hemodialysis patients (Agarwal et al., 2008; Andrulli et al., 2002; Tang et al., 2006). According to
Rocco & Burkart (1993), the most frequent reason for discontinuation of hemodialysis treatments prematurely was muscle cramps. Muscle cramps are painful, sometimes palpable, involuntary skeletal muscle contractions that occur during hemodialysis (McGee, 1990; Miller & Layzer, 2005). They are sometimes preceded by hypotension and generally involve the gastrocnemius muscle and the small muscles of the foot (Hung, Chen, Chen, Yang, & Peng, 2009). Muscle cramps during dialysis can last seconds to minutes, and may recur for several hours after the end of dialysis (Abuelo, 1993; Mujais, 1994).

Electromyographic (EMG) measurements in cramp-prone subjects during dialysis show a progressive increase in tonic activity during the second half of hemodialysis (McGee, 1990), however, recent evidence suggests that cramps arise from spontaneous discharges of the motor nerves rather than from within the muscle itself (Miller & Layzer, 2005). The rapid reduction in peripheral blood volume during hemodialysis has generally been accepted to be the cause of muscle cramps (Mujais, 1994; Shulman, Heidenheim, Kianfar, Shulman, & Lindsay, 2001). This is supported by the common observation that volume expansion with hypertonic solutions often brings relief; however, tissue hypoxia, carnitine deficiency, and most recently a uremic toxin, leptin have been implicated (Bellinghieri et al., 1983; McGee, 1990). The exact mechanism of muscle cramps is still not fully understood.

The management of muscle cramps remains a challenge. Immediate treatment includes stretching of the affected muscles, application of heat to the muscle group, and volume expansion with intravenous normal saline (Robbins, 2006). Numerous pharmacologic and physical measures have been tried with variable success rates.
Several studies revealed that slowing plasma volume reduction by intravenous infusion of hypertonic solutions of dextrose, mannitol, and saline effectively relieved hemodialysis-associated cramps (Abuelo, 1993; Canzanello et al., 1991). An increase of the dialysate sodium concentration has also been shown to decrease the frequency of cramps; however, these interventions have also been shown to increase thirst and interdialytic weight gain resulting in volume overload and hypertension (Meira et al., 2007; Tang et al., 2006).

Quinine sulfate was once the most widely recommended drug for the treatment of cramps. Quinine sulfate decreases the excitability of the muscle cell from nerve stimulation and increases the muscle refractory period (Abuelo, 1993). In 1994, however, the Food and Drug Administration (FDA) banned the over-the-counter formulations of quinine sulfate and subsequently recommended against its use for cramps due to the health problems associated with its use (Miller & Layzer, 2005). Current research has focused on the prevention of muscle cramps through various technologies that preserve central blood volume, including blood volume monitoring, biofeedback, and cool dialysate (Donauer & Bohler, 2003; Selby, Lambie, Camici, Baker, & McIntyre, 2006). Until the exact mechanism or mechanisms that cause muscle cramps are fully understood, symptom management efforts will continue to remain a priority.

**Nausea and Vomiting**

Acute nausea is a common symptom that occurs in up to 19% of patients during episodes of dialysis-induced hypotension (Table 2-2). The symptom of nausea is a subjective phenomenon of an unpleasant sensation centered in the throat or epigastrum, usually described as a conscious awareness of the need to vomit (Steele & Carlson, 2007). Vomiting is the forceful expulsion of the contents of the stomach through the oral
or nasal cavity (Rhodes & McDaniel, 2003). Nausea and vomiting are a symptom and a sign that frequently accompany each other; however, some patients will experience nausea without vomiting, while others will only feel nauseated immediately before vomiting (Thompson, 2004).

The pathophysiology of nausea is poorly understood. The mechanisms leading to vomiting are complex and result from an intricate succession of neurophysiologic events. The two main areas of the brain involved in vomiting are the emetic center, located in the medulla, and the chemoreceptor trigger zone (CTZ), located in the fourth ventrical (Steele & Carlson, 2007). Afferent input to the emetic center is received from four sources: (1) the cerebral cortex pathway, which is stimulated by learned associations; (2) the chemoreceptor trigger zone (CTZ), which is sensitive to chemical stimuli from the cerebrospinal fluid and blood; (3) the vestibular apparatus or pathway, which activates the emetic center through body positional changes; and (4) the peripheral pathway, which is activated by neurotransmitter receptors found in the GI tract, where the vagus nerve communicates with the emetic center (Rhodes & McDaniel, 2003).

Metabolic conditions like uremia initiate the vomiting reflex through stimulation of the chemoreceptor trigger zone (Steele & Carlson, 2007). Nausea and vomiting during dialysis-induced hypotension may occur through the peripheral pathway as a result of ischemia to the gut or through the chemoreceptor trigger zone as a result of ischemia to the central nervous system, or a combination of both. Conditions such as acute hypovolemia and hypoxia also affect the emetic center and the chemoreceptor trigger zone through an increase in sympathetic nervous system activity and catecholamine release, a potent afferent stimulus (Guyton & Hall, 2000). The process of vomiting
occurs when efferent signals are sent from the emetic center to the salivation center, abdominal muscles, respiratory center, and cranial nerves (Rhodes & McDaniel, 2003).

The onset of nausea during hemodialysis is often abrupt, leaving little time for intervention prior to vomiting. Nursing management focuses on prevention, early detection, or measures to support or restore blood volume. Measures to restore blood volume include Trendelenberg position, decreasing the ultrafiltration rate on the dialysis machine, and volume replacement with 100 ml or more of normal saline solution (Robbins, 2006).

Dizziness

The symptom of “dizziness” is common during hemodialysis and it is most frequently associated with dialysis-induced hypotension (Steuer et al., 1996). In one study, “dizziness” occurred in 15% of the patients (Table 2-2). Because of the subjective nature of dizziness, researchers have sub-classified this phenomenon into four descriptive categories which include: vertigo – a false sensation of movement of self or environment, or spinning; presyncope – sensations of light-headedness and impending fainting; disequilibrium – a sensation of imbalance and / or postural instability; and “other types of dizziness” – a vague and floating sensation often accompanied by somatic symptoms (Chawla & Olshaker, 2006; Drachman & Hart, 1972; Sloane et al., 2001).

Dizziness is often described somewhat differently by each patient. Patients and clinicians often use the term “lightheadedness” for dizziness and visa versa. The key feature of lightheadedness is that the sensations are fairly mild. Based on the above definitions, presyncope may be a more appropriate descriptor that best describes the sensations that patients describe during dialysis-induced hypotension. The onset is
abrupt, and the associated signs and symptoms include a buzzing sensation in the head, constriction of the visual field, pallor, diaphoresis, and nausea (Derebery, 1999).

In the context of dialysis-induced hypotension, dizziness is due to cerebral anoxia from poor blood flow to the central nervous system (Chawla & Olshaker, 2006). The severity of the patient’s symptoms depends on the magnitude of the blood flow reduction experienced by the brain (Derebery, 1999). Dizziness is also exacerbated by anemia (Chawla & Olshaker, 2006). As with the other acute symptoms, nursing management focuses on prevention, early detection, and measures to support or restore blood volume.

Summary

Hypotension is the most common hemodynamic complication that patients experience while undergoing life-sustaining hemodialysis therapy. The fundamental dynamics of the circulatory system include volume, pressure, and flow, for the purpose of oxygen delivery to the tissues. Each of these dynamics is affected by the patient’s kidney disease, comorbid conditions and the dialysis treatment. Care of the chronic dialysis patient requires an understanding of normal circulatory physiology in the context of oxygen delivery and consumption, the pathophysiologic effects of end-stage renal disease that affect the patient and dialysis treatment, and the symptom experience of patients undergoing hemodialysis. Monitoring hemodynamic parameters during the dialysis procedure that more directly reflect a mismatch in oxygen supply and demand would be valuable in this patient population.
CHAPTER 3
METHODS

Study Design

This prospective observational cohort study was undertaken to determine whether continuous ScvO2 monitoring as measured by the Crit-Line III™ is related to changes in SBP and acute signs and symptoms in outpatients undergoing chronic hemodialysis.

Sample and Setting

The study included participants ≥ 18 years of age who were able to read and speak English and receiving hemodialysis through a central venous dialysis catheter. Participants were recruited from three hospital-based outpatient dialysis clinics in Northern California following approval from the University of California San Francisco and clinic Institutional Review Boards. Power analysis was conducted a priori using Optimal Design Software Version 2.0 (New York, NY). The primary outcome variable of interest for this exploratory study was the change in ScvO2 over dialysis time among individuals. A sample size of 72 subjects was estimated based on an alpha (α) of 0.05, β of 0.2 and power (1 – β) of 0.8, with an intraclass correlation coefficient of .4 and a medium effect size of .5. Target sample size was set at 80 to allow for attrition of approximately 10% due to illness or death, leaving complete data on 72 subjects.

Study Variables and Measures

The variables of interest included blood pressure, pulse, blood volume change, central venous oxygen saturation (ScvO2), peripheral arterial oxygen saturation (PsaO2), total
fluid removed and signs and symptoms. The study variables and their associated instruments are described in Table 3-1.

Table 3-1. Study variables and their associated instruments.

<table>
<thead>
<tr>
<th>Variable/Measure</th>
<th>Instrument/Source</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent Systolic and Diastolic Blood Pressure (mm Hg) &amp; Pulse (beats/min)</td>
<td>Fresenius 2000K dialysis machine built-in blood pressure module (Fresenius Medical Care, Homburg, Germany).</td>
<td>Continuous</td>
</tr>
<tr>
<td>Blood Volume Change (BV) (%)</td>
<td>Crit-Line III™ (CLMIII) (HemaMetrics, Inc., Kayesville, UT)</td>
<td>Continuous</td>
</tr>
<tr>
<td>Continuous Central Venous Oxygen Saturation (ScvO2) (%)</td>
<td>Crit-Line III™ (CLMIII) (HemaMetrics, Inc., Kayesville, UT)</td>
<td>Continuous</td>
</tr>
<tr>
<td>Intermittent Peripheral Arterial Oxygen Saturation (PsaO2) (%)</td>
<td>PulseOx 5500 Finger Unit (SPO Medical, Simi Valley California)</td>
<td>Continuous</td>
</tr>
<tr>
<td>Total Fluid Removed (liters)</td>
<td>Fresenius 2000K dialysis machine (Fresenius Medical Care, Homburg, Germany).</td>
<td>Continuous</td>
</tr>
<tr>
<td>Acute Signs and Symptoms</td>
<td>Acute Symptom Data Collection Form</td>
<td>Count Data/ Likert Scale</td>
</tr>
<tr>
<td>-Timing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Distress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic Data-</td>
<td>Outpatient chart</td>
<td>Nominal/ Continuous</td>
</tr>
<tr>
<td>-Gender, age, number of comorbidities, length of time on dialysis (months), pre-HD hemoglobin and hematocrit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Blood Pressure and Pulse: Blood pressure and pulse were measured using the automated built-in blood pressure modules of the Fresenius 2000K dialysis machine (Fresenius Medical Care, Homburg, Germany). Accuracy and repeatability has been established by the manufacturer according to the specifications and standards set forth by the Association for the Advancement of Medical Instrumentation (AAMI) (O'Brien & Atkins, 1994). Symptomatic hypotension is operationally defined as a decrease in systolic blood pressure of 20 mm Hg or a decrease in mean arterial pressure of 10 mm Hg associated with symptoms. These symptoms can include: muscle cramps, nausea, vomiting, dizziness or fainting, abdominal discomfort, yawning, sighing, restlessness, and anxiety. This definition is based on the current clinical practice guidelines established by the National Kidney Foundation (National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2005b).

Blood Volume Change (%): Changes in the patient’s blood volume were measured using a blood volume monitor called the Crit-Line III™ (CLMIII) (HemaMetrics, Inc., Kayesville, UT). The CLMIII™ continuously monitors absolute hematocrit, blood volume change, and oxygen saturation (Appendix A). An optical sensor attaches to the blood line of the extracorporeal circuit during hemodialysis. As fluid is removed by ultrafiltration, the blood density increases as intravascular volume decreases. A graphic presentation delineating time on the x axis and percent blood volume change on the y axis shows the percent change in blood volume throughout the dialysis treatment, providing the clinician with a visual guide to intravascular fluid removal (Appendix B). The relative blood volume change is expressed as the percent change from the start of the dialysis treatment and is calculated by changes in hematocrit.
A hematocrit (HCT) is defined in the following formula as the percentage of red blood cells (RCV) to the total blood volume (BV) inside the vascular space (Guyton & Hall, 2000):

$$HCT(\%) = \frac{RCV}{BV} \times 100$$

As fluid is removed, the plasma volume of the intravascular space is reduced. Because red blood cells are too large to pass through the dialyzer membrane, the red blood cell mass remains constant during dialysis; therefore, the changes in blood volume are inversely proportional to the changes in hematocrit (Steuer, Leypoldt, Cheung, Harris, & Conis, 1994). In other words, during the course of ultrafiltration during hemodialysis, the hematocrit increases, and the amount of increase reflects the degree of reduction in plasma volume. Conversely, once ultrafiltration ceases, the rapid refilling of the blood compartment from surrounding hydrated tissue spaces (plasma refilling) will decrease the hematocrit. The relative change in blood volume (%) is calculated as follows (Leypoldt et al., 1995):

$$\frac{\text{Starting Hct}}{\text{Observed Hct}} - 1 \times 100$$

The CLMIII™ is calibrated to the reference standard for hematocrit determination, the Coulter Counter (CC Hct) (Coulter Electronics, Hialeah, Florida)(Hemametrics, 2003). The specification by the manufacturer report hematocrit accuracy between 10 to 60 ± 1 Hct (Hemametrics, 1998).

**Central Venous Oxygen Saturation (ScvO2):** ScvO2 was continuously recorded using the Crit-Line III™. The level of oxygen saturation as determined by the Crit-Line III
Monitor™ is measured by detecting the different absorption characteristics of hemoglobin in its oxygenated and deoxygenated forms using multiple wavelengths of light (Hemametrics, 1998). The CLMIII™ is calibrated using the IL-482 CO-Oximeter as the reference standard. The specification by the manufacturer reports the accuracy of oxygen saturation to be between 55 to 100 ± 2 percent for patients with a hematocrit ≥ 18. The accuracy of oxygen saturation between 10 and 45 percent is unspecified (Hemametrics, 1998). The accuracy of an earlier version of CLM, the CLMIIR, was evaluated by Steuer, et al. (1995) both in-vitro and in-vivo using the IL-282 CO-Oximeter (Instrumentation Laboratory, Inc., Lexington, MA) as the reference standard. Linear regression analysis showed similar results (In-vitro: $r = .99$, standard error = 1.87; In-vivo: $r = .99$, standard error = 1.78), indicating construct validity of the instrument.

Peripheral Arterial Oxygen Saturation (PsaO2): PsaO2 was measured using the PulseOx 550 Finger Unit (SPO Medical, Simi Valley, California). The PulseOx 550 is an FDA approved portable pulse oximeter that is utilized in a variety of clinical settings.

Total Fluid Removed: Total fluid removed was measured by the Fresenius 2000K dialysis machine per manufacturer specifications (Fresenius Medical Care, Homburg, Germany).

Acute Signs and Symptoms: Symptoms are defined as the subjective experience of physical, emotional or cognitive changes as experienced by patients, whereas a sign is defined as any abnormality indicative of disease that is detectable by the individual or others (Dodd et al., 2001). Acute signs and symptoms were identified through ongoing observation and the intermittent questioning of patients at 30 minute intervals and when
the patient reported symptoms. All intradialytic subjective complaints were recorded by
the PI using an Acute Symptom Data Collection form to document symptom description,
timing, severity and level of distress (APPENDIX C). Acute symptoms were
documented as described by patients including start and stop time, concurrent blood
pressure, pulse, % blood volume change, central venous oxygen saturation and relevant
dialysis machine parameters per clinic protocol. Nursing interventions to treat the
symptom(s) were also recorded. Approximately 20 minutes after resolution of the
symptom, patients were asked to describe the severity of their symptom on a scale from 1
– 3 (1 = Mild, 2 = Moderate, 3 = Severe). At the conclusion of a symptomatic dialysis
session, patients were reoriented to the symptom(s) they previously described, then asked
to rate their level of symptom distress or bother on a scale from 0 – 4 (0 = not at all
bothered, 1 = a little bit bothered, 2 = somewhat bothered, 3 = quite a bit bothered, 4 =
very much bothered).

Demographic Data: All relevant data were recorded from the patient’s outpatient record.
Relevant data included gender, age, number of comorbidities, length of time on dialysis
in months, and the most recent pre-dialysis hemoglobin and hematocrit.

Data Collection Procedure

One week prior to the initiation of the study, all clinic staff were oriented to the study
aims and procedures. The clinic charge nurse or manager identified potential study
participants based on the inclusion criteria. During their routinely scheduled dialysis
time, each potential study participant was approached first by clinic staff to ascertain if
there was interest in hearing about a dialysis study. All assenting subjects then met
individually with the PI. The study was reviewed and written informed consent was
obtained for those patients who were willing to participate. Each subject received a copy of the signed consent form as well as the Experimental Subject’s Bill of Rights.

The following week, CLM III™ monitors were placed with each participating subject’s dialysis machine. Sterile blood chamber devices were inserted into the blood circuit pre-dialysis by the PI. Routine hemodialysis was performed by clinic staff as prescribed by the patient’s nephrologist. In order to minimize intervention bias, CLM III™ monitor screens were covered and the clinic staff was blind to the changes in blood volume and central venous oxygen saturation.

All physiologic measurements and subjective complaints were recorded every 30 minutes. Additional measurements triggered manually by the clinic staff during hypotensive/symptomatic events were also recorded. All research data were collected by the PI. At the end of the dialysis session, CLM III™ data was downloaded and hard copies were printed for further analysis. Data collection occurred over the course of one week or three to four dialysis sessions per patient as prescribed by their nephrologist.

Demographic data including the presence or absence of co-morbid conditions, length of time on dialysis and lab work (complete blood count and renal panel) from that calendar month were extracted from the medical record. All patient identifying information was removed and all study subjects were assigned a study subject ID.

Data Analysis

All data were analyzed using SPSS® version 16.0 (SPSS, Inc., Chicago, IL) and STATA™ version 11.1 (StataCorp, TX). Descriptive statistics were generated to characterize baseline demographic and clinical characteristics, physiologic variables, and symptom variables. Differences by Clinic and Symptom Status were examined and
reported within the context of the study aims. A *p*-value of <0.05 was considered statistically significant. Data analysis for each of the aims was conducted as follows:

**Aims 1: To determine the change in central venous oxygen saturation as fluid is removed during outpatient hemodialysis.**

The data set includes subjects who underwent anywhere from one to four dialysis sessions and a varied number of data collection points per dialysis session due to treatment length and/or the presence or absence of symptoms. For example, a single four-hour dialysis session in which the patient presented no symptoms contributed approximately eight data time points. If a patient presented with one or more symptoms, multiple measures were recorded during the symptom event and then resuming with every 30-minute measures. Multi-level regression analysis (Singer & Willett, 2003) was utilized in this analysis because it allows for repeated measures at time points that are variably spaced with a varied number of measurement occasions and inclusion of cases where some data was missing.

ScvO2 was regressed on the two main effects of time, treatment time (every 30 minutes) and treatment day (Day 1, Day 2, Day 3, Day 4). The analysis included an interaction term between time and day. Dialysis treatment time was scaled so that the first measurement occasion was labeled Time 0. A random coefficients model for the analysis was specified by including both random intercepts and slopes for both time and day. The specification for the covariance matrix for the random intercepts and slopes was “unstructured” and estimation was obtained with restricted maximum likelihood due to small sample size. The AIC statistic was used to evaluate model improvement for fixed as well as random effects. Pairwise contrasts were also conducted to examine differences between clinics.
Aim 2: To determine the relationship between central venous oxygen saturation and changes in systolic blood pressure during hemodialysis.

Multi-level regression analysis (Singer & Willett, 2003) was also utilized to model the repeated measures relationship between ScvO2 on SBP over treatment time (Time 30) and treatment day (Day 1, Day 2, Day 3, Day 4). The analysis included SBP as both a fixed predictor at baseline across treatment days (grand mean centered) and as a time varying covariate.

Aim 3: To determine the association between percent change in central venous oxygen saturation and acute signs and symptoms during hemodialysis.

The percent change in ScvO2 over dialysis treatment time was evaluated in relation to the presence or absence of acute signs and symptoms. The percent change in ScvO2 was calculated by taking the first measure at the start of dialysis to the 30-minute measure before the end of treatment or the presence of a symptom. This time interval was considered to represent the period of maximal hypovolemia (Cordtz et al., 2008). For those subjects who demonstrated more than one symptom during a treatment session, the 30-minute measure associated with the greatest percent change was considered to represent the time period of maximum hypovolemia.

The sum of all measurement occasions (Time 30) was calculated to use as a weighting variable and the presence or absence of acute symptoms (Yes/No) by measurement occasion were summed by treatment day. In contrast to the number of measurement occasions, the occurrence of acute symptoms was infrequent and positively skewed, so a regression method that did not assume normality of count data was warranted. However, these data have overdispersion, meaning that the variance is greater than the mean. Multi-level negative binomial regression with a natural log link was utilized to
accommodate overdispersion, skewed symptom count data and the varied number of measurement occasions among subjects. Random effects and restricted maximum likelihood estimation was utilized due to sample size.

Aim 4: To determine the association between the percent change in systolic blood pressure and acute signs and symptoms during hemodialysis.

The percent change in SBP over dialysis treatment time was calculated and evaluated in relation to acute signs and symptoms count data using multi-level negative binomial regression as in Aim 3.

Aim 5: To determine the change in central venous oxygen saturation among patients with symptomatic hypotension compared to those with no symptomatic hypotension.

Any patient who experienced at least one symptom associated with hypotension over the course of the week was identified and coded 1 = Prone. Patients who experienced no symptomatic hypotension over the course of the week were identified and coded 0 = Not Prone. The change in ScvO2 was regressed over treatment time as in Aim 1 in relation to the symptom status of the patient (Prone/Not Prone). Univariate logistic regression of symptom status was used to find relevant predictors of demographic and clinical characteristics.
CHAPTER 4

RESULTS

Sample Characteristics

A total of 39 of 45 patients that were screened were enrolled in three clinical sites (Clinics 1, 2, and 3). Six patients refused participation. Recruitment of additional patients was precluded due to unanticipated changes taking place in local dialysis clinics. The study sample consisted of 21 men and 18 women with a mean age of 60 ± 17 years. Nineteen patients were African American, 11 White, four Asian, four Pacific Islander, and one multiple race.

Table 4-1 shows the demographic and clinical characteristics of the sample by clinic. Throughout the text, tables show data by clinic as well as mean value for the sample in order to provide complete data. All patients had at least one comorbidity. The mean number of co-morbid conditions was 3.2 (range 1-7). Most reported hypertension (95%), diabetes (56%) and cardiovascular disease (56%). Some had respiratory disease (23%), gastrointestinal disease (23%) and cerebrovascular disease (13%). About one-third reported other diseases including hepatitis, HIV, sickle cell, and pancreatitis. The length of time on hemodialysis ranged from three months to 12 years. Forty-six percent of patients were on dialysis for ≤ one year, 25% between two to five years, 13% five to ten years, and 16% > 10 years.

During the study, 113 dialysis sessions were monitored. The number of dialysis treatments monitored per patient ranged from one to four. One patient (2.6%) was monitored for only one session due to an unanticipated hospital admission, four patients (10.3%) were monitored for two sessions due to schedule non-adherence, 32 patients
(82%) were monitored for three sessions, and two patients (5.1%) were monitored for four sessions.

The mean duration of the sessions was 198 ±23 minutes, ranging from 3 to 4 hours.

The number of data collection time points during the study collection period ranged from 8 to 34 for a total of 891 data collection points. The mean dry weight was 77.3 ±21 and the pre-dialysis mean hemoglobin of the sample was 11.0 ±1.3 gm/dl. The study protocol did not alter either the ultrafiltration volume or the duration of treatment.

Table 4-1. Baseline Demographic and Clinical Characteristics. Values are expressed as mean (SD), except gender, months on HD, and Number of Dialysis Treatments. HD = hemodialysis.

<table>
<thead>
<tr>
<th>Gender (M/F)</th>
<th>Clinic 1 (n=12)</th>
<th>Clinic 2 (n=14)</th>
<th>Clinic 3 (n=13)</th>
<th>TOTAL (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 / 8</td>
<td>8 / 6</td>
<td>9 / 4</td>
<td>21 / 18</td>
</tr>
<tr>
<td>Age</td>
<td>60.3 (19.9)</td>
<td>66.6 (13.9)</td>
<td>53.9 (16.4)</td>
<td>60.4 (17.2)</td>
</tr>
<tr>
<td># of Comorbidities</td>
<td>2.9 (1.08)</td>
<td>3.2 (1.37)</td>
<td>3.5 (1.71)</td>
<td>3.2 (1.40)</td>
</tr>
<tr>
<td>Months on HD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>28.4</td>
<td>37.1</td>
<td>57.5</td>
<td>41</td>
</tr>
<tr>
<td>Median (range)</td>
<td>14 (4 – 98)</td>
<td>16 (3 – 137)</td>
<td>60 (3 – 144)</td>
<td>16.5 (3 – 144)</td>
</tr>
<tr>
<td>Number of Dialysis Treatments</td>
<td>35</td>
<td>40</td>
<td>38</td>
<td>113</td>
</tr>
<tr>
<td>Duration of Treatment (min)</td>
<td>196 (20)</td>
<td>198 (28)</td>
<td>201 (21)</td>
<td>198 (23)</td>
</tr>
<tr>
<td>Dry Weight</td>
<td>73.8 (20.4)</td>
<td>83.4 (25.0)</td>
<td>73.9 (16.3)</td>
<td>77.3 (21.0)</td>
</tr>
<tr>
<td>Pre-HD Hemoglobin (g/dl)</td>
<td>11.2 (1.23)</td>
<td>10.9 (1.45)</td>
<td>11.0 (1.30)</td>
<td>11.0 (1.31)</td>
</tr>
</tbody>
</table>
Physiologic Variables of Interest

Physiologic Measures at Treatment Start

Data from the start (Time 0) of all treatment sessions are presented in Table 4-2. The mean SBP was 140 mm Hg ±30 and DBP was 73 mm Hg ±18. The mean pulse was 75 ±14 beats/minute. The mean ScvO2 at treatment start was 61 ±10 percent and the PsaO2 was 97 ±2 percent.

Table 4-2. Mean (SD) Physiologic Measures at Treatment Start: SBP=Systolic blood pressure, DBP=Diastolic blood pressure, Pulse, ScvO2=central venous oxygen saturation; SaO2=peripheral arterial oxygen saturation.

<table>
<thead>
<tr>
<th></th>
<th>Clinic 1  (n=12)</th>
<th>Clinic 2  (n=14)</th>
<th>Clinic 3  (n=13)</th>
<th>TOTAL  (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>128.0 (33.1)</td>
<td>141.7 (29.5)</td>
<td>148.2 (25.5)</td>
<td>140 (30)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>63.5 (16.6)</td>
<td>73.3 (16.2)</td>
<td>82.7 (15.2)</td>
<td>73 (18)</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>71.5 (14.9)</td>
<td>74.1 (12.9)</td>
<td>78.6 (13.9)</td>
<td>75 (14)</td>
</tr>
<tr>
<td>ScvO2 (%)</td>
<td>64.0 (7.6)</td>
<td>59.9 (13.1)</td>
<td>58.3 (7.6)</td>
<td>61 (10)</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>96.6 (2.8)</td>
<td>96.7 (2.6)</td>
<td>97.1 (1.5)</td>
<td>97 (2)</td>
</tr>
</tbody>
</table>

Total Fluid Removed and Percent Change in Physiologic Variables

Data showing the total fluid removed and the percent change in physiologic variables to the point of maximum hypovolemia are shown in Table 4-3. The mean fluid removed per dialysis session was 2.8 ± 1.1 liters, with a mean reduction in SBP of 16.5 ±17.5 percent or approximately 23 mm Hg. The change in pulse over the course of dialysis increased 3.5 ±16.7 percent or approximately 3 beats per minute, and a reduction in blood volume of 8.2 ± 4.6 percent, and a reduction in mean ScvO2 of 5.8 ±18.0 percent or 3.5 points.
Table 4-3. Mean Change in Physiologic Variables During Dialysis: Mean (SD) Total Fluid Removed (L). Mean (SD) values of calculated percent change SBP, Pulse, BV change and ScvO2. Percent change was calculated from the first measurement to the last 30 minutes of treatment or the presence of a symptom. This interval was considered to represent the time of maximum hypovolemia. SBP=systolic blood pressure; BV=blood volume; ScvO2=central venous oxygen saturation.

<table>
<thead>
<tr>
<th></th>
<th>Clinic 1</th>
<th>Clinic 2</th>
<th>Clinic 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Fluid Removed</td>
<td>2.9 (1.0)</td>
<td>2.8 (1.0)</td>
<td>2.7 (1.3)</td>
<td>2.8 (1.1)</td>
</tr>
<tr>
<td>liters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP Change %</td>
<td>-17.4 (20.6)</td>
<td>-12.5 (14.7)</td>
<td>-19.9 (16.6)</td>
<td>-16.5 (17.5)</td>
</tr>
<tr>
<td>Pulse Change %</td>
<td>-9.9 (18.2)</td>
<td>-1.8 (16.3)</td>
<td>0.71 (13.9)</td>
<td>3.5 (16.7)</td>
</tr>
<tr>
<td>BV Change %</td>
<td>-9.5 (4.1)</td>
<td>-6.4 (4.0)</td>
<td>-8.7 (5.2)</td>
<td>-8.2 (4.6)</td>
</tr>
<tr>
<td>ScvO2 Change %</td>
<td>-8.2 (10.2)</td>
<td>1.4 (17.8)</td>
<td>-11.0 (21.6)</td>
<td>-5.8 (18.0)</td>
</tr>
<tr>
<td>Median</td>
<td>-7.8</td>
<td>.000</td>
<td>-7.4</td>
<td>-3.9</td>
</tr>
</tbody>
</table>

_Hypotensive Events Associated With Symptoms_

There were 12 episodes with a drop in SBP of > 20 mm Hg associated with symptoms, however, there were 17 episodes with a gradual decline in SBP to < 100 mm Hg associated with symptoms, for a total of 31 hypovolemic events associated with symptoms. There were two episodes in which the blood pressure fell so low that the monitor was unable to detect a reading during the event and a normal measurement was recorded after the symptomatic event was resolved through nursing intervention, i.e., placing the patient flat, normal saline infusion. The majority of symptomatic events followed a gradual decline versus a sudden drop in SBP. The signs and symptoms included muscle cramps, dizziness, syncope, yawning, nausea, and diaphoresis.
**Acute Signs and Symptoms**

As shown in Table 4-4, there were 27 of 113 dialysis sessions (23.9%) in which patients had one or more signs or symptoms for a total of 35 symptom events. Twenty-one patients had no symptoms, 18 patients had one or more acute symptoms but 15 patients had symptoms consistent with hypovolemia during dialysis. Three patients arrived to the dialysis clinic complaining of shortness of breath and one patient also experienced chills and fever. Thirteen patients had one symptom, three patients had two symptoms, and two patients had three symptoms. The most common signs and symptoms were cramps (42.9%), dizziness (28.5%), shortness of breath (SOB) (8.6%), syncope (5.7%), yawning (5.7%), nausea (2.9%), feeling “tired and sweaty” (2.9%) and chills (2.9%).
Table 4-4. Symptom Frequencies: Number of treatments, number of patients, treatments with symptoms and number and type of symptom over the course of one week of dialysis. *Symptom present on admission to HD clinic. #:Number, Tx=Treatment

<table>
<thead>
<tr>
<th></th>
<th>Clinic 1 (n=12)</th>
<th>Clinic 2 (n=14)</th>
<th>Clinic 3 (n=13)</th>
<th>Total (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of dialysis</td>
<td>35</td>
<td>40</td>
<td>38</td>
<td>113</td>
</tr>
<tr>
<td>treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of treatments with one or more symptoms</td>
<td>8 (22.9%)</td>
<td>7 (17.5%)</td>
<td>12 (31.6%)</td>
<td>27 (23.9%)</td>
</tr>
<tr>
<td>Number of symptom events</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>Number of patients:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>1 Symptom</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>2 Symptoms</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3 Symptoms</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>SYMPTOMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cramps</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>15 (42.9%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>10 (28.5%)</td>
</tr>
<tr>
<td>Shortness of breath*</td>
<td></td>
<td>3</td>
<td></td>
<td>3 (8.6%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td>Yawning</td>
<td>2</td>
<td></td>
<td></td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>1</td>
<td></td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>“Tired/Sweaty”</td>
<td></td>
<td></td>
<td>1</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Chills*</td>
<td></td>
<td></td>
<td>1</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>

Timing, Severity and Distress of Acute Symptoms

As shown in Table 4-5, the majority of symptom events occurred on the first day of the patient’s treatment week (43.6%) followed by day three (30.6%) and day two (18.4%). Of the 35 symptom events, 11.4% occurred during the first hour, 2.8% occurred during the second hour, 54.3% occurred during the third hour, and 31.4% occurred during the fourth hour of dialysis. Within 20-minutes of experiencing an acute symptom, patients were asked to describe the severity of their symptom experience:
1 = “Mild”, 2 = “Moderate” and 3 = “Severe”. Most patients describe their symptom severity as moderate (42.8%) or severe (37.1%) and fewer as mild (20%).

Table 4-5. Timing, Severity and Distress of Acute Symptoms

<table>
<thead>
<tr>
<th>TIMING</th>
<th>Clinic 1 (n=12)</th>
<th>Clinic 2 (n=14)</th>
<th>Clinic 3 (n=13)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom Event by Day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 (39 Txs)</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>17 (43.6%)</td>
</tr>
<tr>
<td>Day 2 (38 Txs)</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>7 (18.4%)</td>
</tr>
<tr>
<td>Day 3 (36 Txs)</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>11 (30.6 %)</td>
</tr>
<tr>
<td><strong>Symptom Event by hour in Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 60 minutes</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4 (11.4%)</td>
</tr>
<tr>
<td>61- 120 minutes</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (2.8%)</td>
</tr>
<tr>
<td>121 – 180 minutes</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>19 (54.3%)</td>
</tr>
<tr>
<td>&gt; 180 minutes</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>11 (31.4%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEVERITY by Event</th>
<th>Clinic 1 (n=12)</th>
<th>Clinic 2 (n=14)</th>
<th>Clinic 3 (n=13)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>15 (42.8%)</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>13 (37.1%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DISTRESS by Treatment</th>
<th>Clinic 1 (n=12)</th>
<th>Clinic 2 (n=14)</th>
<th>Clinic 3 (n=13)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not bothered</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>A little bit</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>Somewhat</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Quite a bit</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Very much</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>8</td>
<td>7</td>
<td>12</td>
<td>27</td>
</tr>
</tbody>
</table>

Patients who identified one or more symptoms during their dialysis session were asked to describe how much their symptom experience bothered them during their dialysis treatment: 0 = “Not at all bothered”, 1 = “A little bit bothered”, 2 = “Somewhat bothered”, 3 = “Quite a bit bothered”, 4 = “Very much bothered”. The majority of patients described being bothered “somewhat” (25.9%) or “quite a bit” (25.9%) while
fewer (14.8%) described being bothered very much. Some patients stated that their symptoms bothered them a little bit (22.2%) or not at all (11.1%).

**Aim 1: To determine the change in central venous oxygen saturation as fluid is removed during outpatient hemodialysis.**

Central venous oxygen saturation was examined over time during each hemodialysis treatment and across treatment day over the period of one week. The distribution for ScvO2 was reasonably normal except for a few outlier measurements. These outliers were examined and found to be valid and included in the analysis.

Data showed a significant quadratic effect for time during treatment session \( (t_{773} = -3.7, p = .00) \), and no significant effect for ScvO2 by day or a day by treatment interaction \( (t_{31} = .39, ns; t_{770} = 1.82, ns) \), meaning that the quadratic effect observed for treatment session did not differ across the days. As can be seen in Table 4-6, for each additional 30 minutes of dialysis, the coefficient for quadratic change in ScvO2 is -.14, meaning that for the sample as a whole, the ScvO2 decreases .14 percent every 30 minutes. The positive linear trajectory of ScvO2 was not significant.

Table 4-6. Parameter Estimates: ScvO2 regressed on dialysis time30 and day.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>60.275483</td>
<td>1.859623</td>
<td>38.619</td>
<td>32.413</td>
<td>.000</td>
<td>56.512854 - 64.038111</td>
</tr>
<tr>
<td>Day</td>
<td>.184855</td>
<td>.477666</td>
<td>30.966</td>
<td>.387</td>
<td>.701</td>
<td>-.789394 - 1.159105</td>
</tr>
<tr>
<td>time30</td>
<td>.497865</td>
<td>.291006</td>
<td>305.636</td>
<td>.701</td>
<td>.088</td>
<td>-.074763 - 1.070493</td>
</tr>
<tr>
<td>time30 * time30</td>
<td>-.138042</td>
<td>.037140</td>
<td>773.352</td>
<td>3.717</td>
<td>.000</td>
<td>-.210949 - .065134</td>
</tr>
</tbody>
</table>

a. Dependent Variable: ScvO2 Central Venous Sat.
Additional models were explored and there was some indication that the linear slope for Scvo2 changed across days but it was not significant, therefore the more parsimonious model is described. As expected, ScvO2 varied among patients. As shown in Table 4-7, the variance component for intercepts and slopes differed significantly from zero, indicating that ScvO2 did vary among individuals as well as in their amount of change over time during dialysis.

Table 4-7. Variance Components: ScvO2 regressed on time30 and day

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Wald Z</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Residual</td>
<td>21.849182</td>
<td>1.134292</td>
<td>19.262</td>
<td>.000</td>
<td>19.735375</td>
</tr>
<tr>
<td>Intercept + Day + time30 [subject = ID]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>123.261922</td>
<td>30.680858</td>
<td>4.018</td>
<td>.000</td>
<td>75.676066</td>
</tr>
<tr>
<td>Slope Covariance for Day</td>
<td>6.988171</td>
<td>2.190393</td>
<td>3.190</td>
<td>.001</td>
<td>3.780597</td>
</tr>
<tr>
<td>Covariance between Random Slopes for Time30 and Intercept</td>
<td>-2.400435</td>
<td>1.988401</td>
<td>-1.207</td>
<td>.227</td>
<td>-6.297630</td>
</tr>
<tr>
<td>Covariance between Random Slope for Day and Time30 Intercept</td>
<td>.145419</td>
<td>.487696</td>
<td>.298</td>
<td>.766</td>
<td>-.810447</td>
</tr>
<tr>
<td>Slope Covariance for Time30</td>
<td>.784254</td>
<td>.232287</td>
<td>3.376</td>
<td>.001</td>
<td>.438875</td>
</tr>
</tbody>
</table>

a. Dependent Variable: ScVO2 Central Venous Sat.
A plot of predicted values ScvO2 on time and day (Figure 4-1) show that there is a slight increase in ScvO2 during the first hour of dialysis, and then a gradual decline over the remaining 2 – 3 hours of a dialysis session. The variation around the predicted plot is due to the fact that the plot is collapsed across treatment days.

Figure 4-1. Plot of Predicted Values: ScvO2 regressed on time

ScvO2 Change Over Time by Clinic

Multi-level modeling of ScvO2 change trajectories over treatment time and day was conducted by clinic. A random coefficients model was specified for the analysis by including both random intercepts and slopes for both day and time. The specification for the covariance matrix for the random intercepts and slopes was “unstructured” and estimation was obtained with restricted maximum likelihood due to small sample size.
Clinics 1, 2, and 3 were dummy coded and pairwise contrasts were analyzed to evaluate differences in ScvO2 change trajectories by clinic.

The data showed a significant quadratic effect for ScvO2 over time during treatment session for Clinics 1 and 3 (data not shown). Data for Clinic 2 showed both a significant linear and quadratic effect for ScvO2 over time during treatment session (linear $t_{122} = 3.0$, $p = .003$; quadratic $t_{775} = -3.66$, $p = .000$). For the sake of parsimony, the model showing Clinic 2 as the reference clinic is displayed in Table 4-8. The parameter estimates for linear and quadratic change in ScvO2 for Clinic 2 indicate that for every 30 minutes of dialysis time, ScvO2 increases 1 percent and then decreases .14 percent.

Table 4-8. Parameter Estimates: ScvO2 on time30 and day by clinic with clinic 2 as the reference clinic

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>59.168364</td>
<td>2.696148</td>
<td>41.697</td>
<td>21.946</td>
<td>.006</td>
<td></td>
<td>53.726147</td>
<td>64.610582</td>
</tr>
<tr>
<td>Day</td>
<td>.190509</td>
<td>.474950</td>
<td>30.869</td>
<td>.401</td>
<td>.691</td>
<td></td>
<td>-.778326</td>
<td>1.159343</td>
</tr>
<tr>
<td>time30</td>
<td>1.050377</td>
<td>.345282</td>
<td>122.209</td>
<td>3.042</td>
<td>.003</td>
<td></td>
<td>.366868</td>
<td>1.733885</td>
</tr>
<tr>
<td>time30sq</td>
<td>-.135639</td>
<td>.037085</td>
<td>775.066</td>
<td>-3.657</td>
<td>.000</td>
<td></td>
<td>-.208438</td>
<td>-.062839</td>
</tr>
<tr>
<td>dclinic1</td>
<td>4.873178</td>
<td>3.722820</td>
<td>36.343</td>
<td>1.309</td>
<td>.199</td>
<td></td>
<td>-2.674578</td>
<td>12.420934</td>
</tr>
<tr>
<td>dclinic3</td>
<td>-1.112260</td>
<td>3.631813</td>
<td>35.889</td>
<td>-.306</td>
<td>.761</td>
<td></td>
<td>-8.478707</td>
<td>6.254187</td>
</tr>
<tr>
<td>time30 * dclinic1</td>
<td>-.805726</td>
<td>.370729</td>
<td>36.251</td>
<td>-2.173</td>
<td>.036</td>
<td></td>
<td>-1.557418</td>
<td>-.054034</td>
</tr>
<tr>
<td>time30 * dclinic3</td>
<td>-.962377</td>
<td>.359148</td>
<td>35.137</td>
<td>-2.680</td>
<td>.011</td>
<td></td>
<td>-1.691385</td>
<td>-.233369</td>
</tr>
<tr>
<td>a. Dependent Variable: Central Venous Sat.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pairwise contrasts showed that Clinic 2 was significantly different than Clinics 1 & 3 in that the amount of linear change in Clinics 1 & 3 was more negative than in Clinic 2. As compared to Clinic 2, for each additional 30 minutes of dialysis time, Clinics 1 had a
.8 percent greater decline in ScvO2 and Clinic 3 had a 1.0 percent greater decline in ScvO2 across treatment sessions. As shown in Table 4-9, the variance components for intercepts and slopes for patients in clinic 2 differed significantly from zero, indicating that ScvO2 did vary among individuals at baseline and in their amount of change over time during dialysis.

Table 4-9. Variance Components: ScvO2 on time30 and day, by clinic.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Wald Z</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercepts &amp; slopes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept Variance</td>
<td>113.206834</td>
<td>29.409683</td>
<td>3.849</td>
<td>.000</td>
<td>(68.036413, 188.366595)</td>
</tr>
<tr>
<td>Covariance for Day Slope</td>
<td>6.883745</td>
<td>2.165152</td>
<td>3.179</td>
<td>.001</td>
<td>(3.716168, 12.751291)</td>
</tr>
<tr>
<td>Covariance between Random Slopes for Time30 and Intercept</td>
<td>-1.812472</td>
<td>1.833006</td>
<td>-.989</td>
<td>.323</td>
<td>(-5.405097, 1.780153)</td>
</tr>
<tr>
<td>Covariance between Random Slopes for Day and Time30 Slope Intercept</td>
<td>-1.174708</td>
<td>1.111356</td>
<td>-.366</td>
<td>.715</td>
<td>(-1.111356, .762120)</td>
</tr>
<tr>
<td>Covariance for Time30 Slope</td>
<td>1.554457</td>
<td>0.206469</td>
<td>3.170</td>
<td>.002</td>
<td>(0.352650, 1.214650)</td>
</tr>
</tbody>
</table>

a. Dependent Variable: Central Venous Sat.

A plot of predicted values of ScvO2 on treatment time (Figure 4-2) displays the significant quadratic change trajectory for Clinics 1 and 3 and the significant linear and quadratic change trajectory for Clinic 2. The variation around the predicted plot is due to the fact that the plot is collapsed across treatment days.
Aim 2: To determine the relationship between central venous oxygen saturation and changes in systolic blood pressure during hemodialysis.

Systolic blood pressure was normally distributed. Central venous oxygen saturation was regressed with SBP in the model as both a time varying predictor (changing over time) and a fixed predictor centered at the grand mean at baseline for each day (Time 0). Controlling for time varying and baseline SBP each day, data showed that there was a significant linear and quadratic effect for ScvO2 over time during treatment session (linear $t_{301} = 3.8, p = 0.000$; quadratic $t_{761} = -5.2, p = .000$). As can be seen in Table 4-10, for each additional 30 minutes of dialysis, the linear and quadratic change trajectory in ScvO2 increases 1.1 percent then decreases .18 percent respectively.
There was also a significant association between the average time varying SBP and ScvO2 ($t_{804} = 8.3, p = .000$). For every mm Hg increase in SBP, there is a .09 increase in ScvO2 percent. Lastly, there is a significant linear and quadratic interaction between SBP at baseline as a fixed predictor and ScvO2 over time ($t_{303} = 2.8, p = .005; t_{760} = -2.5, p = .013$ respectively). For every one mm Hg increase in SBP from baseline, the linear trajectory of ScvO2 increases .03 percent and the quadratic trajectory of ScvO2 decreases .003 percent every 30 minutes.

Table 4-10. Parameter Estimates: ScvO2 regressed on time30 with baseline SBP.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>47.241214</td>
<td>2.411810</td>
<td>110.734</td>
<td>19.587</td>
<td>.000</td>
<td>42.461926 - 52.020502</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>.398476</td>
<td>.450919</td>
<td>33.503</td>
<td>.884</td>
<td>.383</td>
<td>-518402 - 1.315354</td>
<td></td>
<td></td>
</tr>
<tr>
<td>time30</td>
<td>1.065200</td>
<td>.281187</td>
<td>300.903</td>
<td>3.788</td>
<td>.000</td>
<td>.511858 - 1.618541</td>
<td></td>
<td></td>
</tr>
<tr>
<td>time30sq</td>
<td>-.182106</td>
<td>.035093</td>
<td>760.962</td>
<td>-5.189</td>
<td>.000</td>
<td>-.250996 - -.113216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sbpt0c</td>
<td>.011584</td>
<td>.053098</td>
<td>40.970</td>
<td>.218</td>
<td>.828</td>
<td>-.095652 - .118821</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>.069699</td>
<td>.010835</td>
<td>803.588</td>
<td>8.297</td>
<td>.000</td>
<td>.068631 - .111166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>time30 * sbpt0c</td>
<td>.029294</td>
<td>.010332</td>
<td>302.685</td>
<td>2.835</td>
<td>.005</td>
<td>.008962 - .049626</td>
<td></td>
<td></td>
</tr>
<tr>
<td>time30sq * sbpt0c</td>
<td>.003361</td>
<td>.001344</td>
<td>759.561</td>
<td>-2.500</td>
<td>.013</td>
<td>-.006000 - -.000722</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Dependent Variable: Central Venous Sat.
As shown in Table 4-11, the variance components for intercepts and slopes differed significantly from zero, indicating that ScvO2 did vary among individuals as well as in their amount of change over time during dialysis. As expected, these significant variance components indicate that factors other than SBP remain to be examined in order to further explain how ScvO2 changes among these patients.

Table 4-11. Variance Components: ScvO2 regressed on time30 with baseline SBP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Wald Z</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Residual</td>
<td>18.748448</td>
<td>.982306</td>
<td>19.086</td>
<td>.000</td>
<td>16.918720</td>
</tr>
<tr>
<td>Intercept + Day + time30 [subject = ID]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>119.718806</td>
<td>29.778138</td>
<td>4.020</td>
<td>.000</td>
<td>73.525774</td>
</tr>
<tr>
<td>Variance between Random Slopes for Day and Intercept</td>
<td>-17.144730</td>
<td>6.305311</td>
<td>-2.719</td>
<td>.007</td>
<td>-29.502912</td>
</tr>
<tr>
<td>Slope Covariance for Day</td>
<td>6.245296</td>
<td>1.885232</td>
<td>3.313</td>
<td>.001</td>
<td>3.456254</td>
</tr>
<tr>
<td>Covariance between Random Slopes for Time30 and Intercept</td>
<td>-2.160536</td>
<td>1.895664</td>
<td>-1.140</td>
<td>.254</td>
<td>-5.875968</td>
</tr>
<tr>
<td>Covariance between Random Slope for Day and Time30 Intercept</td>
<td>.125913</td>
<td>.438446</td>
<td>.287</td>
<td>.774</td>
<td>-7.33425</td>
</tr>
<tr>
<td>Slope Covariance for Time30</td>
<td>.737637</td>
<td>.218655</td>
<td>3.373</td>
<td>.001</td>
<td>.412584</td>
</tr>
</tbody>
</table>

a. Dependent Variable: Central Venous Sat.

Though the parameter estimates are small, a visual inspection of the plotted estimates of ScvO2 on baseline SBP (using quartiles as cut points) over time, show a discernable difference in change trajectory (Figure 4-3). Patients with a baseline SBP below the first quartile (123 mm Hg) show a change trajectory in ScvO2 that is fairly flat and with little
curvature. In contrast, those patients whose baseline SBP is at or higher than the fourth quartile (158 mm Hg) show the greatest curvilinear trajectory.

Figure 4-3. Plot of the estimates of ScvO2 regressed on time30 with baseline SBP.

**Aim 3:** To determine the association between percent change in central venous oxygen saturation and acute signs and symptoms during hemodialysis.

Multilevel negative binomial regression (Hilbe, 2007) was utilized to examine the relationship between ScvO2 % Change over time and the occurrence of acute signs and symptoms (a time varying predictor). The best fitting model predicting a symptom from the percent change in ScvO2 was statistically significant (Chi-square = 18.89, df = 3,
The predictor ScvO2 % Change was statistically significant ($p=.000$). There was not a significant interaction effect between ScvO2 % Change and day of the week.

As shown in Table 4-12, the expected change in log count for a one-unit increase in ScvO2 % Change was $0.0507622$. The estimate is transformed by taking the exponent ($e$) to the $0.0507622$ power which equals $1.05207$ symptoms for every percent change in ScvO2. The percentage increase in having a symptom ($Y$) expected with each one unit increase in the ScvO2 % Change ($X$) equals 100 times the inverse natural log of the coefficient minus one ($Y\% = 100 \times [e^\beta - 1]$ (as cited in Hutchinson & Holtman, 2005).

The percent increase in having a symptom for each additional unit of ScvO2 % Change, i.e. greater change, would be $100 \times (1.05207 - 1) = 5.21$. A five unit increase in ScvO2 % Change would equal and 29 percent increase in the presence of a symptom and a 10 unit increase in ScvO2% Change would equal a 66 percent increase in the presence of a symptom. These estimates take into account only ScvO2 % Change and treatment day in the model.

Table 4-12. Multi-level negative binomial regression model predicting a symptom from ScvO2 % Change. CI = Confidence Interval

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>z score</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>0.1957119</td>
<td>0.2713275</td>
<td>0.72</td>
<td>0.471</td>
<td>-0.336, 0.728</td>
</tr>
<tr>
<td>ScvO2 % Change</td>
<td><strong>0.0507622</strong></td>
<td>0.013931</td>
<td>3.64</td>
<td><strong>0.000</strong></td>
<td>0.023, 0.078</td>
</tr>
<tr>
<td>ScvO2 % Change by Day Interaction</td>
<td>-0.0148433</td>
<td>0.0112504</td>
<td>-1.32</td>
<td>0.187</td>
<td>-0.037, 0.007</td>
</tr>
</tbody>
</table>
Aim 4: To determine the association between the percent change in systolic blood pressure and acute signs and symptoms during hemodialysis.

The best fitting negative binomial regression model predicting a symptom from the percent change in SBP was statistically significant (Chi-square = 11.83, df = 3, p < .01). The predictor SBP % Change was statistically significant (p < .001). There was not a significant interaction effect between SBP % Change and day of the week.

As shown in Table 4-13, the expected change in log count for a one-unit increase in SBP % Change was .0391289. Taking the exponent (e) to the power of the coefficient .04 equals 1.0399 symptoms for every unit increase in SBP % change. The percentage increase in having a symptom (Y) expected with each one unit increase in the SBP % Change (X) equals 100 times the inverse natural log of the coefficient minus one (Y% = 100 x [e^β – 1]) (as cited in Hutchinson & Holtman, 2005).

The percent increase in having a symptom for each additional unit of SBP % Change, i.e. greater change, would be 100 x (1.0399 – 1) = 3.99. A five unit increase in SBP % Change would equal and 22 percent increase in the presence of a symptom and a 10 unit increase in SBP % Change would equal a 48 percent increase in the presence of a symptom. These estimates take into account only SBP % Change and treatment day in the model.

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>z score</th>
<th>p value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>.3299184</td>
<td>.31985</td>
<td>1.03</td>
<td>0.302</td>
<td>-.297, .957</td>
</tr>
<tr>
<td>SBP % Change</td>
<td>.0391289</td>
<td>.0120849</td>
<td>3.24</td>
<td><strong>0.001</strong></td>
<td>.015, .063</td>
</tr>
<tr>
<td>SBP % Change by Day Interaction</td>
<td>-0.0137104</td>
<td>.0106651</td>
<td>-1.29</td>
<td>0.199</td>
<td>-.035, .007</td>
</tr>
</tbody>
</table>

Table 4-13. Multi-level negative binomial regression model predicting a symptom from SBP % Change across days. CI=Confidence Interval, SBP=Systolic Blood Pressure
Aim 5: To determine the change in central venous oxygen saturation among patients with symptomatic hypotension compared to those with no symptomatic hypotension.

A comparison of demographic, clinical and physiologic variables based on whether or not the patient experienced an episode of symptomatic hypotension (Prone/Not Prone) is shown in Tables 4-14 and 4-15. There were 15 patients who experienced one or more symptoms associated with hypotension (Prone) and 21 patients with no symptoms associated with hypotension (Not Prone). Univariate logistic regression was performed to identify the likelihood that the demographic and clinical characteristics would predict a hypotensive symptom. Only Months on HD was significant $x^2 (1, n=39) = 4.26, p = .039$. The odds ratio of 1.016 for Months on HD was just over 1, indicating that for every month on HD, patients were 1.016 times more likely to have a symptom associated with hypotension.

Table 4-14. Comparison of demographic and clinical characteristics based on Symptom Status. All values are expressed as Mean (SD) except gender. HD=Hemodialysis.

<table>
<thead>
<tr>
<th>Characteristics/Variables</th>
<th>Not Prone (n=21)</th>
<th>Prone (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>12/9</td>
<td>9/6</td>
</tr>
<tr>
<td>Age in years</td>
<td>59 (19)</td>
<td>63 (14)</td>
</tr>
<tr>
<td>Number of Comorbidities</td>
<td>3.3 (1.0)</td>
<td>3.1 (1.9)</td>
</tr>
<tr>
<td>Months on HD Mean</td>
<td>29</td>
<td>60</td>
</tr>
<tr>
<td>Median (range)</td>
<td>8.0 (3-137)</td>
<td>60 (3-144)</td>
</tr>
<tr>
<td>Duration of Treatment minutes</td>
<td>196 (23)</td>
<td>203 (23)</td>
</tr>
<tr>
<td>Dry Weight kilograms</td>
<td>79.6 (19.2)</td>
<td>73.5 (23.8)</td>
</tr>
<tr>
<td>Pre-HD Hemoglobin g/dl</td>
<td>10.8 (1.4)</td>
<td>11.3 (1.1)</td>
</tr>
</tbody>
</table>
Table 4-15. Physiologic Measures by Symptom Status. All values are expressed as Mean (SD). HD=Hemodialysis; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; ScvO2=Central Venous Oxygen Saturation; SaO2=Arterial Oxygen Saturation; BV=Blood Volume.

<table>
<thead>
<tr>
<th>Variables at HD Start</th>
<th>Not Prone (n=21)</th>
<th>Prone (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP mmHg</td>
<td>142.4 (32.3)</td>
<td>135.7 (27.2)</td>
</tr>
<tr>
<td>DBP mmHg</td>
<td>75.1 (18.6)</td>
<td>71.0 (15.9)</td>
</tr>
<tr>
<td>Pulse beats/min</td>
<td>77.3 (13.4)</td>
<td>71.3 (14.3)</td>
</tr>
<tr>
<td>ScvO2 %</td>
<td>59.6 (11.0)</td>
<td>62.1 (8.5)</td>
</tr>
<tr>
<td>SaO2 %</td>
<td>96.7 (2.7)</td>
<td>97.0 (1.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent Change</th>
<th>Not Prone (n=21)</th>
<th>Prone (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Fluid Removed</td>
<td>2.8 (1.1)</td>
<td>2.9 (1.1)</td>
</tr>
<tr>
<td>liters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP Change % Median</td>
<td>-13.7 (16.6)</td>
<td>-20.4 (18.1)</td>
</tr>
<tr>
<td></td>
<td>12.7</td>
<td>21.1</td>
</tr>
<tr>
<td>Pulse Change %</td>
<td>-3.5 (13.2)</td>
<td>-3.5 (20.7)</td>
</tr>
<tr>
<td>BV Change %</td>
<td>-7.4 (4.3)</td>
<td>-9.4 (4.8)</td>
</tr>
<tr>
<td>ScvO2 Change % Median</td>
<td>-.38 (16.8)</td>
<td>-13.3 (17.1)</td>
</tr>
<tr>
<td></td>
<td>-.7</td>
<td>-11.5</td>
</tr>
</tbody>
</table>

Multi-level regression analysis was conducted to explore differences in ScvO2 change trajectory between those patients who experienced a hypotensive symptom (Prone) from those who did not (Not Prone). A random coefficients model was specified for the analysis by including both random intercepts and slopes for both time and day. The specification for the covariance matrix for the random intercepts and slopes was “unstructured” and estimation was obtained with restricted maximum likelihood due to small sample size.

The data showed a significant linear and quadratic effect for ScvO2 over treatment time (Time 30) in patients identified as Not Prone to symptoms (linear $t_{210} = 2.6, p = .010$; quadratic $t_{775} = -3.66, p = .000$) and a significant quadratic effect for ScvO2 over
time in patients identified as symptom Prone ($t_{775} = -3.66, p = .000$). The model best representing the data is shown in Table 4-16. The parameter estimates for linear and quadratic change in ScvO2 for Not Prone patients indicates that for every 30 minutes of dialysis time, ScvO2 increase .81 percent and then decreases .14 percent. Those patients identified as symptom Prone had a .81 percent greater decline in ScvO2 every 30 minutes as compared to patients identified as Not Prone. There was no effect for treatment day.

Table 4-16. Parameter Estimates: ScvO2 regressed on time 30 and day by symptom status.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>df</th>
<th>t</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>59.594929</td>
<td>2.232598</td>
<td>43.832</td>
<td>26.693</td>
<td>.000</td>
<td>55.094936</td>
<td>64.094923</td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>.175823</td>
<td>.478182</td>
<td>31.040</td>
<td>.368</td>
<td>.716</td>
<td>-1.799384</td>
<td>1.151031</td>
<td></td>
</tr>
<tr>
<td>time30</td>
<td>.805972</td>
<td>.308410</td>
<td>210.273</td>
<td>2.613</td>
<td>.010</td>
<td>.198001</td>
<td>1.413943</td>
<td></td>
</tr>
<tr>
<td>time30sq</td>
<td>-.135512</td>
<td>.037078</td>
<td>775.606</td>
<td>-3.655</td>
<td>.000</td>
<td>-.208296</td>
<td>-.062728</td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td>1.764346</td>
<td>3.146006</td>
<td>36.843</td>
<td>.561</td>
<td>.578</td>
<td>-4.610982</td>
<td>8.139674</td>
<td></td>
</tr>
<tr>
<td>time30 * Prone</td>
<td>-.812925</td>
<td>.306433</td>
<td>36.347</td>
<td>-2.653</td>
<td>.012</td>
<td>-1.434194</td>
<td>-.191656</td>
<td></td>
</tr>
</tbody>
</table>

a. Dependent Variable: Central Venous Sat.
As shown in Table 4-17, the variance component for intercepts and slopes differed significantly from zero in patients without symptoms, indicating that ScvO2 did vary among these individuals as well as in their amount of change over time during dialysis.

Table 4-17. Variance Components: ScvO2 regressed on time 30 and day, by symptom status.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Wald Z</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Residual</td>
</tr>
<tr>
<td>Intercept + Day + time30 [subject = ID]</td>
<td>Intercept Variance</td>
<td>126.494723</td>
<td>31.722450</td>
<td>3.988</td>
<td>.000</td>
</tr>
<tr>
<td>Slope Covariance for Day</td>
<td>-16.50840</td>
<td>6.710693</td>
<td>-2.459</td>
<td>.014</td>
<td>-29.653557 - -3.348122</td>
</tr>
<tr>
<td>Covariance between Random Slopes for Day and Intercept</td>
<td>7.004962</td>
<td>2.192118</td>
<td>3.196</td>
<td>.001</td>
<td>3.793434 - 12.935376</td>
</tr>
<tr>
<td>Covariance between Random Slopes for Time 30 and Intercept</td>
<td>-2.518454</td>
<td>1.927489</td>
<td>-1.307</td>
<td>.191</td>
<td>-5.296263 - 1.259356</td>
</tr>
<tr>
<td>Covariance between Random Slope for Day and Time 30 Intercept Slope Covariance for Time 30</td>
<td>.321398</td>
<td>.465026</td>
<td>.691</td>
<td>.489</td>
<td>-.590041 - 1.232836</td>
</tr>
<tr>
<td>Slope Covariance for Time 30</td>
<td>.665016</td>
<td>.206531</td>
<td>3.220</td>
<td>.001</td>
<td>.361808 - 1.222323</td>
</tr>
</tbody>
</table>

a. Dependent Variable: Central Venous Sat.

A plot of predicted values ScvO2 on treatment time by symptom status (Figure 4-4) shows the significant linear and quadratic change trajectory for patients identified as Not Prone to symptoms and the significant quadratic change trajectory for those patients identified as symptom Prone. The variation around the predicted plot is due to the fact that the plot is collapsed across treatment days.
Figure 4-4. Plot of Predicted Values: ScvO2 on time30 by symptom status.
CHAPTER 5

DISCUSSION

The overall findings from this study showed that continuous ScvO2 monitoring using the Crit-Line III™ is a relevant physiologic variable in patients undergoing outpatient hemodialysis. ScvO2 changes over the duration of a dialysis treatment and the amount of change is significantly associated with SBP and acute signs and symptoms. These findings are consistent with earlier data showing that ScvO2 decreases in a subgroup of dialysis patients prone to symptomatic hypotension (Cordtz et al., 2008). These data are particularly important for dialysis nurses as continuous ScvO2 monitoring may be used as a guide to fluid removal strategies and therapeutic interventions to avoid the deleterious effects of symptomatic hypotension. The findings also show that acute signs and symptoms associated with hypotension occurred in 38% of patients and 24% of dialysis treatments and their timing, severity and distress are clinically important. This chapter discusses the study findings in relation to the study aims, conceptual framework and previously reviewed literature. Study limitations are addressed in addition to the implications for nursing and future research.

ScvO2 Change over Time

In a sample of chronic dialysis patients (n=39) with a mean total fluid removal of 2.8±1.1 liters, multi-level regression models show that ScvO2 during dialysis increases slightly over the first hour of a dialysis treatment and then gradually decreases over the remaining two hours of a dialysis treatment, but that this decrease is significantly greater in patients who experience symptomatic hypotension.
According to Fick’s principle, changes in ScvO2 reflect changes in cardiac output (Weinbroum, Biderman, Soffer, Klausner, & Szold, 2008). ScvO2 is an indicator of global tissue hypoxia as was found in cardiac and trauma patients with a reduced cardiac output and hypotension (Jamieson et al., 1982; Reinhart & Bloos, 2005; Rivers, McIntyre, Morro, & Rivers, 2005). The initial increase in ScvO2 during the first hour of hemodialysis may be in indication of an increase in cardiac output and/or improved oxygenation as excess intravascular volume is removed through ultrafiltration. The decrease in ScvO2 over the last two hours of dialysis is consistent with a reduction in cardiac output as the patient approaches their dry weight or period of maximal intravascular hypovolemia.

Findings from this study also show that the change trajectory in ScvO2 over time varies by dialysis clinic. Multi-level regression followed by pairwise contrast reveal that the ScvO2 change trajectory in clinic 2 is significantly different than clinics 1 and 3. As compared to Clinic 2, Clinic 1 had a .8 percent greater decline in ScvO2 and Clinic 3 had a 1.0 percent greater decline in ScvO2 for each additional 30 minutes of dialysis time \( p < .05 \). A comparison of aggregate data support this difference in that there was an overall increase in ScvO2 % Change in clinic 2 and the least reduction in SBP and BV as compared to clinics 1 and 3.

Despite the fact that there is no statistical difference in the mean total fluid removed between clinics (2.8±1.1 liters), patients in clinics 1 and 3 had a greater reduction in SBP and BV and a steeper change trajectory in ScvO2 and presumably cardiac output, as compared to clinic 2. Patients in clinics 1 and 3 may be less hydrated at baseline than those patients in clinic 2. Conversely, patients in clinic 2 may be considerably more
volume overloaded as reflected by minimal reductions in SBP and BV and a small increase in ScvO2. In addition, three subjects from clinic 2 arrived to dialysis complaining of shortness of breath due to volume overload. While shortness of breath may be a patient specific difference, it is noteworthy that no patients from clinics 1 and 3 arrived with similar complaints. These data imply that there is a variation in the overall hydration status of the patients between clinics, suggesting there may be clinic-specific practices that influence fluid removal strategies.

ScvO2 Change over Time Related to SBP

ScvO2 during dialysis using the CLMIII™ is significantly associated with SBP. Multi-level regression analysis show a significant linear and quadratic change trajectory of ScvO2 over dialysis time associated with baseline SBP. Patients starting dialysis with a SBP of 123 or less have a predicted trajectory of ScvO2 that is linear and relatively flat. In contrast, patients with a starting SBP of 158 or higher have a trajectory that is much more curvilinear. It appears that it is their initial status of SBP that makes a difference about how ScvO2 changes across time and as expected, there is substantial variation at baseline and in the amount of change between individuals.

Volume excess in the dialysis patient is associated with high blood pressure and systolic blood pressure is more sensitive to changes in extracellular fluid volume than diastolic blood pressure (Agarwal & Light, 2010). Patients who present to dialysis with high SBP are typically volume overloaded, requiring greater rates of ultrafiltration and intravascular fluid removal, as reflected by a more curvilinear change in ScvO2 and cardiac output. Patients who present to dialysis with a lower SBP typically have a lower
or more conservative ultrafiltration requirement and therefore less intravascular fluid removal, as reflected by a more linear reduction in ScvO2 and cardiac output.

**ScvO2 Change and Symptomatic Hypotension**

In this study, the amount of change in ScvO2 from the beginning of dialysis to the point of maximal intravascular hypovolemia significantly predicted having a symptom associated with hypotension. Negative binomial regression models show that a 5-point decrease in ScvO2 indicates a 29 percent increase in having a symptom and a 10-point decrease in ScvO2 indicates a 66 percent increase in having a symptom ($p = .000$). There has only been only one other study that has investigated ScvO2 during outpatient hemodialysis using the CLMIII™. Cordtz, Olde, Solem, and Ladefoged (2008) compared reductions in mean ScvO2 measures in 11 hypotensive prone and 9 hypotensive resistant patients during dialysis and found that hypotensive prone patients exhibited a decrease in ScvO2 of approximately 14.8 percent or 7 to 8 points from baseline, whereas hypotensive resistant patients had an increase in ScvO2 of 2 percent or 1 point from baseline. Similar findings in the current study show a decrease in ScvO2 in Prone patients of 13.3 percent or 8 points from baseline and in Not Prone patients was 0.4 percent or 0.2 of a point from baseline.

Multi-level regression analyses were conducted to explore differences in ScvO2 change trajectory between those patients who experienced a hypotensive symptom (Prone) from those who did not (Not Prone). Those patients identified as symptom Prone had a .81 percent greater decline in ScvO2 every 30 minutes as compared to patients identified as Not Prone ($p = .01$). Patients who were identified as Not Prone actually had
a linear increase in ScvO2 of .80 percent \((p = .01)\) followed by a gradual decline of only .14 percent \((p = .000)\).

**SBP Change and Symptomatic Hypotension**

The majority of symptomatic events associated with hypotension (55%) were based on a gradual decline to an absolute SBP \(< 100\) mm Hg and slightly fewer (39%) with an abrupt drop of \(> 20\) mm Hg from the previous measure. The mean change in SBP from the start of dialysis to the point of maximal hypovolemia in patients who experienced symptomatic hypotension was approximately 28 mm Hg in contrast to 19 mm Hg in patients with no symptomatic hypotension. Similarly, Cordtz, Olde, Solem, and Ladefoged (2008) found a reduction of 27 mm Hg in patients with symptomatic hypotension but an increase of 3 mm Hg in patients with no symptomatic hypotension.

Negative binomial regression models in this study show that there was a significant association between the amount of change in SBP and the presence of symptoms associated with hypotension. The data show that with a 10 percent reduction in SBP, there would be a 48 percent increase in the presence of a symptom. Though the amount of change in SBP related to symptomatic hypotension may be interesting, blood pressure is a highly variable parameter and the clinical relevance is precluded by the fact that it remains an intermittent measure, giving little advance warning to impending ischemic symptoms. The emphasis in defining dialysis-induced hypotension as a standardized amount of change or absolute cut-off in BP will always be prone to error because of individual differences; therefore, greater attention needs to be given to exploring continuous monitoring parameters as well as understanding the timing, severity and distress of the symptoms associated with this phenomenon.
Occurrence of Acute Symptoms

In this study, 15 patients described 31 symptoms consistent with dialysis-induced hypotension. Most of the patients experienced one symptom, but some patients up to three symptoms. The two most frequently occurring symptoms were muscle cramps (42.9%), followed by presyncopal dizziness (28.5%). The length of time that symptoms occurred ranged between approximately 30 seconds for dizziness, up to 20 minutes for severe muscle cramps. All of the symptoms in this study required nursing interventions which included reducing the ultrafiltration rate of the dialysis machine, placing the patient flat, giving a rapid infusion of normal saline and/or administering oxygen by nasal cannula.

What is unique about this study is that in addition to a predicted change of physiologic variables, the timing, severity and distress of the acute symptom experience present important findings. This study found that the majority of acute symptoms occurred on the first and last treatment day of the week (43.6% and 30.6%, respectively) and during the final hour of dialysis (85.7%), regardless of the treatment length. These patterns of symptoms represent periods of maximal hypovolemia and are consistent with findings associated ScvO2 % Change.

Chronic dialysis patients are typically scheduled to receive hemodialysis three times a week on a Monday, Wednesday, Friday or Tuesday, Thursday, Saturday. This type of schedule results in a fixed two-day period of toxin and fluid accumulation between dialysis weeks, requiring that the clinician accommodate this accumulation in their fluid removal strategy. The findings from this study indicate that symptom prevention
strategies need to be targeted to periods of maximal hypovolemia associated with treatment duration and treatment day.

Severity and Distress of Acute Symptoms

The severity of acute symptoms in this study was described as being moderate to severe by over 80% of those affected and 41% of the patients described their symptom distress as “quite a bit” and “very much”. Muscle cramps, dizziness and syncope were described as being the most severe and causing the greatest level of distress. These are important findings as acute symptoms have been implicated as reasons for patients to terminate their dialysis treatment early, or skipping their treatment altogether (Rocco & Burkart, 1993). In the current study, eight patients terminated their treatment early due to cramping, and four patients skipped a treatment for reasons unknown to this investigator. The perception and response to the symptom experience is affected by the frequency, severity and distress of symptoms (Portenoy et al., 1994). No studies that examine the degree of symptom severity or symptom distress related to symptomatic hypotension during hemodialysis have been reported.

Surprisingly, three patients (11.1%) (one of whom experienced loss of consciousness) said that they were “not bothered” by their symptom experience. Two patients stated that symptoms “were just part of the package, you just put up with it”, “not much they could do about it”. This is important because it speaks to the possible underreporting of symptoms experienced by dialysis patients. Symptoms that are not reported cannot be treated and the ischemic effects mitigated.

There are a variety of definitions that characterize dialysis-induced hypotension. Staff education about dialysis-induced hypotension that emphasizes the presence of signs and
symptoms is important because it is the symptom experience that directly impacts the patient, and the severity of hypovolemic symptoms is an indication of the magnitude of blood flow reduction (Derebery, 1999). As an observation, the clinic staff in all three sites was very attentive to monitoring and treating blood pressure measurements, but less attentive to the patient’s symptom experience. When asked in advance, several nurses and technicians were largely unaware of their patients history related to the type and frequency of acute symptom occurrence. An awareness and understanding of the symptom experience during the dialysis procedure is necessary to ensure appropriate fluid removal and that patient specific symptom management strategies are implemented.

A comparison of aggregate symptom data by clinic show a pattern consistent with ScvO2 change trajectories. Patients in clinic 3 described the greatest number of symptoms events, the greatest severity, and the most distress. Patients in clinic 3 had a significantly greater reduction in ScvO2 change trajectory compared to clinics 1 and 2. These findings support the data showing that greater change in ScvO2 and SBP significantly predict acute signs and symptoms during dialysis.

Oxygen delivery in hemodialysis patients also is a concern. Earlier work has shown that oxygen delivery in dialysis patients is reduced as compared to healthy individuals (Nielsen, Jensen, Hegbrant, Brinkenfeldt, & Thunedborg, 1995b). Mixed venous oxygen saturation is reduced in patients with end-stage renal disease as compared to healthy controls (53±8 percent versus 79±2 percent, respectively) (Kong, Thompson, & Imms, 1990). Findings from the current study show that the oxygen carrying capacity in this sample equates to approximately 14.7 ml/dl, a 24.4% reduction of that of healthy individuals. Oxygen delivery is often reduced in older patients and those with
cardiovascular and pulmonary disease (Kosmadakis & Medcalf, 2008). The mean age of the sample was 60.4 with a mean number of co-morbid conditions of 3.2, including diabetes, hypertension and cardiovascular disease. Hypovolemia during hemodialysis has been shown to trigger cardiac events in already vulnerable HD patients, including muscle damage, heart failure, and cardiac arrhythmias (Bos et al., 2000). There is substantial evidence that the process of dialysis itself can reduce myocardial blood flow (Dasselaar et al., 2009) and induce myocardial ischemia as measured by ST depression, even in the absence of atherosclerosis (Conlon et al., 1998; Mohi-ud-din et al., 2005; Narula et al., 2000; Selby & McIntyre, 2007). Additionally, Shoji, Tsubakihara, Fujii, & Imai (2004) investigated dialysis-induced hypotension in approximately 1244 dialysis patients over a two year period and found that dialysis-induced hypotension is a significant and independent risk factor affecting mortality in this population. The oxygen content may not be enough to satisfy the metabolic demands of the body in vulnerable patients undergoing rapid volume shifts during hemodialysis and these studies support the fact that continuous oxygen saturation monitoring would be a valuable monitoring tool in this population.

Strengths and Limitations

This is the first study to use multi-level modeling to examine the change in ScvO2 over time during outpatient hemodialysis. Though many of the findings were statistically significant, this study was carried out on a small number of patients. Due to the sample size, the regression models did not include additional predictors such as total fluid removed and physiologic variables at the start of dialysis, therefore the findings should be interpreted with caution. The sample was limited to patients with a central venous
hemodialysis access and primarily African American, so the results cannot be generalized to all hemodialysis patients.

Measurement reliability of the timing, severity and distress of acute symptom symptoms may have been impacted by attention bias during the study. Also, some patients had difficulty distinguishing among the categories on the acute symptom data collection tool. For example, some patients had difficulty distinguishing between “a little bit” and “somewhat”. Further research is warranted to develop a more refined instrument.

Implications for Nursing and Future Research

Symptomatic hypotension remains one of the most frequent and significant complications of dialysis therapy. Continuous ScvO2 monitoring during hemodialysis as an indicator of impending hemodynamic instability shows promise and further research is needed. Studies to validate continuous ScvO2 using the CLM III™ against traditional fiber optic techniques related to blood pressure and acute symptoms are warranted. One focus needs to be to understand how much of the change in ScvO2 is the result of a compensatory response versus actual tissue ischemia and whether ScvO2 is an indicator of volume status in the dialysis population.

Increased tissue oxygen demand through shivering, positioning and fever affect ScvO2 as well as situations of reduced oxygen supply such as in anemia, airway obstruction (sleep apnea) and altered diffusion of oxygen in the lung. Studies to further investigate the variability in ScvO2 measurements associated with these conditions in hemodialysis patients are necessary. Analytic approaches that include multi-level
regression techniques to identify patterns of change over time as well as variations among patients and dialysis clinics will help improve care and patient outcomes.

It is important for nurses to be attentive to symptomatic hypotension within the context of fluid removal strategies over the course of both the dialysis treatment time and treatment day. The timing, severity and distress of acute symptoms should be routinely assessed and documented by all providers to ensure that appropriate fluid removal strategies are incorporated into the patients’ plan of care. Additional research on acute symptoms during dialysis is essential. Evaluating the patients’ acute symptom experience may be better understood within the context of the patients overall symptom burden (Thong et al., 2008).

Clinical decisions are rarely based on single measurement parameters, but should always reflect various measurements and the trend of these measurements (Dueck et al., 2005). Continuous ScvO2 monitoring may offer dialysis nurses an additional tool to inform us of the pathophysiological events that occur during hemodialysis. Other investigators have identified the prognostic significance of ScvO2 monitoring in patients experiencing trauma (Scalea et al., 1990), myocardial infarction (Sumimoto et al., 1991), cardiogenic shock (Ander et al., 1998), high-risk surgery (Pearse et al., 2005), and sepsis (Rivers, Nguyen et al., 2001). While ScvO2 has been studied in animals and has been applied clinically in several patient populations, only one other study has investigated ScvO2 in dialysis patients in the outpatient setting using the CLMIII™. The findings from the current study confirm that the change trajectory of ScvO2 during outpatient dialysis is relevant and related to SBP and acute signs and symptoms.
References


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standard and biofeedback dialysis. *American Journal of Kidney Diseases, 47*(5), 830-841.


Crit-Line III™ Blood Volume Monitor with Sensor Clip
HCT-based Blood Volume Monitor – Continuous monitoring of changes in hematocrit allows visual display of the percent blood volume change on the y axis over time on the x axis.
Acute Signs and Symptom Data Collection Form

**INSTRUCTIONS:**
1. Record subject id, date, day and DIH prone*
   
   *DIH=Dialysis-induced hypotenion prone as identified by clinic staff
2. Record dialysis starting time and starting BP, HR, and peripheral O2 sat.
3. When subject reports signs or symptoms, use the symptom key to document type.
4. Record start and stop times of each symptom including the severity, BP, HR, ScvO2, and %BVΔ at the start of the sign or symptom.
5. Record any intervention(s) by clinic staff using the intervention key.
6. Record dialysis end time and ending BP, HR, and peripheral O2 sat.

---

**Subject ID__________________**

**Treatment Date/Day__________________________**

**DIH Prone: 0 = No 1 = Yes**

---

**Dialysis Start Time:_______**

Pre BP:_______

Pre HR:_______

SaO2:_________

ScvO2 @ start_________

**Symptom** | **Timing** | **Severity** | **Monitoring Variables** | **Intervtn**
--- | --- | --- | --- | ---
Start Time: | Stop Time: | BP: | HR: | ScvO2: | %BVΔ: |
Start Time: | Stop Time: | BP: | HR: | ScvO2: | %BVΔ: |
Start Time: | Stop Time: | BP: | HR: | ScvO2: | %BVΔ: |
Start Time: | Stop Time: | BP: | HR: | ScvO2: | %BVΔ: |
Start Time: | Stop Time: | BP: | HR: | ScvO2: | %BVΔ: |
Start Time: | Stop Time: | BP: | HR: | ScvO2: | %BVΔ: |
Start Time: | Stop Time: | BP: | HR: | ScvO2: | %BVΔ: |
Start Time: | Stop Time: | BP: | HR: | ScvO2: | %BVΔ: |
---

**Dialysis End Time:_______**

Post BP:_______

Post HR:_______

SaO2:_________

ScvO2 @ end_________

---

**KEY:**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Severity</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1=Dizziness</td>
<td>1=Mild</td>
<td>1=Decrease UF</td>
</tr>
<tr>
<td>2=Nausea</td>
<td>2=Moderate</td>
<td>2=Trendelenburg</td>
</tr>
<tr>
<td>3=Vomiting</td>
<td>3=Severe</td>
<td>3=NS Bolus</td>
</tr>
<tr>
<td>4=Muscle Cramps</td>
<td>4=Medications</td>
<td></td>
</tr>
<tr>
<td>5=Other</td>
<td>5=Other</td>
<td></td>
</tr>
</tbody>
</table>

**POST-DIALYSIS SYMPTOM DISTRESS:**

0=Not at all bothered
1=Somewhat bothered
2=Moderately bothered
3=Quite a bit bothered
4=Very much bothered
Dear Paul Smith,

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