ABSTRACT

Transjugular Hepatic Venous Pressure Assessment and Mortality Risk in Patients with End-Stage Renal Disease Presenting with Non-Cirrhotic Ascites

James Tacker Patton

Director: Bill Neilson, MD

Patients with end-stage renal disease (ESRD) maintained on hemodialysis who develop ascites are presumed to have underlying cirrhosis with portal hypertension; however, in many cases they do not have chronic liver disease and are considered to have nephrogenic ascites. Nephrogenic ascites in patients on hemodialysis may in fact be cardiogenic as a consequence of high-flow arteriovenous fistulas, although reports and characterization of this clinical presentation are limited. Retrospective cohort study of patients with ESRD on hemodialysis who presented with new onset ascites from 2011 to 2018 in a large tertiary care hepatology practice affiliated with a liver transplant program. Patients were evaluated with echocardiography, transjugular liver biopsy with hepatic venous pressure gradient (HVPG), and analysis of peritoneal fluid. Patients with intra-abdominal malignancy or infection were excluded. In patients with ESRD presenting with non-cirrhotic ascites, right-sided heart failure with passive hepatic congestion may be a major cause of ascites and mortality. Further study of the cardiovascular effects of hemodialysis in this population, including attention to high-output heart failure and arteriovenous fistula hemodynamics, may be important in defining risk and management strategies.

APPROVED BY DIRECTOR OF HONORS THESIS:

_____

Bill Neilson, MD
Department of Biology

APPROVED BY THE HONORS PROGRAM:

_____

Dr. Elizabeth Corey, Director

DATE: _____

TRANSJUGULAR HEPATIC VENOUS PRESSURE ASSESSMENT AND MORTALITY RISK IN PATIENTS WITH END-STAGE RENAL DISEASE PRESENTING WITH NON-CIRRHOTIC ASCITES

A Thesis Submitted to the Faculty of

Baylor University

In Partial Fulfillment of the Requirements for the

Honors Program

By

James Tacker Patton

Waco, Texas

May 2020

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

I wold like to thank Dr. Stevan Gonzalez and Dr. Mohanakrishnan Sathyamoorthy for assisting me with data collection and analysis for the hepatic venous pressure gradient and echocardiography procedures. Their guidance was of the utmost help for the completion of this project. The wisdom that they imparted regarding medicine and clinical applications was vital to my understanding of this Honors thesis.

Additionally, I would like to thank the committee members, Dr. Vanessa Castleberry and Dr. Mojgan Parizi, who contributed their time to reviewing my thesis and serving on my defense panel. Their constructive criticism and challenge to think critically was great value for this thesis.

I would like to extend a special thanks to Dr. Bill Neilson, my advisor and mentor throughout this process. The completion of this thesis would have been impossible without his commitment, guidance, and encouragement. Dr. Neilson made this experience enriching and satisfying and devoted many hours to its successful completion. I could not have done it without his assistance, and I greatly appreciate his investment in my education.

CHAPTER ONE

Review of Physiology and Anatomy

Cardiovascular Physiology

General Cardiovascular Anatomy

The cardiovascular system can be thought of as the transport system of the body. This system has three main components: the heart, the blood vessel, and the blood itself. The heart is the system's pump and the blood vessels are like the delivery routes. Blood can be thought of as a fluid which contains the oxygen and nutrients that the body needs and carries the wastes which need to be removed.[1] The following information describes the structure and function of the heart and cardiovascular system as a whole.

The heart itself is made up of four chambers, two atria, and two ventricles. De-oxygenated blood returns to the right side of the heart via venous circulation. It is pumped into the right ventricle and then to the lungs where carbon dioxide is released, and oxygen is absorbed.[1] The blood is now oxygenated and travels back to the left side of the heart and into the left atrium, then and into the left ventricle from where it is pumped into the aorta and the remainder of arterial circulation. The pressure created by the arteries by the contraction of the left ventricle is the systolic blood pressure.[2] Once the left ventricle has fully contracted it begins to relax and refill with blood from the left atria. The pressure in the arteries decreases once more while the ventricle refills. This in known as the diastolic blood pressure.[1] The atrio-ventricular septum completely separates the two sides of the heart. Except for the instance of a septal defect, the two

sides of the heart never directly communicate.[2] Blood travels from the right side to the left side of the heart via the lungs only. However, the chambers themselves work together with both the atria and ventricles contracting simultaneously.

Cardiac Output and Frank-Starling Mechanism

Cardiac output, expressed in liters/minute, is the amount of blood the heart pumps in 1 minute, and it is dependent on the heart rate, contractility, preload, and afterload.[3] Understanding the applicability and practical relevance of each of these four components is important when interpreting cardiac output values. Cardiac output is logically equal to the product of the stroke volume and the number of beats per minute (heart rate).[3] The heart rate is the simplest determinant of cardiac output: the faster the heart beats, the more blood can be pumped over a particular period of time. An increase in the contractility of the heart will result in an increased cardiac output.[3]

Preload is the degree of myocardial distension prior to shortening. An intrinsic property of myocardial cells is that the force of their contraction depends on the length to which they are stretched; the greater the stretch, the greater the force of contraction until a certain point.[3] An increase in the distension of the ventricle will therefore result in an increase in the force of contraction, which will increase cardiac output. Preload largely depends on the amount of ventricular filling.[3] It should not, however, be confused with venous return. The amount of blood returning the heart in any period of time must be equal to the amount of blood pumped by the heart in the same period, as there is no place for the storage of blood in the heart.[3]

Afterload is the force against which the ventricles must act in order to eject blood and is largely dependent on the arterial blood pressure.[1] Reducing afterload can increase cardiac output, especially in conditions where contractility is impaired.

The Frank-Starling relationship is based on the link between the initial length of the myocardial fibers and the force generated by contraction. There exists a predictable relationship between the length of sarcomeres and the tension of muscle fibers.[3] This is an optimal length between sarcomeres at which the tension of the muscle fibers is the greatest, resulting in the greatest force of contraction. The greater the ventricular diastolic volume, the more myocardial fibers are stretched during diastole.[3] The Frank-Starling relationship is predicated on the observation that ventricular output increases as preload increases.[3]

The Frank-Starling curves relate to pre-load, measured as ventricular end-diastolic volume (EDV) or pressure, to cardiac performance, measured as ventricular stroke volume or cardiac output.[4] On the curve of a normally functioning heart, cardiac performance increases continuously as preload increases. During states of increased ventricular contractility, there is greater cardiac performance for a given preload. This is represented graphically as an upward shift on the normal curve.[4] Conversely, during states of decreased left ventricular contractility associated with systolic heart failure, there is less cardiac performance for a given preload as compared to the normal curve.[3] This is represented by a downward shift of the normal curve. It is also important to note, that decreased contractility can result from a loss of myocardium as with myocardial infarction, beta-blockers, and dilated cardiomyopathy.

Changes in afterload, will also shift the Frank-Starling curve. A decrease in afterload will cause an upward shift of the ventricular performance curve in a similar fashion to an increase in inotropy.[4] Conversely, an increase in afterload will cause a downward shift of the curve in a similar fashion to a decrease in inotropy.

The Frank-Starling mechanism plays a role in the compensation of systolic heart failure, buffering the fall in cardiac output to help preserve sufficient blood pressure to perfuse the vital organs.[3] Heart failure caused by the impaired contractile function of the ventricle causes a downward shift of the ventricular performance curve. At any given preload, the stroke volume will be decreased as compared to normal.[3] This reduced stroke volume leads to incomplete left ventricular emptying. Consequently, the volume of blood that accumulates in the left ventricle during diastole is greater than normal. This residual volume increases the stretch of the myocardial fibers and induces greater stroke volume with the next contraction, via the Frank-Starling mechanism.[3] This allows for better emptying of the enlarged ventricle and preserves cardiac output.

The Venous System

Blood vessel are tubes which carry blood. Veins are blood vessels which carry blood from the body back to the heart and arteries are blood vessels which carry blood from the heart to the body.[2] Additionally, there are microscopic blood vessels which connect the arteries and veins together called capillaries. There are several main blood vessels which connect to different chambers of the heart. The aorta is the largest artery in the human body. The left ventricle pumps blood into the aorta which then carries it to the rest of the body through the smaller arteries.[5] The pulmonary trunk is the large artery which the right ventricle pumps into. It splits into pulmonary arteries which take the

blood to the lungs. The pulmonary veins take blood from the lungs to the left atrium. All other veins in the human body drain into the inferior vena cava (IVC) or the superior vena cava (SVC).[5] The two large veins then take the rest of the blood into the right atrium.

Valves are fibrous flaps of tissue found between the heart chambers and in blood vessels. They contribute to the unidirectional flow thus preventing blood from flowing in the wrong direction. Valves between the atria and ventricles are known as the right and left atrioventricular valves, otherwise known as the tricuspid and mitral valves respectively.[2] Valves between the ventricles and the greater arteries are known as the semilunar valves. The aortic valve is found at the base of the aorta, while the pulmonary valve is found at the base of the pulmonary trunk.[1]

The Cardiac Cycle

The cardiac cycle is the sequence of events that occurs in one complete beat of the heart. The pumping phase of the cycle, also known as systole, occurs when the heart muscle contracts. The filling phase, which is known as diastole, occurs when the heart muscle relaxes. At the beginning of the cardiac cycle, both the atria and the ventricles are in diastole.[6] During this time, all of the chambers of the heart are relaxed and are receiving blood and the atrioventricular valves are open.[6] Atrial systole follows this phase. During atrial systole, the left and right atria contract at the same time and pump blood into the and right ventricles, respectively.[7] The next phase is ventricular systole. During ventricular systole, the left and right ventricles contract at the same time and pump blood into the aorta and pulmonary trunk, respectively.[6] In ventricular systole, the atria are relaxed and receive blood. The atrioventricular valves close immediately after

this phase of the cardiac cycle begins, stopping blood from going back into the atria.[8] However, the semilunar valves are open during the phase to allow the blood to flow into the aorta and pulmonary trunk.[6] Following this phase, the ventricles relax, and ventricular diastole occurs. The semilunar valves close to prevent blood from flowing back into the ventricles from the aorta and pulmonary trunk.[6] The atria and ventricles once again are in diastole together and the cycle begins anew.

Cardiovascular Electrophysiology

The heart is capable of creating its own electrical impulses and controls the route that the impulses take via a specialized conduction pathway. This pathway is comprised of five elements: the sino-atrial (SA) node, the atrio-ventricular (AV) node, the bundle of His, the left and right bundle branches, and the Purkinje fibers.[9] The SA node is widely regarded as the natural pacemaker of the heart.[9] The SA node releases electrical stimuli at regular intervals where the rate is dictated by the needs of the human body.[2] Each stimulus passes through the myocardial cells of the atria and creates a wave of contraction that spreads rapidly though the walls of both atria.[10] The heart is comprised of a half billion cells and the majority of the cells make up the ventricular wall. The rapid atrial contraction occurs as a result of 100 million myocardial cells contracting in less than one third of a second.[9]

The electrical stimulus from the SA node eventually reaches the AV node and is delayed briefly so that the contracting atria have enough time to pump all blood into the ventricles. Once the atria are empty of blood the valves between the atria and ventricles close. At this point the atria begin to refill and the electrical stimulus passes through the AV node and the bundle of His into the Bundle branches and the Purkinje fibers.[9] As the

ventricles contract, the right ventricle pumps blood to the lungs where carbon dioxide (CO_2) is released and oxygen is absorbed, while the ventricle pumps blood into the aorta from where it passes into the coronary and arterial circulation.[5]

At this stage in the cardiac cycle, the ventricles are mostly empty, and the atria are full and the valves between them are closed. The SA node is about to release another electrical stimulus and the process is about to repeat itself. The SA node and AV node contain only one stimulus.[9] Therefore, every time the nodes release a stimulus they must recharge before they can do it again. In this case, the SA node recharges while the atria are refilling, and the AV node recharges when the ventricles are refilling.[9] Again, this process takes less than one third of a second.

Right Heart Dysfunction

Right ventricular failure may be defined as the inability of the right ventricle of the heart to provide adequate blood flow through the pulmonary circulation at a normal central venous pressure.[11] Right ventricular failure is usually due to a combination of right ventricular pressure overload and contractile abnormalities on the right ventricular free wall. Decompensation may occur abruptly and catastrophically because of the unique aspects of right ventricular physiology.[11] With long-standing severe right-sided heart failure, the central areas of the liver can become fibrotic, creating so-called cardiac cirrhosis.[11]

Hepatic Physiology

General Hepatic Anatomy

The liver is the largest organ in the human body. The liver is comprised of two lobes that are typically described in two ways, by morphologic anatomy and by functional anatomy.[12] Located in the upper right quadrant of the abdominal cavity beneath the right hemidiaphragm, the liver is protected by the rib cage and maintains it position through peritoneal reflections, referred to as ligamentous attachments.[12] Although not true ligaments, these attachments are avascular and are in continuity with the Glisson capsule or the equivalent of the visceral peritoneum of the liver.

The liver is a very vascular organ and at rest receives up to 25% of the total cardiac output, which is more than any other organ. Its dual blood supply is uniquely divided between the hepatic artery, which contributes to 25% to 30% of the blood supply, and the portal vein, which is responsible for the remaining 70% to 75% of the blood supply.[12] The arterial and portal blood ultimately mixes within the hepatic sinusoids before draining into the systemic circulation via the hepatic venous system.[12]

Portal Venous System

The portal vein provides the bulk of the nutritive blood supply to the liver. The portal vein forms from the confluence of the superior mesenteric vein and splenic vein behind the neck of the pancreas. Additional venous branches that drain into the portal vein include the coronary (left gastric) vein, cystic vein, and the tributaries of the inferior mesenteric, right gastric, and pancreaticoduodenal veins.[13] The portal vein does not possess any valves and is a low-pressure system, typically measuring between 3 to 5 mmHg. The coronary vein is of particular importance clinically as is becomes a major

portasystemic shunt in the face of portal hypertension and feeds the gastroesophageal variceal complex.[13] The main portal vein courses cranially toward the liver as the most posterior structure within the hepatoduodenal ligament to divide into the left and right portal veins at the liver hilum.[14]

The venous drainage of the liver is through the intrahepatic veins that ultimately coalesce into three hepatic veins that drain into the IVC superiorly. The left and middle hepatic veins may drain directly into the IVC but more commonly form a short common trunk before draining into the IVC.[13] Additional drainage occurs directly into the IVC via the short retrohepatic veins, and on occasion, an inferior right accessory hepatic vein.[13]

Cirrhosis

Cirrhosis is the final pathological result of various chronic liver diseases and fibrosis is the procures of cirrhosis.[15] Many types of cells, cytokines, and miRNAs are involved in the initiation and progression of liver fibrosis and cirrhosis. Defenestration and capillarization of the liver sinusoidal endothelial cells are a major contributing factor to the hepatic dysfunction in cirrhosis.[16] The etiology of cirrhosis varies geographically, with alcoholism, chronic hepatitis C virus infection, and non-alcoholic fatty liver disease (NAFLD).[16] Although the causes of cirrhosis are multifactorial, there are several pathological characteristics that are common to all cases of cirrhosis, including degradation and necrosis of hepatocytes, and replacement of liver parenchyma by fibrotic tissue and regenerative nodules, and loss of liver function.[15] Fibrosis as a precursor of cirrhosis is a pivotal pathological process in the evolution of all cirrhosis.

Ascites and Portal Hypertension

The manifestation of ascites is an important landmark in the progression of cirrhosis. Ascites is a pathological accumulation of peritoneal fluid commonly observed in decompensated cirrhotic states. Its causes are multifactorial, but principally involve significant volume and hormonal dysregulation in the setting of portal hypertension.[17] The diagnosis of ascites is considered in cirrhotic patients given a constellation of clinical and laboratory findings, and ultimately confirmed, with insight into etiology, by imaging and paracentesis procedures.[17] Ascites is associated with numerous complications including spontaneous bacterial peritonitis, hepatohyrdothorax, and hepatorenal syndrome. Given the complex nature of ascites and associated complication, it is not surprising that it heralds increased morbidity and mortality in cirrhotic patients.[8]

Portal hypertension is defined as being 6 mmHg or greater as measured by the wedged hepatic vein gradient, and in particular, ascites formation usually occurs at 8 mmHg or greater. Thus, in the setting of portal hypertension, backflow and stasis of vasodilatory substances being to accumulate. Appropriately in this sense, the renin-angiotensin-aldosterone system (RAAS) is activated and leads to aggressive fluid retention.[8] In brief, renin is secreted from the renal juxtaglomerular apparatus (JG) around the proximal nephrons in response to changes in vascular pressures, changes in serum sodium, and from activation of the sympathetic nervous system.[8] It in turn will convert angiotensinogen (made in the liver) to angiotensin I which is further converted to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II has multiple important functions that drive fluid acquisition and retention, including stimulation of thirst drive, release of aldosterone from the adrenal cortex, and secretion of vasopressin

from the posterior pituitary.[18] The excess retained blood volume is thought to filter directly from both the liver surface and the mesenteric vessels.[18] This is due to increased hydrostatic pressure and vascular wall permeability, and concurrently decreased oncotic (osmotic) fluid retention in the form of absolute or relative hypoalbuminemia.[18]

Ascites represents a very common manifestation of decompensated cirrhosis and thus on presentation if cirrhosis has not already been defined for the patient, risk factors for its usual precursors, namely alcoholic use, viral hepatitis, and NASH should be explored. The clinical presentations of ascites are variable: it can occur slowly as observed in common and classical liver diseases or suddenly in new mechanical obstruction of the major vessels.[19] While ascites represents a natural result of cirrhosis, its appearance should prompt a careful investigation for other causes and complications as well. The most common clinical presentations associated with liver related ascites are an increased abdominal girth, abdominal fullness, discomfort or ache, shortness of breath, early satiation, and sense of reduced mobility.[19]

Renal Physiology

Kidney Function and Filtration

The kidneys function in a wide variety of ways necessary for health. They excrete metabolic waste, regulate fluid and electrolyte balance, promote none integrity, and more. These two bean-shaped organs interact with the cardiovascular system to maintain hemodynamic stability. Renal blood flow (RBF) and glomerular filtration are important aspects for sustaining proper organ functions.[20] A delicate balance exists between renal blood flow and the glomerular filtration rate as changes in one may ultimately affect the other.[20]

Urine is a waste product formed from excess water and metabolic waste molecules during the process of renal system filtration. The primary function of the renal system is to regulate blood volume, plasma osmolarity, and waste removal via urine. Urine formation occurs during three processes: filtration, reabsorption, and secretion.

During filtration, blood enters the afferent arteriole and flows into the glomerulus where blood components that can be filtered, such as water and nitrogenous waste, will move towards the inside of the glomerulus, and nonfilterable components, such as cells and serum albumin, will exit via the efferent arteriole.[20] These filterable components accumulate in the glomerulus to form the glomerular filtrate. Normally about 20% of the total blood pumped by the heart each minute will enter the kidneys to undergo filtration; this is known as the filtration fraction. The remaining blood flows through the rest of the body to facilitate tissue perfusion and gas exchange.[20]

The next step is reabsorption, during which molecules and ions will be reabsorbed into the circulatory system. The fluid passes through the proximal and distal convoluted tubules, loop of Henle, and collecting duct as water and ions are removed. In the collecting duct, secretion will occur before the fluid leaves the ureter in the form of urine.[20] During secretion some substances such as hydrogen ions and creatinine will be removed from blood through the peritubular capillary network into the collecting duct.[20] The end product of all these processes is urine, which is essentially a collection of substances that were not reabsorbed during glomerular filtration or tubular reabsorption.

An important interplay between RBF and proper kidney function is the renin-angiotensin-aldosterone system, also known as RAAS. The specific mechanisms that describe this pathway are noted above. RAAS preferentially constricts efferent arterioles

to increase the filtration when RBF is low.[21] Angiotensin II also induces expression of aldosterone in the adrenal cortex which increases the number of sodium channels. Furthermore, RAAS activation increases the activity of the sodium/potassium pump and enhances potassium/hydrogen excretions in principal cells.[21] These simultaneous effects act to create a gradient for sodium and water reabsorption.

Glomerular Filtration Rate

The glomerular filtration rate (GFR) is the amount of fluid filtered from the glomerulus into Bowman's capsule per unit time. It indicates the condition of the kidney and can be used to help guide management in cases such as chronic kidney disease. The glomerular filtration barrier is uniquely designed to prevent passage of certain substances according to size and charge.[20] It is composed of an inner layer of fenestrated capillary endothelium which is freely permeable to everything except blood cells and 100 nm or greater molecules.[20] The GFR can be determined by the Starling equation, which is the filtration coefficient multiplied by the difference in glomerular capillary oncotic pressure and Bowman space oncotic pressure subtracted from the difference between glomerular capillary hydrostatic pressure and Bowman space hydrostatic pressure. Increases in glomerular capillary hydrostatic pressure cause increases in the net filtration pressure and GFR. However, increases in Bowman space hydrostatic pressure causes a decrease in the filtration pressure and GFR.[22] Increases in protein concentration raise glomerular capillary oncotic pressure and draw in fluids through osmosis, thus decreasing GFR.[22]

The kidneys have mechanisms designed to preserve GFR within a certain range. If GFR is too low, metabolic wastes will not get filtered from the blood into renal tubules. If GFR is too high, the absorptive capacity of salt and water by the renal tubules becomes

overwhelmed. Autoregulation manages these changes in GFR and RBF. There are two mechanisms by which this occurs. The first is known as the myogenic mechanism. During increased stretch, renal afferent arterioles contract to decrease GFR.[22] The second mechanism is called tubuloglomerular feedback. Increased renal arterial pressure increases the delivery of fluid and sodium to the distal nephron where the macula densa is located. In this mechanism, ATP is released, and calcium increases in the granular and smooth muscle cells of the afferent arteriole. This causes arteriole constriction and decreased renin release. This process helps decrease GFR and maintain it within a limited range. The result is vasodilation and decreased release of renin in an attempt to increase the glomerular filtration rate.[20]

End Stage Renal Disease

The process of the removal of waste and extra water from the blood is called dialysis. It serves as an artificial replacement to kidney functioning, especially in the case of renal failure. Dialysis cannot completely replace lost kidney function, but to some extent manages its activities by means of diffusion and ultrafiltration. It is commonly done in chronic renal failure (CRF) when the glomerular filtration rate falls below normal levels.[23] CRF is a condition where there is a loss of kidney function over a period of months or years. CRF can be diagnosed and measured via serum creatinine levels, which are a degradative product of muscle protein. There are five stages of CRF based on the GFR, and dialysis is preferred in stage five; this stage is also known as end stage renal disease (ESRD).[23] Dialysis is the preferred way to treat ESRD and remove accumulated toxins from the body.

A vascular access is a hemodialysis patient's lifeline. Hemodialysis is a treatment for kidney failure that uses specialized machinery to send the patient's blood through a filter, called a dialyzer, outside the body. The access is a surgically created vein that is used to remove and return blood during hemodialysis. Inside the dialyzer, the blood flows through thin fibers that filter out the wastes and extra fluid.[23] The machine returns the filtered blood to the body through a different tube. A vascular access allows for large amounts of blood to continuously flow during hemodialysis treatments to filter as much blood as possible per treatment. Two types of access points are designed for long-term use and include the arteriovenous (AV) fistulae and the AV graft.[24]

An AV fistula is a connection, made by a vascular surgeon, of an artery to a vein.[24] The surgeon commonly creates the AV fistula in the forearm or upper arm. An AV fistula will cause additional pressure and extra blood to flow into the vein. The larger vein provides easy and reliable access to the blood vessels. Without this kind of access, regular hemodialysis would not be possible.[24] Untreated veins could not withstand dialysis needle insertion because they would collapse under such strong amounts of suction. An AV fistula procedure is considered a minor surgery and is typically performed on an outpatient basis.[24]

CHAPTER TWO

Methods and Materials

Hypotheses

The aim of this study was to determine the prevalence of high-flow AV fistula access in patients with chronic HD and determine the effects that they impose on cardiac function. Three hypotheses served as the principle guidelines for the collection and interpretation of clinical patient information. First, right-sided heart failure with pulmonary hypertension and cardiogenic ascites may occur in the majority of patients with ESRD who present with ascites. Second, the degree of hepatic congestion on liver biopsy with HVPG assessment may be associated with outcomes, including survival. Third, AV fistula velocities may have an impact on development of high-output congestive heart failure, pulmonary hypertension, and sequela adverse events.

Patient & Cohort Selection

Given the parameters defined during the initial stages of this research project, a retrospective cohort of consecutive patients who presented with end-stage renal disease (ESRD) was developed. These patients were maintained on hemodialysis and presented with evidence of new onset ascites. The vast majority of patient information was obtained through the review of medical records from a large-scale outpatient hepatology clinic. The procedural goals associated with this observational study were to describe the causes, characteristics, and factors associated with ascites in this cohort of patients.

Patients were recruited for this retrospective cohort study from hepatology clinics that were affiliated with the Baylor Scott and White Health All Saints Medical Center from 2011 to 2019. Twenty-seven patients were included in this study with a higher percentage of male participants than female participants; 52% were males and 48% were females. The median age of patients in this study was 56 years and the age range spanned from 28 years to 75 years. In addition, this cohort study was comprised of a diverse patient population from varying demographic backgrounds.

All patients included in this cohort were identified with symptoms and complications attributed to ESRD. In addition to this clinical presentation, comorbidity was documented for each patient in the population. Comorbidity is frequently associated with declined health outcomes and increased complications during clinical management. Comorbid conditions were noted for all patients in the population; 63% had diabetes mellitus (DM), 26% had coronary artery disease (CAD), and 93% had hypertension (HTN). These were assessed as additional risk factors and were handled on a case-to-case basis during the course of diagnosis and clinical treatment. In order to further enhance the level of comprehensive patient analysis, hepatomegaly and splenomegaly were evaluated via imaging techniques. Enlargements in the liver and spleen were noted as possible evidence of cirrhosis or other liver conditions.

Patients were evaluated with echocardiographic assessment, transjugular liver biopsy with hepatic venous pressure gradient (HVPG), and analysis of peritoneal fluid. Laboratory results for each individual patient were assessed for a myriad of physiological values. The most frequently utilized laboratory tests were complete metabolic panel (CMP), complete blood count (CBC), and prothrombin time with international

normalized ratio (INR). In addition, patients with malignancy, thrombotic disease, or infection were excluded from this study. History of acute viral hepatitis further excluded patients from being included in this retrospective cohort study.

Study Design

Definitive evaluation of ascites in patients with ESRD maintained on dialysis was performed via a variety of methods with the intent to classify and diagnose symptoms. Risk factors were identified for the development of ascites and outcomes in this patient population. A prospective cohort of patients was developed based on the parameters defined in the hypothesis for this study.

A chart review was preformed to gather clinical and demographical data regarding the patients that comprise this prospective cohort. All patients included in this analysis were diagnosed with ESRD and required hemodialysis. These patients presented in clinic with refractory ascites which did not resolve after treatment with paracentesis. Patients with underlying hepatitis (i.e. HCV) were included in this study if the liver biopsy did not reveal any significant activity, fibrosis, or portal hypertension that could potentially be attributed to chronic Hepatitis C. Laboratory results were obtained from all patients, including CMP, CBC, and prothrombin time with INR. When available, peritoneal fluid was reviewed for total protein, cell count, albumin, and serum-ascites albumin gradient.

All patients included in this study underwent echocardiographic assessment. Echocardiographic data was reviewed with particular attention given to specific parameters that described the ventricular function and potential for right-sided congestive heart failure. The size of the right atrium (RA) and the right ventricle (RV) were

measured and evaluated for dilation. In addition, the right ventricular systolic pressure (RVSP) was analyzed and patient data was recorded regarding the pressure generated in mmHg. If patients in the prospective cohort demonstrated a RVSP above 40mmHg, this was noted as abnormally high when compared to the standard systolic pressure value for the right ventricle. The combination of increased right-heart size and atypical pressure gradients provides clinical indication of a reduced systolic function. Further assessment of echocardiographic data included analysis of pulmonary velocity acceleration time (PVAT). In this prospective cohort study, patients were assessed for a normal PVAT of 120 msec. Patients who demonstrated a PVAT below the standard value were considered for additional cardiovascular assessment in order to determine the extent of right heart function.

A large portion of this patient population underwent paracenteses and transjugular liver biopsy with HVPG assessment. Hepatic vein catheterization with measurement of HVPG is currently the standard procedure for determining portal pressure. It is calculated as the difference between the wedge hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP). The WHVP is measured by occluding the main hepatic vein which prohibits blood flow and indicates the pressure that is present in the right hepatic vein. In addition, FHVP is a measure of the pressure of the unoccluded hepatic vein. The combination of these measurements reflects the portal pressure. Liver catheterization allows for a transjugular biopsy to be performed during the same procedure in order to obtain these data points. Since HVPG reflects portal pressure, changes in this measurement indicate alterations in the factors that determine portal pressure and hepatic vascular resistance.

Data regarding HVPG measurements in this cohort population were tabulated and summarized. Data included histopathological findings, evidence of hepatic congestion, and HVPG values. This data was tabulated and summarized with a Kaplan-Meier curve, also known as a product limit estimator, which was utilized as a non-parametric statistic to estimate the survival function from longitudinal patient data. This mortality assessment estimated the fraction of cohort participants living for a specified amount of time after receiving treatment.

Arteriovenous (AV) fistula velocities were obtained through the review of hemodialysis records, as well as pertinent data points related to hemodialysis settings. Information regarding dialysis units were obtained from patient information and these centers where contacted and presented with an internal review board (IRB) certificate in order to acquire the patient data. AV fistula velocity was the principle variable that was examined when reviewing patient data from the dialysis centers. The start date and duration of patient treatment was noted in order to assess the longitudinal effects of dialysis on AV fistula blood flow and its potential relation to the pressures in the right heart chambers. Additional parameters regarding patient AV fistulas were noted to include information such as AV fistula ligation, newly created AV fistulas, and multiple AV fistula access points.

Statistical Analysis

All patient-specific data was de-identified to ensure patient confidentiality and access to data was only granted to co-investigators who were approved and credentialed. Frequencies and percentages were computed for different categorical variables. Statistical analysis was performed using STATA (Version 16.1, STATA Corp., College Station,

TX). Pairwise comparisons between categorical variables were assessed using the chi-square and Fisher's exact tests. Continuous variables were assessed for normal distribution and comparisons among variables with normal distribution were made using the two-sample T test (student's T test) and variables with nonparametric distribution were made with Wilcoxon rank-sum test. Kaplan-Meier analysis with log-rank test of equality was used to examine survival. A p-value of 0.05 was considered statistically significant and all comparisons were two-tailed.

CHAPTER THREE

Results

Demographics and Comorbidity

Patient demographics were utilized as a method of patient categorization which allowed for statistical analysis of comorbidities and medical laboratory results. Twenty-seven patients with ESRD and ascites were identified and selected for this retrospective cohort study. The range of patient ages spanned from 28 to 75 years and the median age range of participants in this study was 56 years. A slight majority of the patient population was comprised of males with an overall percentage of 52% male and 48% female. The average BMI recorded for each patient was approximately 26.2 (range 17.4 to 35.5). Comorbidities were evaluated in this patient population in order to assess the potential for worsened health outcomes in patients diagnosed with diabetes (DM), coronary artery disease (CAD), and hypertension (HTN). Based on the patient data that was obtained from this study, 63% of patients had diabetes, 26% had coronary artery disease, and 93% of patients had hypertension. In addition, abdominal imaging techniques were utilized in order to assess enlargements in either the liver (hepatomegaly) or the spleen (splenomegaly).

Patient Demographics	
Age (median, range)	56 (28-75)
Male	52%
White	43%
Hispanic	38%
Black	19%
Died during follow up	38%
Diabetes	62%
Coronary Artery Disease	24%
Hepatomegaly as evidenced on imaging	28%
Splenomegaly as evidenced on imaging	48%

Table 1. Patient demographics were evaluated and analyzed throughout the course of this study. The average age of patients involved was recorded along with patient ethnicity. Comorbidities and evidence of hepatomegaly or splenomegaly were noted for analysis.

Results from Paracenteses

The vast majority of patients (82%) required procedural intervention in order to manage recurrent ascites. When abdominal distention would not subside, paracentesis was performed in order to mitigate abdominal pain and conduct peritoneal fluid analysis (Figure 2). All patients with peritoneal fluid available (19/19) demonstrated an elevated protein level of 4.3 g/dL (range 3.0 to 6.0 g/dL) and 84% of these patients had a serum-ascites albumin gradient (SAAG) of less than or equal (≤) to 1.1 approximately. The ascites albumin gradient was measured in order to assess the degree of portal hypertension present in patients with ascites.[25] It should be noted that SAAG is determined by measuring the serum albumin and ascitic fluid albumin concentrations simultaneously and then subtracting the ascitic fluid albumin from the serum albumin. In addition to paracenteses, complete blood count (CBC) and complete metabolic panel (CMP) laboratory tests were conducted in order to assess a variety of clinical factors including prothrombin time with INR and albumin concentrations.

Peritoneal Fluid Analysis (N=12)	
Patients with high-protein ascites	100%
Ascites protein (g/dL; median, range)	4.5 (3 - 6)
Patients with low serum-ascites albumin gradient, SAAG (≤ 1.1) *	75%
Ascites albumin (g/dL; median, range)	2.1 (1.3 - 3.0)

Table 2. Analysis of peritoneal fluid in patients presenting with ascites was conducted via paracentesis procedures. All patients were evaluated for high protein levels in abdominal fluid. Ascites protein was measured in standard units of g/dL and serum ascites albumin gradients (SAAG) were noted if they were below standard values.

Laboratory Data	Median	Range
Bilirubin (mg/dL)	0.7	0.3 - 2.0
INR *	1.2	1.0 - 1.5
Albumin (g/dL)	3	2.3 - 4.3
Alkaline phosphatase (U/L)	137	60 - 811
AST (U/L)	18	6 - 94
ALT (U/L)	15	8 - 53
Platelets (x10_3 μg/L)	173	81 - 430

Table 3. Patient laboratory data included results from several blood panels including CBC, CMP, and INR. Parameters were recorded in order to evaluate the potential for liver damage with particular emphasis on bilirubin (mg/dL) and albumin (g/dL). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were also recorded.

Results from Liver Biopsy

Liver biopsies were performed for twenty-three of the twenty-seven (85%) patients that comprised this retrospective cohort. Given this data population, eighteen of the patients (78%) underwent transjugular liver biopsy with a HVPG assessment. Within the context of a clinical environment, HVPG measurements are the most efficient method for evaluating the presence and severity of portal hypertension.[26] Among the patients with liver biopsies, seventeen of the twenty-three (74%) had none to minimal (stage 0 to 1) evidence of fibrosis and six patients presented with evidence of mild to moderate (stage 2 to 3) fibrosis. Biopsy evidence of passive hepatic congestion was present in

fourteen of the twenty-three patients (61%). Values obtained for analysis of passive hepatic congestion were used to determine potential dilation of the central hepatic veins and subsequent hepatomegaly via CT scans. In those patients who underwent transjugular liver biopsies, fifteen of the eighteen (83%) had normal HVPG (< 6 mmHg) and three demonstrated mildly elevated HVPG (6 to 8 mmHg).

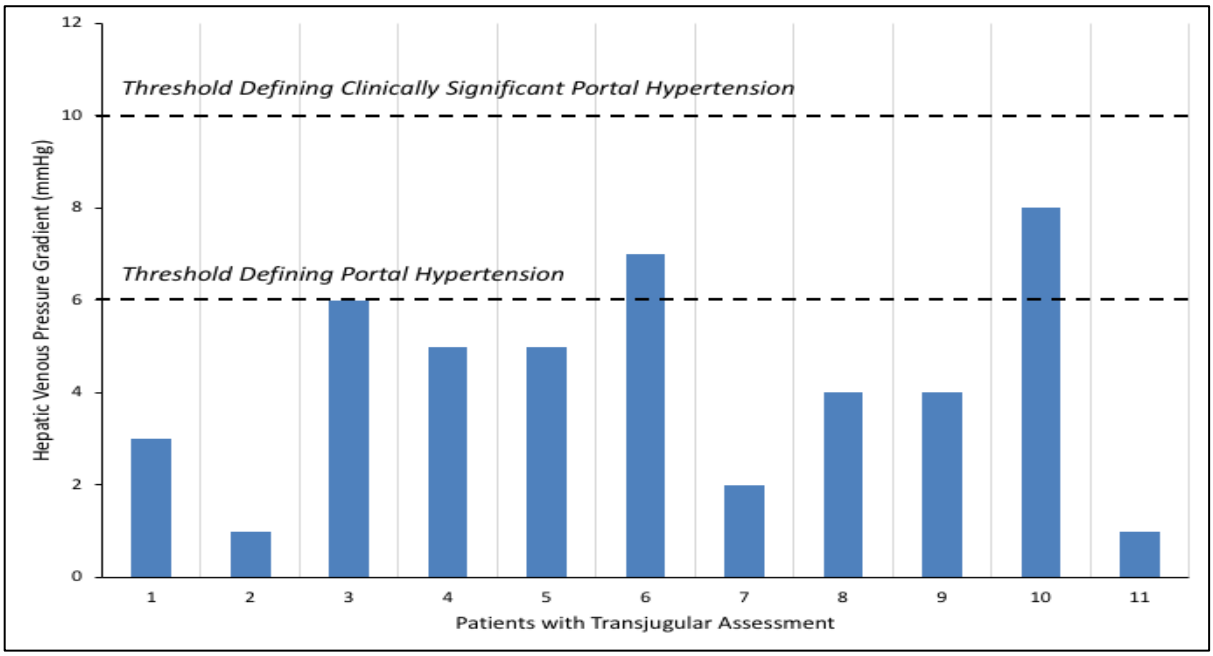

Figure 1. Transjugular hepatic venous pressure gradient measurements were recorded and evaluated during liver biopsy. The majority of patients presented with no evidence of portal hypertension and only three patients had mildly evaluated HVPG. In this study, no patients presented with severe or clinically significant portal hypertension. The median HVPG measurement was 4 mmHg and the median free HVPG was 10 mmHg.

Results from Echocardiography

Echocardiographic assessment was performed in twenty-six of the twenty-seven (96%) patients that comprised this retrospective cohort study. It should be noted that assessment via liver biopsy in one patient without an echocardiogram revealed overt hepatic congestion. This provided evidence for definitive clinical results and no

further assessment tests were conducted. These right heart parameters included right ventricular (RV) systolic pressure greater than (>) 40 mmHg, reduced RV systolic function, right atrial or right ventricular dilation, and tricuspid valve regurgitation. At least one parameter that pertained to right heart dysfunction was observed in twenty-four of the twenty-six (92%) patients. Data obtained from echocardiography was analyzed in order to determine the efficiency of the generation of stroke volume in the right-heart.[27]

Echocardiogram - Right Heart Dysfunction	
Right Ventricular Systolic Pressure, RVSP (median, range)	50 (22 - 80)
RVSP > 40 mmHg *	16/20 (80%)
RVSP > 50 mmHg *	10/20 (50%)
Right Atrial/Right Ventricle Dilation	9/20 (47%)
Reduced Right Ventricular Systolic Function	6/20 (30%)
Tricuspid Valve Regurgitation	14/20 (70%)

Table 4. Evaluation of RVSP was the primary method of assessment for right-heart function within the patient population. Systolic pressures above 40 mmHg and 50 mmHg were noted as statistically significant. In addition, tricuspid valve (TV) regurgitation was evaluated in all patients with echocardiographic assessment.

Kaplan-Meier Assessment

In the majority of cases, patients were followed for a median of seven months and up to five years during the course of this longitudinal analysis. Given the progression of clinical complications and the age of this cohort population, eight of the twenty-seven (30%) patients died during the course of follow-up. In select cases, longitudinal patient data was not available due to missing information from failure of patients to attend follow-up appointments. Furthermore, it should be noted that ascites resolved in one patient and cardiovascular function improved following arteriovenous fistula ligation. The presence of elevated free hepatic venous pressure greater than (>) 12 mmHg was

associated with an overall increased risk in mortality (p = 0.07) and on longitudinal follow-up (p = 0.04; Kaplan-Meier).

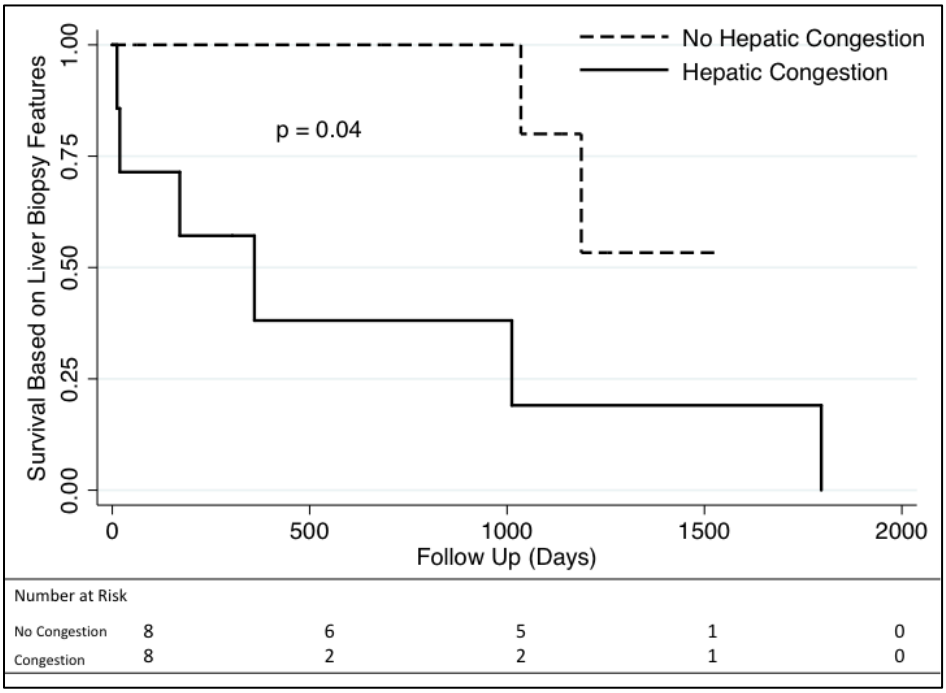

Figure 2. Kaplan-Meier Survival curve based on the presence of sinusoidal dilation of liver biopsy indicating overt hepatic congestion. Survival based on clinical features examined during liver biopsy were observed and a statistically significant value (p = 0.04) was noted for analysis of hepatic congestion during follow-up.

CHAPTER FOUR

Discussion

Ascites and Overall Cardiac Function

The pathogenesis of non-cirrhotic or cardiogenic ascites is not well understood. The formation of ascites is a dynamic process that is often dependent on factors that are influenced by the formation and resorption of fluid. Patients with ESRD who are maintained on hemodialysis who present with ascites are presumed in many cases to have underlying cirrhosis with portal hypertension. However, as investigated in this study, onset of ascites in patients with ESRD on hemodialysis may in fact be cardiogenic as a consequence of right-sided heart failure.

This study reported characteristics of ascites, end-stage renal disease (ESRD), and arteriovenous (AV) fistula velocities in 27 patients who were maintained on hemodialysis. According to the literature, ascites is characterized by a marked center to center variability in incidence and a wide range of onset conditions. The results from this study are consistent with the complications experienced by patients who present with ESRD. Specifically, this study examined non-cirrhotic and non-nephrogenic forms of abdominal fluid collection which, for the intensive purposes of this study, are referred to as cardiogenic ascites.

In this study, the majority of patients who presented with abdominal distention had ascites which was moderate in intensity. This can be attributed to the fact that multiple factors are known to simultaneously contribute to ascites, including volume overload, elevated hepatic venous pressure, increased membrane permeability, and

impaired lymphatic drainage. The degree of severity of ascites was noted to correlate with a low serum albumin level and a low cardiac ejection fraction. In the study conducted by Han *et al*., nephrogenic ascites was shown to have an elevated protein content, low SAAG values, and low leukocyte counts.[28] Since cardiac failure is not uncommon in patients with ESRD, it can reasonably be inferred that high SAAG values are correlated with ascites in this patient population.[28] Furthermore, several patients noted in this study presented with portal hypertension secondary to heart failure. This shows that not all patients with ascites have cirrhosis. Rather, it is the combined effects of cardiac disease that may lead to the development of so-called nephrogenic or non-cirrhotic ascites.

The use of liver biopsy in order to obtain tissue for histological interpretation is a long-standing procedure in the field of hepatology. This procedure remains the standard for diagnosis to which numerous other equivalent medical tests are held. Examination via liver biopsy provides reliable data points regarding HVPG which contribute to the diagnosis of ascites in patients with ESRD. This study provides a unique setting in which HVPG has significant diagnostic utility when investigating ascites that is not obviously caused by portal hypertension. HVPG can assist when differentiating between cardiogenic ascites, tumoral ascites, or ascites from portal hypertension in the setting of cirrhosis.

Stable and reliable vascular access is a fundamental requirement for the maintenance of patients on long-term hemodialysis. For most patients on hemodialysis, a surgically constructed arteriovenous fistula is the most suitable option for vascular access. Alternatively, other long-term vascular access options such as an arteriovenous

graft are plausible for specific patients on hemodialysis within a given population. Selection of either an arteriovenous fistula or graft primarily depends on the "target" vein that the vascular surgeon intends to use for access. While the development of these forms of vascular access have made hemodialysis are the foremost option for long-term maintenance, they are not without their challenges.

The decision-making procedures in regard to where to place a fistula can be quite challenging. This decision-making process is often guided by the size and quality of the vessels in the chosen arm which is balanced against the complexity of the surgery and the fistula that will ultimately develop.[29] There is increasing evidence that physicians should actively question the wisdom of retaining unused fistulas and carefully consider the position and size of fistulas in patients who require ongoing vascular access for hemodialysis. Some of this evidence points to increased risk of cardiovascular morbidity and mortality that could be associated with these arteriovenous fistulas.[28]

It can be observed from the results of this study that right-sided heart failure can cause ascites by increasing the hepatic venous pressure gradient (HVPG). The combination of this specific form of cardiac failure along with passive hepatic congestion can be a major cause of non-cirrhotic ascites. In this study, the majority of patients who presented with ascites displayed symptoms that were either mild or moderate in intensity. The degree of severity for ascites can be attributed to the fact that multiple factors can contribute simultaneously to the development of abdominal distention.[29] These clinical factors can include, but are not limited to volume overload, elevated free hepatic venous pressure, increased permeability of the peritoneal membrane, and impaired drainage of the lymphatic system. This study further examined the severity of ascites in relation to

the right-sided cardiac function of this patient population. Since it was theorized that cardiac dysfunction intensified the severity of ascites, cardiovascular referral was made essential for such cases in order to achieve optimization of therapy.

A relatively infrequent but important complication of both arteriovenous fistulas and grafts is cardiac failure. While the association of an arteriovenous fistula with heart failure is not all that common, this study demonstrates that there is increasing evidence that an AV fistula has the potential to add to the extremely high burden of cardiovascular disease risk in patients with advanced kidney disease. Implementation of standardized screening to include extensive echocardiographic examinations to evaluate all structural heart abnormalities may help identify hemodialysis patients at high risk for cardiogenic ascites.[30] These cardiovascular complications may be induced by the creation of an arteriovenous fistula access point for dialysis. It can be conceded from the results of this retrospective cohort study that accurate models to predict cardiac pressures and risk for hepatic congestion following surgical creation of arteriovenous fistulas are urgently needed. These models can help in choosing the best vascular access and treatment protocol for each patient.

The prevalence and pathophysiology of pulmonary hypertension in patients on hemodialysis has been extensively studied. However, this study examined data on the development of right ventricular (RV) dysfunction in ESRD patients who were maintained on hemodialysis and peritoneal dialysis (PD). A few recent studies have examined similar effects of AVF's on the echocardiographic parameters associated with RV dysfunction.[30] Han *et al*. studied the degree of right heart dysfunction in patients on hemodialysis.[28] Specifically, Han observed that the right ventricular ejection fraction

was preserved in the majority of patients. Furthermore, right ventricular dysfunction was more prevalent in hemodialysis patients when compared to PD patients. The results of this study suggest that the development of RV dysfunction in ESRD patients could be a result of AVF-dependent high-output congestive heart failure (CHF) in patients undergoing hemodialysis.

Preserving dialysis access is a priority to both dialysis patients and the physicians who oversee their care. Ligation or closure of arteriovenous fistulas in patients who are treated with hemodialysis has typically been reserved for those patients who experience complications with apparent access failure.[29] Broadly, the majority of transplant physicians suggest that ligation of an AVF is not routinely required whereas others believe that AVF ligation is associated with significant beneficial effects on cardiac functions and survival. Many studies have investigated the impact of AVF's on echocardiographic indices of cardiac morphology and function.[29] These studies have demonstrated increases in stroke volume, LV end-diastolic measurements, and contractility within one week after the surgical construction of an AVF.[28,29] It should be noted that the impact of the physiological effects of an AVF on cardiac function are not well-defined within the existing literature. While this study, among many others, suggests that an AVF compounds several factors for worsening heart failure, others suggest that when combined with an increased ejection fraction they could be potentially beneficial. Ultimately, the benefits associated with AVF maintenance or closure should be weighed against the small but known potential complications associated with the ligation procedures.

CHAPTER FIVE

Conclusion

This retrospective cohort analysis is not intended to undermine the use of an arteriovenous fistula for vascular access for hemodialysis. However, there are circumstances in which an AV fistula is either not required or has the potential to cause deleterious effects on overall cardiac function and increased patient mortality risk.

All patients included in this study presented with evidence of cardiogenic ascites and features that were consistent with right-heart failure or hepatic congestion. In patients who present with end-stage renal disease, right-heart failure with evidence of passive hepatic congestion can be identified as a major contributor in non-cirrhotic ascites. It was demonstrated that echocardiography and transjugular liver biopsy assessment can define both the cause and prognosis associated with ascites in patients with ESRD. Overt hepatic congestion on liver biopsy was associated with increased risk in mortality.

Right-heart failure may be an under-recognized cause of ascites in patients with ESRD on hemodialysis. AV fistula and graft velocity could influence risks associated with the onset of right heart failure, hepatic congestion, and ascites. Assessment of the cardiovascular effects of hemodialysis on ESRD, including special attention to high output heart failure and arteriovenous fistula hemodialysis, may be important in further defining risk factors and management strategies. Elevated free hepatic venous pressure gradients (HVPG) by transjugular liver biopsy assessment may be associated with

increased mortality risk in patient populations. Ultimately, further study is required in order to obtain a more comprehensive understanding of this atypical clinical presentation.

REFERENCES

1. Anderson RH, Razavi R, Taylor AM. Cardiac anatomy revisited. *J Anat*. 2004;205(3):159-177. doi:10.1111/j.0021-8782.2004.00330.x

2. Buckberg GD, Nanda NC, Nguyen C, Kocica MJ. What Is the Heart? Anatomy, Function, Pathophysiology, and Misconceptions. *J Cardiovasc Dev Dis*. 2018;5(2). doi:10.3390/jcdd5020033

3. Delicce AV, Makaryus AN. Physiology, Frank Starling Law. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2018. http://www.ncbi.nlm.nih.gov/books/NBK470295/. Accessed March 8, 2019.

4. Oberman R, Bhardwaj A. Physiology, Cardiac. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2020. http://www.ncbi.nlm.nih.gov/books/NBK526089/. Accessed March 25, 2020.

5. Greyson CR. Pathophysiology of right ventricular failure. *Crit Care Med*. 2008;36(1 Suppl):S57-65. doi:10.1097/01.CCM.0000296265.52518.70

6. Fukuta H, Little WC. The Cardiac Cycle and the Physiological Basis of Left Ventricular Contraction, Ejection, Relaxation, and Filling. *Heart Fail Clin*. 2008;4(1):1-11. doi:10.1016/j.hfc.2007.10.004

7. Alkhouli M, Sandhu P, Boobes K, Hatahet K, Raza F, Boobes Y. Cardiac complications of arteriovenous fistulas in patients with end-stage renal disease. *Nefrol Publicacion Of Soc Espanola Nefrol*. 2015;35(3):234-245. doi:10.1016/j.nefro.2015.03.001

8. Cleland JGF, Mareev Y. CRT for Heart Failure and ESRD. *J Am Coll Cardiol*. 2015;66(23):2630. doi:10.1016/j.jacc.2015.10.022

9. Costantini O. Basic Principles of Cardiac Electrophysiology. *Med Clin North Am*. 2019;103(5):767-774. doi:10.1016/j.mcna.2019.04.002

10. Foley RN, Parfrey PS. Cardiovascular disease and mortality in ESRD. *J Nephrol*. 1998;11(5):239-245.

11. Rao N, Worthley M, Disney P, Faull R. Dramatic Improvement in Decompensated Right Heart Failure due to Severe Tricuspid Regurgitation Following Ligation of Arteriovenous Fistula in a Renal Transplant Recipient. *Semin Dial*. 2014;27(2):E24-E26. doi:10.1111/sdi.12145

12. Abdel-Misih SRZ, Bloomston M. Liver Anatomy. *Surg Clin North Am*. 2010;90(4):643-653. doi:10.1016/j.suc.2010.04.017

13. Babadjanov J, Miler R, Niebauer K, Kirksey L. Arteriovenous Fistula Creation for End-Stage Renal Disease May Worsen Pulmonary Hypertension. *Ann Vasc Surg*. 2016;36:293.e1-293.e3. doi:10.1016/j.avsg.2016.03.020

14. Giallourakis CC. Liver Complications in Patients with Congestive Heart Failure. *Gastroenterol Hepatol*. 2013;9(4):244-246.

15. Zhou W-C, Zhang Q-B, Qiao L. Pathogenesis of liver cirrhosis. *World J Gastroenterol WJG*. 2014;20(23):7312-7324. doi:10.3748/wjg.v20.i23.7312

16. Skorecki KL, Brenner BM. Body fluid homeostasis in congestive heart failure and cirrhosis with ascites. *Am J Med*. 1982;72(2):323-338.

17. Unal A, Tasdemir K, Oymak S, et al. The long-term effects of arteriovenous fistula creation on the development of pulmonary hypertension in hemodialysis patients. *Hemodial Int Int Symp Home Hemodial*. 2010;14(4):398-402. doi:10.1111/j.1542-4758.2010.00478.x

18. MacRae JM, Levin A, Belenkie I. The cardiovascular effects of arteriovenous fistulas in chronic kidney disease: a cause for concern? *Semin Dial*. 2006;19(5):349-352. doi:10.1111/j.1525-139X.2006.00185.x

19. Chiejina M, Kudaravalli P, Samant H. Ascites. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2020. http://www.ncbi.nlm.nih.gov/books/NBK470482/. Accessed March 25, 2020.

20. Dalal R, Sehdev JS. Physiology, Renal, Blood Flow and Filtration. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2018. http://www.ncbi.nlm.nih.gov/books/NBK482248/. Accessed March 4, 2019.

21. Di Benedetto A, Marcelli D, D'Andrea A, et al. Risk factors and underlying cardiovascular diseases in incident ESRD patients. *J Nephrol*. 2005;18(5):592-598.

22. Vadakedath S, Kandi V. Dialysis: A Review of the Mechanisms Underlying Complications in the Management of Chronic Renal Failure. *Cureus*. 9(8). doi:10.7759/cureus.1603

23. Sharma S, Farrington K, Christopoulos C, Kozarski R, Gorog D. IMPAIRED ENDOGENOUS THROMBOLYSIS PREDICTS FISTULA THROMBOSIS IN END STAGE RENAL DISEASE. *J Am Coll Cardiol*. 2012;59(13 Supplement):E2097. doi:10.1016/S0735-1097(12)62098-1

24. Ori Y, Korzets A, Katz M, Perek Y, Zahavi I, Gafter U. Haemodialysis arteriovenous access--a prospective haemodynamic evaluation. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 1996;11(1):94-97.

25. Shahed FHM, Mamun-Al-Mahtab, Rahman S. The Evaluation of Serum Ascites Albumin Gradient and Portal Hypertensive changes in Cirrhotic Patients with

Ascites. *Euroasian J Hepato-Gastroenterol*. 2016;6(1):8-9. doi:10.5005/jp-journals-10018-1157

26. Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. *Nat Rev Gastroenterol Hepatol*. 2009;6(10):573-582. doi:10.1038/nrgastro.2009.149

27. Bellofiore A, Chesler NC. Methods for measuring right ventricular function and hemodynamic coupling with the pulmonary vasculature. *Ann Biomed Eng*. 2013;41(7):1384-1398. doi:10.1007/s10439-013-0752-3

28. Han SH, Reynolds TB, Fong TL. Nephrogenic ascites. Analysis of 16 cases and review of the literature. *Medicine (Baltimore)*. 1998;77(4):233-245. doi:10.1097/00005792-199807000-00002

29. Faull R, Rao N, Worthley M. Do arteriovenous fistulas increase cardiac risk? *Semin Dial*. 2018;31(4):357-361. doi:10.1111/sdi.12687

30. Ragupathi L, Johnson D, Marhefka GD. Right Ventricular Enlargement within Months of Arteriovenous Fistula Creation in 2 Hemodialysis Patients. *Tex Heart Inst J*. 2016;43(4):350-353. doi:10.14503/THIJ-15-5353