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FRAILTY IN PATIENTS UNDERGOING LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Nursing at the University of Kentucky

By
Candice Harvey Falls

Lexington, Kentucky

Director: Dr. Debra Moser, Professor of Nursing

Lexington, Kentucky

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ABSTRACT OF DISSERTATION

FRAILTY IN PATIENTS UNDERGOING LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION

Heart failure is a progressive condition that affects over 5.7 million Americans and costs associated with heart failure account for 2-3 % of the national health care budget. The high rates of morbidity and mortality along with increased costs from readmissions associated with advanced heart failure have led to the exploration of advanced treatments such as left ventricular assist devices (LVADs). LVADS have demonstrated morbidity and mortality benefit but cost remains extensive with costs per quality-adjusted years > $400,000. With this in mind, it is important to identify those who are most likely to benefit from an LVAD to avoid unfavorable outcomes and cost. Although general guidelines and criteria for patient eligibility have been established, choosing patients for LVAD implantation remains challenging. A new focus on patient selection involves the presence of frailty. While frailty has been studied in the elderly population and in patients undergoing cardiac surgery, frailty in patients undergoing left ventricular assist device (LVAD) remains controversial. The purpose of this dissertation was to examine measures of frailty in patients undergoing LVAD implantation. The specific aims of this dissertation were to: (1) identify a feasible frailty measure in adults with end-stage heart failure who underwent LVAD implantation by testing the hypothesis that frailty would predict 30 day rehospitalization rates using Fried's criteria, Short Physical Performance Battery test, handgrip strength, serum albumin and six minute walk test (2) Determine whether frailty measures improve 3 months post LVAD implantation (3) compare sensitivity of these three measures to change in frailty.

Surgical approaches, including heart transplantation and LVAD implantation, for patients with end-stage heart failure was discussed in this dissertation. Data from two subsets of participants who underwent LVADS at the University of Kentucky between 2014 and 2017 were included in the analysis for this dissertation. In the first study, we found that none of the measures are good predictors of frailty in patients with advanced heart failure who undergo LVAD implantation. Handgrip was the only marker of frailty that predicted 30 day readmission but the relationship was a negative association. In the second study, six-minute walk and low serum albumin levels reflect short-term

improvement in frailty. These simple measures may be used to determine those patients who are responsive to LVAD implantation.

The findings of these studies filled some gaps in our understanding of markers of frailty in patients undergoing LVADs. We gained a better understanding of which markers of frailty are likely to improve in most people after LVAD implantation and thus frailty should not preclude candidate selection for an LVAD. Subsequently, more research is needed to investigate these markers and outcomes.

KEYWORDS: left ventricular assist device; frailty, six minute walk test, albumin, hand grip strength

Candice Harvey Falls

July 24, 2019

FRAILTY IN PATIENTS UNDERGOING LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION

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July 24, 2019
Date

To my children, Montgomery and Maddison,

the loves of my life and sunshine of my soul

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Chapter One: Introduction

Heart failure is a progressive condition that affects 5.7 million Americans with more than 670,000 new cases a year. Costs of heart failure care account for 2-3% of the national health care budget.[-] Heart failure readmissions remain a burden with re-hospitalization rates of 20% at one month and 50% at 6 months. Over 43% of patients diagnosed with heart failure are hospitalized at least five times or more within 5 years of being diagnosed. There has been very minimal improvement in survival with medical treatment, particularly for patients with end stage heart failure with 1 year mortality in such patients of 15-35%.

The high rate of morbidity and mortality, and poor quality of life associated with heart failure has led to exploration of additional treatments for those with advanced heart failure that include left ventricular assist devices (LVADs). There is a morbidity and mortality benefit with use of LVADs, although the cost associated with their use is extensive.[-] In addition to fixed cost from the LVAD, which is greater than $100,000, LVADS may result in complications, such as bleeding and infection, that contribute to increased cost due to re-hospitalization, treatment and prolong hospitalization.

For the past decade, improvements have occurred in device technology, patient selection and postoperative management, which have led to decreased cost but despite these advances, costs per quality-adjusted years is still >$400,000. Iyengar et al examine the relationship between length of stay and cost and demonstrated that in the LVAD population, a 25% decrease in average length of postoperative stay was associated with a 40% decrease in average costs. They also reported that complications such as bleeding,

respiratory failure and infections after LVAD implant were associated with increased cost of $20,000-$50,000.

In order to gain better insight into to the expenses associated with complications associated with LVAD implantation, a multidisciplinary team approach was incorporated. This additional focus not only examined risk factors associated with complications, which includes hypotension, inotrope requirements, obesity and RV dysfunction, but also included physical therapy and nutritional assessment. By providing more focus on patient education in regards to physical and nutritional needs and risk factors associated with complications, a reduction in cost associated with LVADs was noted.

With this in mind, it is important to investigate factors that could potentially decrease further cost and complications without compromising treatment outcomes. One possible way which expands on the study posed by Iyengar et al is to consider whether the patient meets criteria for frailty that could be addressed before or during hospitalization. Many elderly heart failure patients, especially those who are hospitalized, are frail. Frailty has been identified as an important prognostic marker for adverse outcomes including death, disability and re-hospitalization. - Thus, identifying patients with frailty while they are hospitalized may promote intervention to manage frailty and its consequences, thus decreasing cost.

Frailty is a construct that includes assessment of physiological insults across many organ systems that result in increased vulnerability to physical and psychological stressors. - While a few investigators have examined the relationship of frailty and outcomes of advanced heart failure patients, no one has examined the relationship between frailty and hospital length of stay and readmissions in patients who receive an

LVAD.[illegible] The purpose of this dissertation is to determine markers of frailty in patients undergoing LVAD implantation and the association of pre-operative frailty with post-operative frailty on length of stay and re-admissions and to determine whether the components of frailty are stable or whether they change after LVAD implantation.

In the second, third and fourth chapters of this dissertation, I examine how end-stage heart failure is treated with LVADs. In addition, I examine how frailty impacts length of stay, 30 day readmissions and if frailty improves 3 months after LVAD implantation. I also compare my proposed markers of frailty to an existing model to determine if the measurements are similar. The final chapter of the dissertation summarizes the findings of the previous chapters and bridges gaps in current research.

End-Stage Heart Failure

Heart failure currently affects more than 5.7 million Americans and more than 26 million people worldwide and attributes to substantial costs of more than $30.7 billion annually. It is estimated by 2030 that heart failure will affect more than 8 million adults in the United States and costs associated with heart failure will continue to increase to exceed more than $69.7 billion.[illegible] A majority of cost are attributed to frequent hospitalizations as the disease progresses toward end-stage heart failure. More than 43% of patients are hospitalized more than 5 times within 5 years of being diagnosed. It is estimated that approximately 5-10% of patients with heart failure are end stage or stage D and have persistent symptoms despite guideline-directed medical therapy (GMDT) resulting in more frequent hospitalization. Approximately 15-35% of patient with end stage heart failure have a1 year mortality.[illegible]

Once diagnosed with heart failure, patients are placed on GMDT in an attempt to not only provide symptom relief and prevent hospitalizations, but also improve mortality and decrease the risk of major cardiovascular events. As the disease continues to progress, more definitive treatments for end-stage heart failure should be considered. Due to disease severity, limited therapeutic options are available including inotropic support, cardiac transplantation or left ventricular assist device (LVAD).

The American College of Cardiology/American Heart Association and the Heart Failure Society of America recommend continuous inotropic support for the treatment of advanced heart failure to patients who have failed GMDT in an attempt to improve quality of life and reduce symptom burden. Inotropic support may be used to stabilize patients as a bridge to cardiac transplant or mechanical support, or discharge home. Patients initiated on inotropic support require close monitoring due to the potential of symptomatic hypotension, life-threatening arrhythmias or worsening renal dysfunction.

While inotropic support may provide symptom relief, there is no mortality benefit and 1 year survival rate on inotropic support is approximately 10-15%. For patients who are discharged home on inotropic support, palliative care should be involved to assist with end of life care as they start to fail inotropic support. For those who are on inotropes as a bridge therapy, close monitoring for signs of deterioration is crucial for timing of surgical intervention.

Definitive surgical intervention for end-stage heart failure includes ventricular assist device or cardiac transplantation. Heart transplant remains the preferred treatment of end-stage heart failure with an estimated survival rate of 90%. However, in the United States the number of people waiting for a heart transplant continues to increase and is

approximately 3,805 which is a 25% increase over the past decade. The number of donations remains stable around 3.5 per 1000 deaths and wait times continue to increase. Due to donor shortage, mortality on the heart transplant wait list is high with approximately 10% of patients dying per year while waiting for a heart transplant.[,,] LVADs are increasingly being utilized in patients with end stage heart failure to bridge patients to heart transplant and as destination therapy for those who are not transplant candidates.

LVADs were originally designed as a bridge to cardiac transplants but have evolved to include destination therapy for treatment of end-stage heart failure in those who meet eligibility requirements. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial established the use of LVADs as a treatment for patients with end stage heart failure and reported a 48% reduction in death from any cause. LVADs have an estimated 1 year survival of 89% and over 68% report improvement in quality of life. Additionally, over 77% of patients implanted with LVAD report improvement in NYHA class.[,,]

Left Ventricular Assist Device

The rise in the healthcare budget and increased incidence and prevalence of heart failure has led to the exploration of advanced therapies for heart failure to improve treatment outcomes and decrease cost associated with this devastating disease. As heart failure progresses, the addition of continuous intravenous inotropic support, such as dobutamine and milrinone, may improve clinical outcomes, but is associated with a poor survival rate at 1 year of 10-30%. These patients have diminished functional status, poor quality of life and have frequent readmissions. Only a minority of patients are eligible for

heart transplantation, and of those, many will not receive a transplant because of the limited supply of donor hearts. This situation leaves a substantial number of patients with limited options. The addition of LVADs as an adjunct to traditional medical treatment for heart failure patients who require advanced therapies to improve long-term survival is gaining acceptance.[,,,]

LVAD is a type of implantable mechanical circulatory support that assist the native left ventricle. It consists of internal and external components that work to increase cardiac output. The LVAD has an inflow cannula which is inserted into the left ventricle and connects to a pump, which is connected to an outflow cannula that attaches to the aorta. Blood is propelled by a rotor through the system into the aorta and systemic circulation. The pump also has a driveline, which connects the internal pump to an external power source.

LVADs which were originally used as a bridge to heart transplantation are now approved as destination therapy in patients who cannot receive heart transplant or cannot wait for a heart transplant. Randomized clinical trials have noted a 48% risk reduction of death in LVAD patients compared to patients on medical therapy. In the USA, the incidence of LVAD implantations has increased from 2006 to 2010 from 206 to 1451 while the number of heart transplants remains unchanged. According to the 2014 ITERMACS registry 3500 continuous flow-LVADs (CF-LVADs) were implanted in 2013, while the number of heart transplants remains around 2200 implants per year in the US. In addition, hospital cost associated with heart failure improved over the last 10 years as the number of LVAD implants increased with approximately $14,000 or 3.6% per patient.[,]

While the overall survival of patients on CF- LVADs has an increased at 1 year to 85% (HeartMate II) and 92% at 6 months (HeartWare), the CF-LVAD is not without burden. Although the implantation of CF-LVAD is considered safe and effective, adverse events with CF-LVADs can lead to poor outcomes and re-hospitalization. The most common complications associated with second generation CF-LVAD include bleeding and infection.

Gastrointestinal (GI) bleeding is the most common complication and cause of re-hospitalization in patients with CF-LVAD. The incidence of GI bleeding in patient with CF-LVADs is between 18.9% and 22.3%. Risk factors for GI bleeding in patients with CF LVADs included older age (20.5 x greater risk of bleeding) and chronic renal insufficiency.

GI bleeds in patient with CF-LVADs stems from a combination of factors including anticoagulation, anti-platelet therapy, Von Willebrand disease, impaired platelet aggregation and formation of arteriovenous malformations in the GI tract. When CF-LVADs are implanted, a non-biological surface is placed in the body. Blood flows over this surface, which predisposes the blood to clotting. To reduce the incidence of clotting, there is a need for anticoagulation. CF-LVADs require anticoagulation with warfarin, which increases risk of bleeding. Nearly all patients who experience GI bleeding have therapeutic or subtherapeutic INRs at the time of bleeding suggesting that antithrombotic therapy alone does not account for higher bleeding rate in patients with CF-LVADs.

Physiological changes related to the lack of pulsatility also contribute to increased rate of GI bleeding in patients with CF-LVADs. Native hearts create pulsatility, which

results in pressure and flow changes. The human cells detect and adapt to these changes. Pulsatility results in shear and strain forces on the endothelium, smooth muscle and fibroblast cells in the circulation which in turn results in vasodilatation and vascular remodeling.[-] Without pulsatility, the normal processes do not occur. Instead there is a thinning of the vasculature, decreased bradykinin-dependent vascular relaxation. There is also increased vascular oxidative stress which results in degradation of vascular cell proliferation. This results in angiodysplasias, which attribute to approximately 55% of bleeding lesions in patients with CF-LVADs.[-]

Acquired von Willebrand syndrome has also been noted to be a common cause of bleeding in patients with CF-LVADs. Von Willebrand factor is necessary for platelet aggregation. When the blood passes through the pump, shear stress disrupts multimers associated with factor VIII, which leads to acquired von Willebrand deficiency resulting in coagulopathy.[-]

While the etiology of GI bleeding is found in over 70% of cases by upper endoscopy or capsule endoscopy, GI bleeding continues to be problematic in patients with CF- LVAD and treatment of GI bleeding is essential to lowering healthcare cost associated with readmissions. Few investigators have examined medications to assist with preventing or slowing GI bleeding in patients with CF-LVADs but all of these medications are still under investigation and attribute to significant costs. Additional factors that can decrease cost associated with GI bleeds need to be examined and studied.

As the number of LVAD implants increase, complications of device related infection emerge. Approximately 17% of patients with LVADs develop infection within the 1st year post-implant and the risk increases to 33% and 45% at 3 and 5 years

respectively. One of the most common infections associated with LVADS is driveline infection with a rate of 7%, 20% and 29% at 1, 3 and 5 years respectively. Patients are at risk of developing driveline infection due to a percutaneous driveline that extends from the internal pump, out the skin, to an external energy source. Most driveline infections are at the driveline exit site and if untreated, travel up the driveline to the pump resulting in a pump pocket infection. Once a patient has a pump pocket infection, the risk of bacteremia and sepsis increase. As a result, patients are often hospitalized due to the complexity of medical care and require extensive, long-term antibiotic coverage and 70% require surgical revisions which results in substantial cost. Infection associated with LVADs contributes to 41% of deaths.

Due to the expense associated with readmissions, increased length of stay, morbidity and mortality associated with infection, researchers have focused on factors linked to increased risk of infection post-LVAD. Heart failure patients are already at higher risk of morbidity and mortality due to nutritional disorders, cachexia, and being overweight. These same co-morbidities are being examined in patients with LVADs. Nutritional factors such as low albumin are associated with increased post-surgical risk of infection and research has demonstrated that low albumin levels and BMI are independent predictors of readmission due to drivel line infection. Research regarding BMI is controversial. Some research supports that BMI is not a relevant factor in determining post-operative risk associated with infection while other studies support that overweight and obesity contribute to increased risk of infection post LVAD.

Readmissions due to these complications is common and results in a significant percentage of health care costs in this population. While the overall cost-effectiveness of

treatment with an LVAD continues to improve, 5 year cost is estimated at $360,000. To minimize expense associated with complications post VAD and re-hospitalization, it is necessary to investigate factors or ways to decrease cost. One such way is to focus on patient selection prior to LVAD implant. Patients with advanced heart failure already have a wide range of comorbidities that can lead to unplanned hospital readmissions and increased length of stay and this risk increases after LVAD implantation. These patients are at increased risk of poor baseline health status, function decline and decreased quality of life, all of which are predictors of mortality.[illegible] While previous research has focused on reducing hospital cost and readmissions due to bleeding and infection, a new focus on patient selection prior LVAD implantation, which has extensively been studied in other populations, is frailty.

Overview of Frailty

Frailty is an evolving concept that is gaining interest in a variety of populations. Over 6 million people in the United States are frail and this number is believed to be underestimated. It is recognized as a prognostic indicator and is a risk factor for adverse clinical outcomes including mortality and prolonged hospitalization.[illegible] Approximately 45% of patients who are frail have a 1 year mortality rate. In addition frailty is also predictive of falls, institutionalization and is independently associated with post-operative complications.

Frailty is a complex syndrome that affects many organ systems as a result of stressors in the setting of a vulnerable state. Many suggestions have been proposed to define frailty, but no formal definition has been recognized due to the complexity of the

syndrome and inconsistencies in measurement. In this dissertation, I will define frailty in the following section.

Frailty has extensively been studied in the community dwelling geriatric population, and more recently has been investigated in patients with cardiovascular disease and patients undergoing cardiac surgery. Studies suggest that frailty exists in 25%-50% of patients with cardiovascular disease, 7% of people age 65-75 years and 26% of people over the age of 75 years. Frailty occurs in 65-75% of patients with heart failure and is a significant predictor for frequent hospitalization. Patients who are frail have a 65% higher hospitalization rate than non-frail patients. In addition, frailty in patients with cardiovascular disease have a 2 fold increase in mortality and women with coronary artery disease (CAD) are more likely to develop frailty.

Multiple studies have been examined to assess the prevalence of frailty in community dwelling older adults with cardiovascular disease. The Cardiovascular Health Study (CHS) (n=4735), Zutphen Elderly Men's Study (n=420), Beaver Dam Eye Study (n=2962) and French 3 City Study and Health ABC study (n=3208) and Women's Health and Aging Studies (n=670) all noted an association between frailty and cardiovascular abnormalities. Older community dwelling women were noted to be at higher risk of developing frailty compared to men and were more likely to develop CAD events. In addition, CAD and stroke were at highest risk of developing frailty and frailty was strongly predictive of long-term survival.

Outside of community dwelling adults, there have been few studies examining the impact of frailty in older hospitalized adults. In a study by Purser et al, patients with cardiovascular disease admitted to the hospital were noted to be frail which was

measured by slow gait speed and have a fourfold increase in mortality over 6 months (n=309).[,] Patients with heart failure are 54% more likely to be frail and frailty was more predictive of mortality than New York Heart Association Class. Another study by Lee et al focused on patients admitted after undergoing cardiac surgery noted that frailty was associated with a 43% increased risk of post-operative complications, length of hospitalization and inability to be discharged home. Frailty was also highly correlated with 30 day, 1 year and 2 year mortality due to the patients having a decreased ability to mobilize and ambulate which contributed to additional complications such as post-operative pneumonia and re-intubation. Approximately 50% of patients in this study had frailty measured by gait speed.

Frailty is also pertinent to the development and prognosis of patients with heart failure. The Health ABC study concluded that frailty correlated with a 30% higher risk of developing heart failure.[,] Patients with heart failure who are frail have a higher 1 year mortality risk than those who are not frail (17% vs 5%) and have more hospitalizations (21% vs 13%) and impaired quality of life. In addition, patients with frailty had prolonged hospital length of stay. The CHS study supported previous findings that frailty in heart failure patients is associated with functional decline and increase risk of hospitalization.

Frailty has also been studied in patients undergoing cardiac surgery to predict post-operative outcomes. The Frailty Assessment Before Cardiac Surgery (Frailty ABC) noted a 46% incidence of mortality in patients with slow gait speed compared to a 6% incidence in those with normal gait speed. Additional studies also noted that pre-operative frailty was associated with post-operative mortality at 30 days and 1 year.[,] In addition,

frail patients were less likely to be discharged home and were more likely to need rehabilitation.

To date, few investigators have examined frailty in patients who undergo LVAD implantation. Their findings have provided conflicting data (Table 1.1). Three investigators examined the association of frailty with an increased time to extubation. Only one group of investigators found a significant association between frailty and longer time to extubation. Five groups of investigators compared hospital length of stay, which found conflicting results. Prolonged length of stay was reported in 2 groups and no difference in hospital length of stay was noted in the remaining 3 groups. Three investigators examined short term mortality (less than 30 days) and found no difference between frail and non-frail patients. Additionally, seven groups of investigators examined long term mortality and only one reported increased mortality associated with frailty. The most commonly used measurement tool for these studies was Fried's phenotype.

Handgrip strength is a marker of frailty in other populations. A study by Chung et al noted that impaired handgrip strength correlated with global myopathy, higher postoperative complication rates and increased mortality following LVAD implantation. While this study did not examine frailty, Chung et al makes reference that measures of skeletal muscle function, such as handgrip strength, are part of the frailty phenotype and may have prognostic value in patients undergoing LVAD implantation.

No studies have focused on interventions that slow or improve frailty in both the LVAD and non-LVAD population but some have focused on interventions that may improve physical function. Studenski et al analyzed 9 large prospective studies and

found that for every 0.1 m/s increase in gait speed, there was a 10% improvement in survival in patients with heart failure. Maurer et al discuss that there were some improvements to physical function in patients 3 months post LVAD implantation but frailty itself was not reversed. It was suggested that to better assess improvements in frailty additional components such as nutritional support should be incorporated into the assessment. A study by Fiatarone et al attempted to expand on this by adding nutritional support to their program, which did support that a high intensity exercise training improved muscle strength and noted improvement in mobility and gait speed. However, even with nutritional intervention, the nutritional status remained compromised.

Due to the implications of previous research and statistics, it is important to focus on ways to prevent or slow the progress of frailty. In order for this to be effective, one must first understand the variables that result in frailty. Due to the complexity of frailty, there is no standard definition, which makes it difficult to conceptualize. Various attempts have been made to try and operationalize and define frailty. This will be discussed in the following section.

Defining Frailty: Conceptual Framework

While it is well known that frailty is a predictor of poor prognosis, defining frailty has not been established. Even identifying criteria for frailty has been difficult due to the complexity of the syndrome. Most variables that affect frailty are commonly associated with other co-morbid conditions and aging which makes it difficult to distinguish between the attributes. Some conditions such as cardiovascular disease, stroke, depression, obesity and osteoarthritis, share the same characteristics as frailty leading to

the potential for misclassification. Disputes continue as to what criteria should be used to define frailty due to the relationship of frailty with aging, disability and chronic disease.

Research proposes that frailty is caused by underlying processes separate from aging, but these processes have similar manifestations as other conditions as mentioned previously. Patients with frailty and other co-morbid conditions such as cardiovascular disease, arthritis, depression, obesity often have chronic low-grade inflammation. After a stressor event, there is further disruption of homeostasis, which results in a decline of status due to increased circulation of inflammatory markers. This results in a "cascade of events" in which musculoskeletal, nutritional and hormonal defects interplay resulting in further inflammatory and hormonal response causing further decline.[,] This cycle continues resulting in changes to skeletal muscle, leading to profound muscle loss and impairs the body's ability to maintain and repair itself, which promotes further decline in physical performance, mental status and malnutrition.[,] While frailty may encompass the resulting components of this cycle such as malnutrition, loss of dependence, decreased gait, generalized weakness, weight loss, muscle loss and exhaustion it is difficult to discern frailty from other underlying conditions.[,] This supports the importance of further defining and conceptualizing frailty for better understanding.

The concept of frailty is complicated by the lack of a consistent definition. Several definitions of frailty are discussed in the literature. Some of the more frequently used definitions of frailty define frailty as a "state of increased vulnerability to adverse outcomes," an age associated biological condition and a dynamic state affecting an individual who losses function and a geriatric syndrome due to a decline in physiological reserve.[,,,] Frailty has become increasingly relevant due to increased risk for

decompensation, adverse events, complications, mortality and functional decline and finding ways to measure frailty is on the rise.

Frailty is multi-factorial and includes deficits that accumulate throughout life. Frailty encompasses several attributes including skeletal muscle mass loss, decreased activity levels, poor endurance, decline in walking performance and decreased activities of daily living. Several measures of frailty have been examined but due to variability in definition, no standard measurement of frailty has been identified. Over 20 assessment tools have been developed to measure frailty and more than 70 variables have been examined in these models to assess frailty, yet there is no formally objective measure. These instruments share common core items including slowness, weakness and physical inactivity.

The most common measurement of frailty in patients with heart failure is the frailty phenotype developed by Fried and colleagues (Table 1.1). The frailty phenotype defines frailty as the presence of 3 or more of the following 5 physical indicators: low physical activity, weakness (measured by hand grip strength), slow walking speed, unintentional weight loss (>10 lbs in 1 year) and self- reported exhaustion. The Fried scale has demonstrated to predict mortality and disability in community dwelling elders, patient with cardiovascular disease, patients with heart failure and patients undergoing cardiovascular surgery or procedures. Several modifications of the Fried scale have been widely used to assess frailty in several substrates of population with over 200 modifications with physical activity and weight loss being modified most often.

While the Fried score is one of the most widely used measurements, some of the individual components have been studied and are associated with frailty. Single item

measures appear to be sufficient at assessing frailty and are more practical. Gait speed is commonly used to measure frailty and is associated with a 3 fold increase in post-operative mortality and morbidity for patient undergoing cardiac surgery. In addition, slow gait speed is associated with a 30% increase of hospitalizations in patients with heart failure. Gait speed alone was also the most accurate predictor of 6 month mortality in a study assessing frailty in patients with coronary artery disease. It is easily applicable without much time or cost and doesn't rely on subjective questionnaires. The patients use little effort and walk comfortably.

Poor grip strength is also predictive of frailty and is used often due to patients not being able to ambulate or being to deconditioned to perform other measures of frailty. Handgrip strength correlated with operative risk in patients undergoing cardio-surgery, as well as increased length of stay and was independently predictive of 30 year mortality. Handgrip strength was also noted to be predictive of disability and functional decline over 25 years.

Another common measurement of frailty in patients with cardiovascular disease, older adults and patients with heart failure is the Rockwood's frailty index of multiple deficits, also known as the deficit index. Measuring frailty through the deficit index allows one to determine the severity of frailty through age associated health disorders such as symptoms, diseases, disabilities. The index is associated with negative health-related outcomes including hospitalizations and mortality. This measurement is more commonly used in community dwelling elderly population due to the ease of use. In addition, the deficit index is more sensitive predictor of outcomes than Fried's frailty phenotype because it is a more sensitive measure of a patients vulnerability to stressors.

While it is comprehensive, administration of the assessment is time consuming which limits its use. Frailty is determined based on a calculated index. A Score 0.21 < FI < 0.45 = frail and FI > 0.45 most frail. This concludes that the frailer person is the more vulnerable they are to adverse outcomes.

The CHS scale and the MacArthur Study of Successful Aging (MSSA) are additional instruments used to measure frailty in patients undergoing cardiac surgery. The CHS scale includes the 5 items of Fried's Criteria: gait speed, weakness measured by handgrip strength, physical inactivity measured by questionnaire, exhaustion measured by questionnaire and unintentional weight loss > 10 lbs in 1 year. If three or more items are positive, one is classified as frail. In addition, the CHS has several modifications some of which have been expanded to include cognitive impairment and mood disturbance. The MSSA also includes 5 items; cognitive impairment, self-reported weakness, anorexia, high IL-6 and high CRP. Four or more items are required to be deemed frail.

The Short Physical Performance Battery (SPPB) test is an instrument for measuring physical performance in the aging population and has been used to measure frailty. This measurement of frailty has also been extensively examined in older adults with cardiovascular disease. The SPPB measures frailty by examining slowness, weakness and balance. Three timed physical performance tests are performed: gait speed, chair rises and tandem balance. Each is scored on a 0 to 4 scale and one is considered to be frail if they have a total score < 5 of 12.

The SPPB has been identified as one of the best physical performance tests to identify frail adults and is associated with disability and mortality. It has good concurrent

validity when compared to other measures of frailty. Patients with lower SPPB score are more likely to be disabled and have a higher mortality rate or re-hospitalization rate over 1 year. In addition, patients who had a score of 8 out of 12 had a significantly shorter length of hospital stay compared to the subgroup with a score of 4 or less.

Multiple attempts at defining and conceptualizing frailty have been attempted, but all populations are different and are affected by different variables, which makes it difficult to generalize one specific instrument to measure all populations. In addition, it is difficult to discern underlying conditions associated with co-morbid conditions and frailty itself. A systematic review of the literature on frailty led to exploration of a new conceptual framework to further define frailty in the LVAD population.

This conceptual framework (Figure 1.1) incorporates the most important components of frailty in the LVAD population. A full understanding of the concept of frailty in this population is necessary to understand how it impacts health outcomes. Further definition of some of the variables of the concept were explored.

Malnutrition and weight loss

Patients with advanced chronic heart failure often experience progressive unintentional weight loss, as a result of decreased appetite and malabsorption due to gastro-intestinal congestion. Unintentional weight loss (> 10 lbs in on year) has been shown to be associated with post-operative complications, prolonged hospitalization, decreased survival and greater burden of morbidity and mortality in patients with heart failure.[illegible] Unintentional weight loss occurs in approximately 50 % of patient with heart failure and approximately 15% of heart failure patients are found to have cardiac cachexia.[illegible]

Cardiac cachexia is a multifactorial metabolic and inflammatory response associated with increased morbidity and mortality. Cachexia was a predictor of 18 month mortality in patients who had percutaneous coronary intervention. Cardiac cachexia occurs as a result of decreased absorption of nutrients through the gastrointestinal system and increase metabolic demands leading to a catabolic state resulting in muscle wasting which leads to further weight loss and malnutrition.[,,] Inadequate nutrition is associated with poor outcomes, increases length of hospitalization and results in postoperative complications.[,] Cardiac cachexia is a strong indicator for mortality in patients with heart failure and when combined with low peak oxygen consumption, it identifies patients at high risk of death. Some research supports more favorable outcomes with higher BMI and survival, but there is limited data on the effects of weight loss on survival.

Due to the negative impact of cardiac cachexia and malnutrition on outcomes of patients with heart failure, measures of nutritional status are being examined. One such measure is by examining albumin levels. Low albumin levels < 2.5 mg/dl are associated with increased morbidity and mortality in patients who have had general cardiac surgery, as well as all cause mortality in older adults.[,,] Hypoalbuminemia in heart failure patients is also being examined. In the heart failure population, low albumin is due to inflammatory stress, hepatic congestion and impaired protein syntheses. Albumin levels are associated with higher NT-proBNP levels and worse NYHA status. Low albumin levels decrease intravascular osmotic pressure of the capillary beds. This leads to loop diuretic resistance due to a decrease of albumin-loop diuretic binding capacity. The binding of albumin to diuretics is key for effective diuresis.

Additional research has examined the relationship of low albumin levels and BMI. Patients with serum albumin levels of less than 2.5 g/dl have an increased risk of death and post-operative bleeding.[7] In combination with a low BMI less than 20, these patients were at increased risk of death, stroke and bleeding, while patients with BMI over 30 had increased risk of arrhythmias and infection. An additional study by Rapp-Kesk also supported that patients with low BMI and low serum albumin levels were at increased risk of death and infection post cardiac surgery.

Nutritional status has been studied in patient with heart failure through various screening tools such as the Mini Nutritional Assessment Short Form, Nutritional Risk Screening and the Prognostic Nutritional Index. These screening tools are complex and subjective and an easy and more objective form of measuring nutritional status, via serum albumin levels, is gaining acceptance. Serum albumin levels are an easy and objective measure of nutritional status. As mentioned previously, serum albumin levels have been well studied in the general cardiac surgery population and are associated with poor outcomes and has also been studied as a predictor for survival in patient with heart failure.[7,8] More recently, limited studies have examined low albumin levels in the LVAD population. Low albumin levels (<2.5 mg/dl) are associated with morbidity and mortality after LVAD implant and decreased survival. However, one study noted that low albumin levels are corrected within six months after LVAD implantation. Further analysis of albumin is needed before conclusions can be made regarding postoperative outcomes in patients with LVADs.[7]

Strength

Loss of muscle mass and changes in muscle metabolism are well known markers of frailty in patients with cardiovascular disease, coronary artery disease and cardiac surgery patients.[,] In patients with heart failure, global myopathy results in decreased strength. Hand grip strength is a marker of frailty that has been correlated to outcomes and mortality in these populations. It is independently recognized as a predictor of mortality and functional decline. Several frailty scoring systems measure handgrip strength due to the ease of administration with minimal physical stress on patients. In addition, it is measured by a dynamometer, which is relatively inexpensive and can be tested in patients who are ambulatory and non-ambulatory. This is important for patients with advanced heart failure due to severity of their illness resulting in deconditioning and frequent hospitalizations. Most patients with advanced heart failure who are being considered for LVAD are weak and cannot tolerate testing that results in stress.

While several studies in other populations have examined handgrip strength as a measure of frailty and how it relates to outcomes, few studies have examined hand grip strength as a measure of frailty in the LVAD population. Handgrip strength defined as at least 25% of body weight was associated with decreased survival and increased complications including bleeding and infection in patients undergoing LVAD implantation.[,] While patients in this study were thought to have more physical limitations than patients in other studies, almost 1/3 of patients had noted improvement in handgrip strength 6 months after LVAD implantation.

Functional Capacity

Deterioration in skeletal muscle associated with advanced heart failure is currently being studied. Changes in muscle fibers, decrease in type 1 fibers and increase in type 2 fibers, occurs as a result of the metabolic demands associated with cardiac cachexia, which results in a decline in functional capacity. In addition, these changes to the muscle structure result in changes to muscle mitochondrial and enzymatic capacity which are usually measured by VO2 max. Measuring peak oxygen consumption requires complicated and expensive equipment. Most studies to date that are examining frailty have assessed exercise capacity by measuring gait speed because it is a time and resource efficient prognostic indicator of mortality.[,] It has been well studied in other populations and is associated with mortality, functional decline and increased operative risk.[,] However, gait speed does not measure VO2 max, which leads to the assumption that the 6 minute walk test may be a more accurate predictor in patients with heart failure since it has been established as a measure of aerobic capacity. The 6MWT best correlates with maximal oxygen consumption compared to other measures and is easy to be administered, well tolerated by patients and reflects daily activities. Several studies have reported that the 6 MWT is a reliable measure of increased mortality and re-hospitalization and is a strong indicator of poor prognosis in patients with heart failure.

Studies in patients with heart failure have demonstrated that the 6 minute walk test is a valid measurement of functional capacity and have found an association with mortality and outcomes.[,,] Walking less than 300 meters is a predictor of increased morbidity and mortality. Mortality was 3.5 times higher if subjects walked less than 350 meters than those walking over 450 meters. The 6 min walk test is a feasible measure in

patients with heart failure and is already incorporated into routine care. The 6MWT also encompasses may domains of physical function, which are part of the frailty phenotype. A comparison between the 6 minute walk test and frailty using gait speed demonstrated a high correlation between the two measures in patients with heart failure. Another recent study reported that the 6 minute walk test was the strongest predictor of post- LVAD survival. Further research is needed to understand how to best assist frail patients to improved post LVAD implant.

This analysis of the concept of frailty provides a framework for the important variables that contribute to frailty in the LVAD population and it was used in the studies reported in this dissertation. It is important for the purpose of this dissertation that the concept of frailty be efficiently defined, as there has been inconsistency in the literature and has not been well studied in the LVAD population.

Gaps

This dissertation will fill some of the gaps in the literature by increasing our understanding of how variables of nutrition, functional status, and strength result in frailty. Many assessment tools and measurements of frailty have been well studied in other populations but are not well known in the LVAD population. Part of the issue may be that patients undergoing LVAD are critically ill and may not be able to participate in some of the previously reported measures.

In exploring the influence of the different measurements of frailty, more research is needed to examine and compare previously reported measures of frailty post VAD. Current literature by Maurer et al notes that handgrip strength and gait speed improved 6 months post LVAD implant but weight loss is resistant to change which contradicts

previously reported research supporting that LVAD implantation results in weight gain. The study was small and did not provide meaningful results of frailty on length of stay and survival. Most studies have also focused on older adults (> 60) which limits generalizability of the previous studies. With LVADs increasing as destination therapy and bridge for transplant, a wider age range needs to be examined. In addition, while some assessment tools examine physical capabilities and nutrition as markers or frailty, further studies are needed to assess if interventions are beneficial in slowing or preventing frailty in these areas prior to procedures and surgery. Additional research is needed to assess whether any markers of frailty will predict or effect current standards for patient selection.

Summary of subsequent chapters

The impact of frailty on outcomes and rehospitalization in patients who receive LVADs was studied in this dissertation. I explored markers of frailty in this population. The variables discussed in this conceptual framework were used to guide the study, designs, data collection, data analysis and interpretation of the results.

Chapter two was the discussion of surgical approaches to patients with end stage heart failure. This chapter was important because it discussed the pathophysiology of end stage heart failure and surgical approaches including heart transplantation and LVAD as treatment options for this population. This is important because it provides the background on how patients are selected for LVADs. Patients undergoing LVAD implantation have to meet criteria to qualify for candidacy but additional conditions such as frailty should also be considered to select patients who will benefit from implantation. Patients with LVADs are at increased risk of complications post LVAD, rehospitalization

and increased health care cost associated with these complications and it is important to gain a better understanding to improve patient selection for LVADs, reduce readmissions, reduce hospital cost and decrease hospital length of stay.

Chapter three was the report of a study in which markers of frailty included in the proposed conceptual framework to define frailty was compared to previously reported markers of frailty which include Fried's criteria, SPPB, 6MWT, Albumin and handgrip strength. This study was important because it established if markers of frailty included in the proposed conceptual framework are appropriate markers of frailty in patient undergoing LVAD implantation.

Chapter four was the report of a study conducted to determine whether frailty improved 3 months post LVAD. This is important because only one study to my knowledge have examined frailty post LVAD. A study by Maurer et al reported that frailty measured by the Fried frailty criteria, decreased in approximately half of patients 6 months after receiving LVAD support. This study was important as it lays the ground for future research to assess how improvements in frailty impact readmissions, length of stay, complications post LVAD and cost post LVAD.

Chapter five is the integration of the previous chapters. It provides further explanation of the link between the different variables of frailty and how they impact outcomes. The comparison between variables and outcomes was further explored.

Table 1.1: Frailty in LVADs

Author	Sample Size (n)	Outcome Measurement	Results	Frailty Measurement
Joseph 2017	75	-Time to extubation -Hospital LOS -Short Term Mortality -Long Term Mortality	-Significant -Significant -Not significant -Not significant	Fried Score
Jha 2017	77	-Time to extubation -Hospital LOS -Long Term Mortality	-Not significant -Not significant -Not significant	Fried Score
Mangehelli 2014	45	-Time to extubation -Short Term Mortality	-Not significant -Not significant	Fried Score
Cooper 2017	2469	-Hospital LOS -Long Term Mortality	-Significant -Not significant	Provider assessed frailty and gait speed
Heberton 2016	100	-Hospital LOS -Long Term Mortality	-Not significant -Not significant	Sarcopenia
Dunlay 2014	99	-Hospital LOS -Long Term Mortality	-Not significant -Significant	Deficit Index > 0.25
Sundararajan 2016	154	-Short Term Mortality	-Not significant	Cachexia > 10 kg weight loss or absolute BMI < 20
Fan 2017	50	Long-Term Mortality	-Not Significant	Fried Score

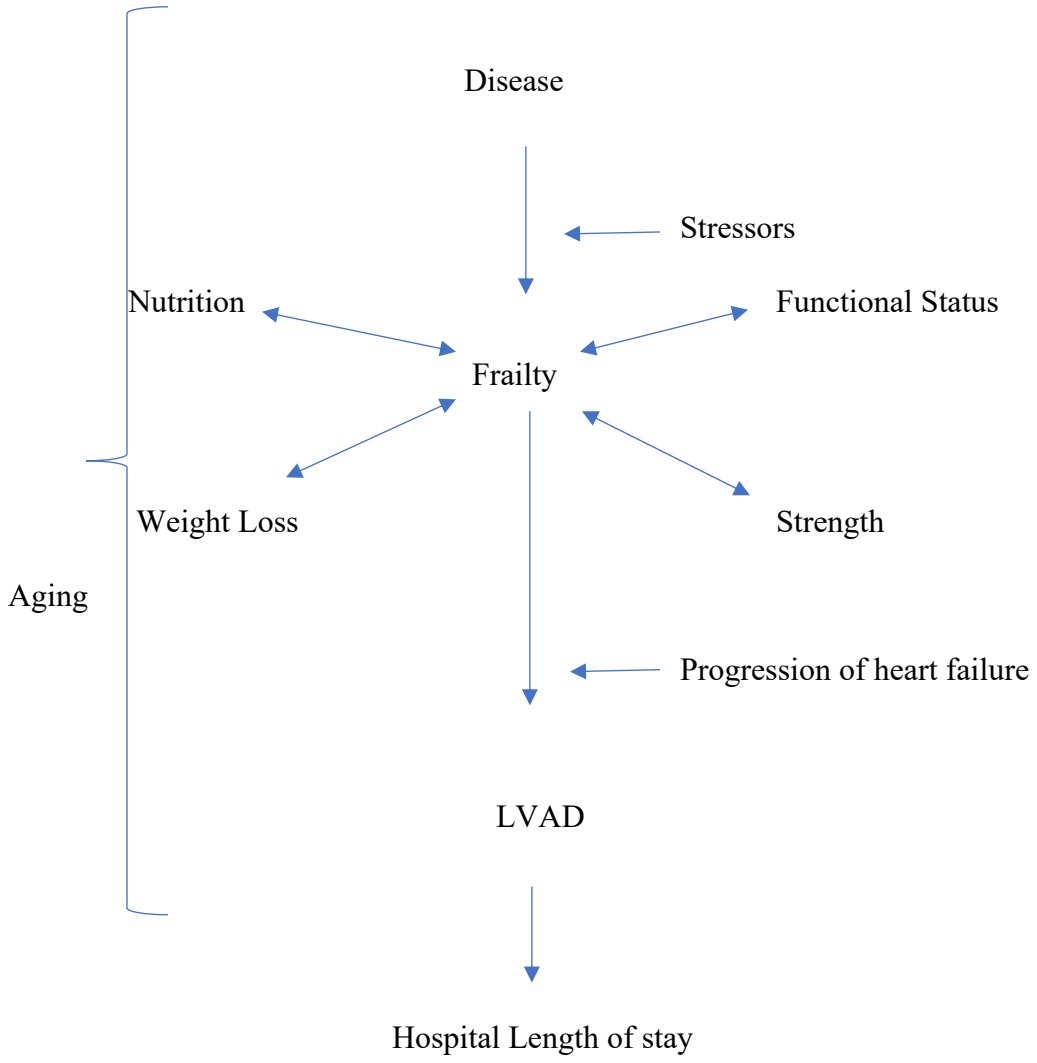
Table 1.2: Review of most common assessment tools for frailty

Frailty Measure	Criteria	Determinants of Frailty
Fried Criteria	5 Criteria; Unintentional weight loss of > 10 lbs in one year; Weakness measured by handgrip strength; Exhaustion that was self-reported Slowness measure by gait speed; Low physical activity self-reported	Positive 3 of 5 phenotypic criteria
Deficit Index	Cognitive status; Mood and motivation; Communication; Mobility; Balance, Bowel function, bladder function; ADLs; Needing help from nutrition or social resources; Number of comorbidities divided by 2	Has at least 30 assessed health variables FI = Deficits / n- missing values FI < 0.10 nonfrail 0.21 < FI < 0.45 Frail FI > 0.45 most frail
Gait Speed	Time to walk 5 meters	Time to walk 5 meter > 6 seconds
Handgrip	Handgrip measured with hand dynamometer	HGS < 85% normal
Short Physical Performance Battery	Gait speed; Time taken to stand from sitting in a chair 5 times without using arms; Tandem balance	Each is scored on a 0 to 4 scale: frail if they have a total score < 5 of 12
Comprehensive Assessment of Frailty	Handgrip Strength; Gait Speed; Activity level; Standing balance; Body control	HGS < 85% normal; > 6 seconds to walk 5 meters; Questionnaire regarding IADLs to calculate weekly kcal expenditure; Standing balance assessed by amount of time individuals could stand with both feet together, semi-tandem, full tandem and make a 360 degree turn; Body control assess by time individuals could get up and down from chair 3 times, pick up a pen from floor and put on and remove a jacket

Table 1.2, continued

Frailty Staging System	Disability; Mobility disability; Cognitive impairment; Visual Impairment; Hearing impairment; Total urinary incontinence	Disability: loss of > 1 BADL, Mobility inability to do housework, Cognitive by mini-mental status exam; 0-1 impairments = class 1 2-3 impairments = class 2 4-7 impairments = class 3
Canadian Study of Health and Aging Clinical Frailty Scale	Very fit (regular exercise); Well (no active disease); Well (with treated disease); Vulnerable (complain of being slowed by disease); Mildly frail (limited dependence for ADLs); Moderately frail (limited dependence for ADLs and IADLS); Severely frail (complete dependence for ADLs and IADLs or terminally ill)	Assess by a physician, nurse, physiotherapist and occupational therapist
Cardiovascular Health Study	5 items: gait speed, weakness measured by handgrip strength, physical inactivity measured by questionnaire, exhaustion measured by questionnaire and unintentional weight loss > 10 lbs in 1 year	Presence of 3 or more
MacArthur Study of Successful Aging	5 items; cognitive impairment, self-reported weakness, anorexia, high IL-6 and high CRP.	4 or more items deem frailty

Figure 1.1: Conceptual framework of frailty in patients with heart failure



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Chapter Two: Surgical Approaches in Heart Failure

Introduction

Heart failure is a progressive condition that continues to rise in both incidence and prevalence accounting for more than 2-3% of the national health care budget.[-] Despite improvements in treatment for end stage heart failure, the costs per quality-adjusted years is still greater than $400,000. The high rate of morbidity and mortality associated with advanced heart failure has led to exploration of additional treatments, which include surgical interventions to improve outcomes.[-] This article will focus on the most common surgical interventions that have demonstrated improvement in morbidity and mortality for patients with heart failure.

Epidemiology of HF

The epidemiology of heart failure has been extensively studied for the past several decades with a large contribution of literature stemming from the Framingham Heart Study. Major findings in the 1980's noted that heart failure increases with age, is higher in men that women. In addition, hypertension, coronary artery disease and diabetes mellitus are associated with increased risk of heart failure. In the 1980's the prevalence of heart failure was 24 per 1,000 in men and 25 per 1,000 in women with a median survival time of 1.7 years in men and 3.2 years in women.

Longitudinal analysis of the Framingham Study noted in the 1990's that heart failure continued to rise in incidence and prevalence affecting about 1% of persons in their 50's with progressive increases to about 10% of persons in their 80's. The incidence also increased with age from 0.2% in persons 45 to 54 years to 4% in those 85 to 94 years. Mortality was noted to be around 37% within 2 years of diagnosis.[,,,]

Continued analysis of epidemiologic data from the Framingham Study in the 2000s further supported the burden of heart failure effecting over 5 million Americans with more than 550,000 new cases a year.[illegible] Median survival was noted to be similar for men and women as in the 1990's with a 5 year survival rate of 25% of men and 38% of women. Hypertension was noted to have the largest impact on heart failure, followed by myocardial infarction, valvular heart disease and diabetes.[illegible]

At present, heart failure affects more than 5.7 million Americans with more than 670,000 new cases a year. Readmissions related to heart failure continue to remain a burden with rates of 20% at one month and 50% at 6 months with more than 43% of patients being hospitalized more than five times or more within 5 years of being diagnosed. Heart failure related admissions account for 56.7% of all heart failure episodes with heart failure, with heart failure being the most common reason for hospitalization in adults aged 85 years and older and the second most common for adults aged 65- 84 years.[illegible] Approximately 15 to 35% of patient with end stage heart failure have a 1 year mortality. Hypertension and diabetes remain the top co-morbidities linked to the high prevalence of heart failure.[illegible]

Pathophysiology of systolic HF

Heart Failure is defined as "a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood". This condition can ultimately lead to decreased exercise tolerance as well as symptoms of dyspnea at rest and/or exertion as well as fatigue and edema with variable severity. However, premise of heart failure physiology is increased intracardiac filling pressures, which is further explained in the following section.

Although there are two basic verities of heart failure, systolic as well as diastolic, this article focuses on systolic heart failure. Systolic heart failure whether treated according to guideline directed approach or not, ultimately leads to advancement of myocardial dysfunction with end-organs being affected, which brings up the concept of advanced heart failure. This entity is associated with refractory heart failure symptoms despite medical therapy as well as persistently elevated intracardiac filling pressures, inability to exercise as well as recurrent hospitalizations, which in turn is associated with increased mortality. At this stage there are further options in treatment of heart failure such as inotropic support but inevitably surgical approach such as heart transplant as well as mechanical circulatory support.

Strength of myocardial contraction has been shown to be related to the preload and thus the stretch of the fibers, which was first described by Otto Frank in 19th Century. This finding was elegantly confirmed a century later by Ernest Starling and colleagues where they have shown that increasing venous return and subsequent filling of heart chambers increased stroke volume. Thus a principal described by "the *ability of the heart to change its force of contraction and therefore stroke volume in response to changes in venou*s return and subsequent chamber *filling pressure" came to be known as* Frank–starling principle. This is illustrated in Figure 2.1.

Note the myocardium does not operate on the single Frank-Starling curve but rather its function as defined by multiple curves, as noted in Figure 2.2. These curves represent myocardial physiology based on its afterload as well as inotropic state as illustrated in Figure 2.2.

In order to improve the understanding of heart failure pathophysiology, it is important to understand frank starling curve, its principal of preload and how this correlates with intracardiac filling pressures and thus the concept of pressure volume loops.

Looking at the Frank Starling curve, we can visualize the effects of increased preload in the form of left ventricular end-diastolic pressure (LVEDP) on the stroke volume. In a normal functioning heart the higher the LVEDP the higher the stroke volume with the curve theoretically not reaching its plateau as illustrated by Figure 2.1. In contrast, increased inotropy increases the slope of this line, making the myocardium more responsive and sensitive to preload with higher rate of stroke volume increased to the amount of preload increase as denoted by line B in Figure 2.2. Decreased inotropy, as in heart failure, appears to reach a plateau point of the curve at lower LVEDP, as represented by line C in Figure 2.2.

To further visualize this principle, looking at pressure-volume loops becomes evident when venous return is increased, there is increased filling of the ventricle leading to an increase in end-diastolic volume (see Figure 2.3). If the ventricle now contracts at this increased preload the ventricle empties to the same end-systolic volume, thereby increasing its stroke volume, which is defined as end-diastolic minus end-systolic volume, provided that the afterload and inotropy are held constant. The increased stroke volume is displayed as an increase in the width of the pressure-volume loop. The *normal* ventricle, therefore, is capable of increasing its stroke volume to match physiological increases in venous return. This is not, however, the case for ventricles that are in failure.

In a failing heart and thus systolic dysfunction, there is evidence of downward and rightward shift of the Frank-Starling curve indicating loss of inotropy with resultant increase in left ventricle (LV) filling pressures. Initially there are multiple compensatory mechanisms in place to maintain stroke volume such as increased preload associated with neurohormonal upregulation and retention of Sodium leading to increased blood volume and thus increased filling pressures. Subsequently, these compensatory mechanisms result in chamber remodeling manifested by dilatation, which initially is in essence another compensatory phenomenon. This remodeling ultimately leads to decreased stroke volume and persistently elevated filling pressures and volume overload. These physiologic phenomena are illustrated in Figure 2.4.

Principle of treating advanced heart failure

The premise of treating heart failure is through control of congestion and thus preload as it has been shown that the predominant majority of symptoms and recurrent hospitalizations in heart failure patients are related to congestive exacerbation. In addition, an important concept in treating heart failure is through controlling afterload. This in turn can be achieved through neurohormonal blockade, which ultimately leads to decrease in intracardiac filling pressures. The strategy of achieving neurohormonal blockade through medical therapy by utilizing the combination of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) with beta-blockers (BBs) as well as more recently angiotensin receptor–neprilysin inhibitor, have reached a Class I recommendation by the ACCF/AHA/HFSA.

Luckily for those patients refractory or intolerant to guideline directed medical therapy, clinicians are now able to either replace the organ completely or support it with

implantable pumps. Replacing the organ improves the physiology drastically but holding true to the hemodynamic principle of heart failure the premise of treatment is to offload the heart decreasing intracardiac filling pressures through decreasing volume overload and improving the Frank-Starling forces such that it restores the pressure-volume loop position to the right, with concomitant improvement in stroke volume.

Surgical Options

Heart Transplant

Despite advances in pharmacological as well as device therapy for chronic systolic heart failure, long-term morbidity and mortality remain unacceptably high. Five-year mortality rate for patients with advanced heart failure is about 80% and thus further surgical approaches are necessary. One of those options and a gold standard treatment of advanced end-stage systolic heart failure is heart transplant. The fundamental indication for heart transplantation is poor quality of life as well as rapidly progressive physiology such as cardiogenic shock.

Since the first orthotropic, inter-human heart transplant performed on December, 3rd, 1967, at the Groote Schuur Hospital, in Cape Town, South Africa by Dr. Christian Neethling Barnard, great progress has been made. By end of 1968, 102 transplants were made in 17 countries and 52 centers. Only a third of these patients lived longer than three months. It was not until 1980 with the dictation of cyclosporine, borrowed from renal transplant, that ultimate successful progress resulted in improved survival. To date, worldwide, about 3,500 heart transplants are performed annually. The vast majority of these are performed in the United States (2,000–2,300 annually) with an average 1 year survival rate of 90% with conditional half-life of 13.2 years. [illegible] Heart transplant remains

to gold standard of advanced heart failure treatment for carefully selected patients. Box 1 summarizes indications and contraindications for heart transplant.

Surgical Considerations

Orthotopic placement (organ placed in the anatomically original position) is the most commonly utilized placement of donor heart during surgery. There are two main techniques of anastomosing the recipient vasculature/structures to the donor heart: Bicaval as well as Biatrial techniques. Biatrial technique represents the most widely utilized approach to orthotropic heart transplant although this really depends on the transplant surgeon. Figure 2.5.

Medical Considerations

As noted in Figure 2.6, early graft failure over the first year is the most common cause of post transplant complications, including death. Graft failure downtrends with the first year primarily due to acute rejection while infectious complications associated with aggressive immunosuppression begins to take the stage during that time period. Ultimately resurgence of graft failure as well as concomitant cardiac allograft vasculopathy in addition to malignancy predominate long-term outcomes.

Mechanical Circulatory Support

Even though over the last 5 decades, heart transplantation has been the goal standard of care for carefully selected patients with end-stage heart disease, challenges continue to exist in this patient population. These challenges include complications associated with post-transplant care, but more importantly increasing number of potential recipient's compared to the number of donor organs. Approximately 117,000 people need a lifesaving organ. Every 10 minutes someone is listed for transplantation and every 22

minutes someone dies while waiting for an organ. Because of this limiting factor, there has been increase in technological advances in order to be able to keep patients with end-stage, advanced heart failure alive in order to ultimately offer them the gold standard of care. This technology being mechanical circulatory support, both short as well as long term.

Interest in mechanical circulatory support (MCS) dates back to 1950's during the time of development of cardiopulmonary bypass and open-heart surgery. The first successful implantation of a left ventricular assist device was completed in 1966 by Dr. DeBakey. A paracorporeal (external) circuit was able to provide mechanical support for 10 days after the surgery. The lack of heart donors and contraindications to heart transplantation further stimulated the necessity for development of this technology. The first successful long-term implantation of an artificial LVAD was conducted in 1988 by Dr. William F. Bernhard of Boston Children's Hospital Medical Center.

Initially pulsatile pumps were the standard of care given the thought that pulsatility is a necessary physiologic phenomenon. Both Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) and Investigation of Non-Transplant Eligible Patients Who Are Inotrope Dependent (INTrEPID) trials evaluated the role of pulsatile pumps in patients with advanced heart failure who were ineligible for heart transplant and noted 48% reduction in mortality compared with optimal medical therapy. The caveat and ultimately demise of pulsatile pumps was their durability. Having a device which durability reaches about 24 months could only serve as a prolonged bridge to transplant for patients who were too sick and thus required implementation of mechanical circulatory support in order to improve end-

organ function and finally be placed on heart transplant list. And thus how about the patients who were not transplant candidates to begin with? Further endeavors with other devices gave rise of continuous-flow pumps. In 1987 in a pediatric patient shed some light in this regard when was implanted with a variation of continuous flow device as bridge to transplant. Dr. Frazier, in his case report states that this procedure "prompted us to speculate about broader application of nonpulsatile flow, to the development of fully implantable devices for long-term cardiovascular support of the terminal heart disease patient….*The potential for long-term benefit lies in meeting the requirements of the circulatory system with a nonpulsatile pump"*. At the same time interests for more durable devices has led to HeartMateII pump (a continuous-flow LVAD), replacing pulsatile technology after a study showed that continuous flow LVADs improve survival from disabling stroke and device failure as compared its predecessor (Heartmate XVE).

Currently all devices on the market are continuous-flow pumps based on axial or centrifugal mechanism (See Figure 2.7). The axial-flow rotary pump consists of a rotating, screw-like propeller within a tube housing. The energy from the rotating element increases blood pressure and flow. The centrifugal pump with spinning blades captures and throws fluid forwards, which results in essentially pulseless physiology, depending on the residual left ventricular function.

Because temporary devices such as extracorporeal membrane oxygenation (ECMO) will be discussed elsewhere in this issue, this section will focus primarily on durable devices, namely LVADs as well as briefly discuss total artificial heart technology. LVADs unload the left ventricle and thus, because of the fact that blood is withdrawn directly from the left atrium (LA)/LV (considering there is no mitral stenosis),

pulmonary capillary wedge pressure (PCWP) and LV EDP decrease. This is shown by the Pressure-Volume (PV) loop left-ward as noted in Figure 2.8A. It should be noted that although it appears that stroke volume decreases even though there is significant left ventricular unloading as noted by the pressure volume loop, at the same time, arterial pressure increases as noted in Figure 2.8B. Although peak LV pressure and arterial pressure become increasingly dissociated compared to systemic, arterial blood pressure significantly increased and thus ultimately improving end organ perfusion often resulting in reversal of end-organ dysfunction. Figure 2.7B; Table 2.1.

Four major indications for LVAD implantation exist:

1. Bridge to transplantation (BTT),
2. Destination therapy (DT),
3. Bridge to recovery, and
4. Bridge to decision.

Indications and Contraindications for LVAD implantation are listed in Box 2.

Bridge to transplantation remains the most common indication for implantation of LVADs. As mentioned earlier, due to the growing population of patients with advanced HF and stagnant numbers of donor organs, improved durability of the newer devices offers select patients increased survival and improvement of quality of life. This ultimately may let those patients remain candidates for transplant later down the line. Alternatively, destination therapy is offered to particularly selected patients with advanced HF who are not candidates for heart transplantation (Figure 2.9).

Temporary Options

Temporary Options are listed in Table 2.2.

Durable Options

There are basically two types of devices used: para-corporeal (percutaneous ventricular assist device [PVAD]) and totally implantable (LAVDs or biventricular assist devices (BiVADs)) (Table 2.3).

Total Artificial Heart

The first successful implantation of total artificial heart which led to subsequent heart transplantation was performed in 1969. Subsequent successful implantations did not occur until beginning of 1980. Since that time there are many models she had been implanted but only one remains to be the most commonly utilized; SynCardia™ TAH (SynCardia Systems, Inc., Tuscon, AZ, USA) Figure 2.10. This particular device is intracorporeal, pneumatically driven biventricular system, which completely replaces the failing heart. The use of TAH as a bridge to transplant has demonstrated a 79% survival to transplantation vs. 46% in patients not receiving a TAH in a small observational prospective study. Box 3 summarizes indications and contraindications for TAH implantation.

Surgical considerations

Because of the fact that human body generates a significant amount of scar tissue around the device, reentry for future heart transplantation becomes significantly more difficult. For this purpose the device itself as well as proximal vasculature are covered by

a Gore-Tex material in order to facilitate future reentry and minimize necessity for dissecting the structures.

Medical considerations

Most recent analysis of INTERMACS registry reveals that about 80% of people are alive one year. Another analysis shows that survival to transplantation was 68.3% with strokes occurring in 7.9% of the population.

Post implant management revolves around proper anticoagulation as well as management of end organ dysfunction. The most common organs involved are liver kidneys with renal dysfunction being related to lack of natriuretic peptides (ANP and BNP). Level of post-operative end organ dysfunction is dependent on severity of decompensated state prior to implantation.

Conclusion

Heart failure continues to increase in incidence and prevalence despite pharmacological therapy and additional therapies such as cardiac resynchronization therapy and remains the most common cause of hospitalization. Heart failure is associated with poor quality of life and has an overall 1 year mortality rate of 20%. Due to the morbidity, mortality and costs associated with heart failure surgical advances are becoming more widely accepted.

Although heart transplantation remains the gold standard, organ availability remains a major limitation. Due to the persistent donor shortage and increasing number of patient with advanced heart failure, mechanical circulatory support is gaining acceptance and can be used as a bridge to heart transplant for those eligible or as destination therapy.

The current strategy for the management of advanced heart failure with reduced ejection fraction (HFrEF) patients is to initially screen for heart transplant, with destination therapy ventricular assist device considered as secondary treatment for those who do not qualify for heart transplant. Regardless of which option is decided upon, the benefits of heart transplantation or ventricular assist devices outweigh those of pharmacological treatment of heart failure alone. Heart transplantation and ventricular devices improve symptoms and survival in advanced heart failure with a 1 year survival of 90% compared and should be considered in those who qualify.

Table 2.1. INTERMACS Profiles

Level	Symptoms	Signs and Hemodynamics	Need for LVAD
1	"crash and burn"	Critical cardiogenic shock,	Within hours
2	"sliding on inotropes"	Progressive decline on inotropic support	Within days
3	"dependent stability"	Stable but inotropic dependent	Elective over weeks to months
4	"frequent flyer"	Resting symptoms although remains home on oral therapy with frequent hospitalizations.	Variable urgency, dependent on nutrition and organ function
5	Housebound	Exertion intolerant	Variable urgency, dependent on nutrition and organ function
6	"walking wounded"	Exertion limited to symptoms, although still responding to oral guideline-directed medical therapy	Variable urgency, dependent on nutrition and organ function
7	Advanced NYHA III symptoms	NYHA class II or III, responding to oral guideline-directed medical therapy.	Not currently indicated

Abbreviation: NYHA, New York Heart Association

Table 2.2. Temporary Devices:

Device	**Mechanism**	**Duration**
IABP	Counterpulsation	Days
Impella	Axial Flow	Days
ECMO	Continuous Flow	Days to weeks
Centrimag	Centrifugal	Weeks
Tandem Heart	Centrifugal	Days

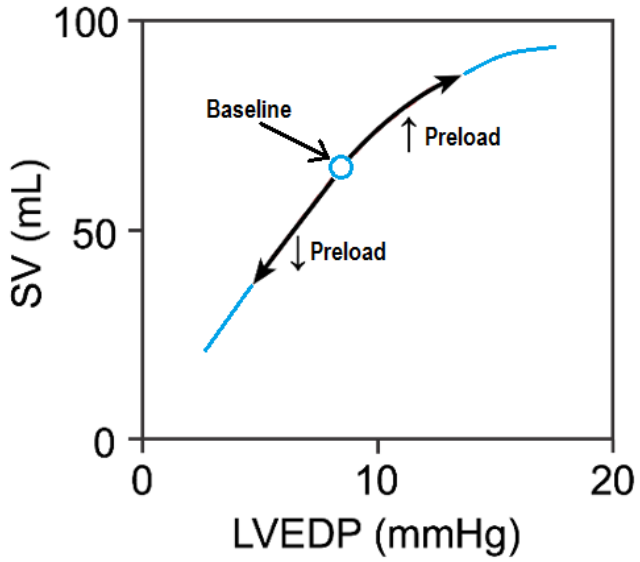
Abbreviations: ECMO, extracorporeal membrane oxygenation; IABP; intra-aortic balloon pump.

Table 2.3. Durable Devices:

Device	Mechanism	Indications
HeartMate II	Axial Flow	BTT, DT
HeartMate III	Centrifugal flow	BTT
HeartWare	Centrifugal flow	BTT, DT
TAH	Pulsatile	BTT

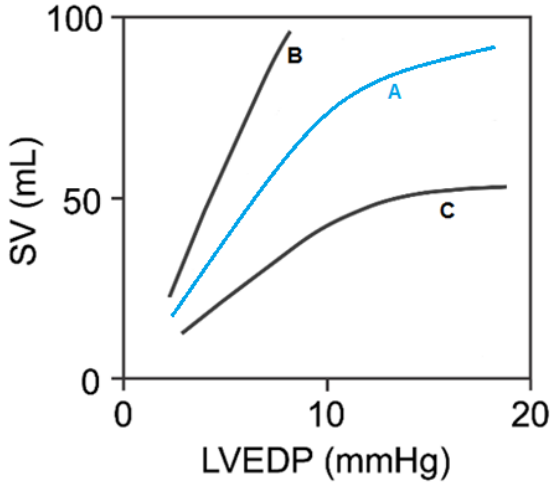
Abbreviations: BTT, bridge to transplant; DT, destination therapy; TAH, total artificial heart.

Figure 2.1. Effects of Preload on Left Ventricular Filling Pressures and Ventricular Function: Frank-Starling Principle



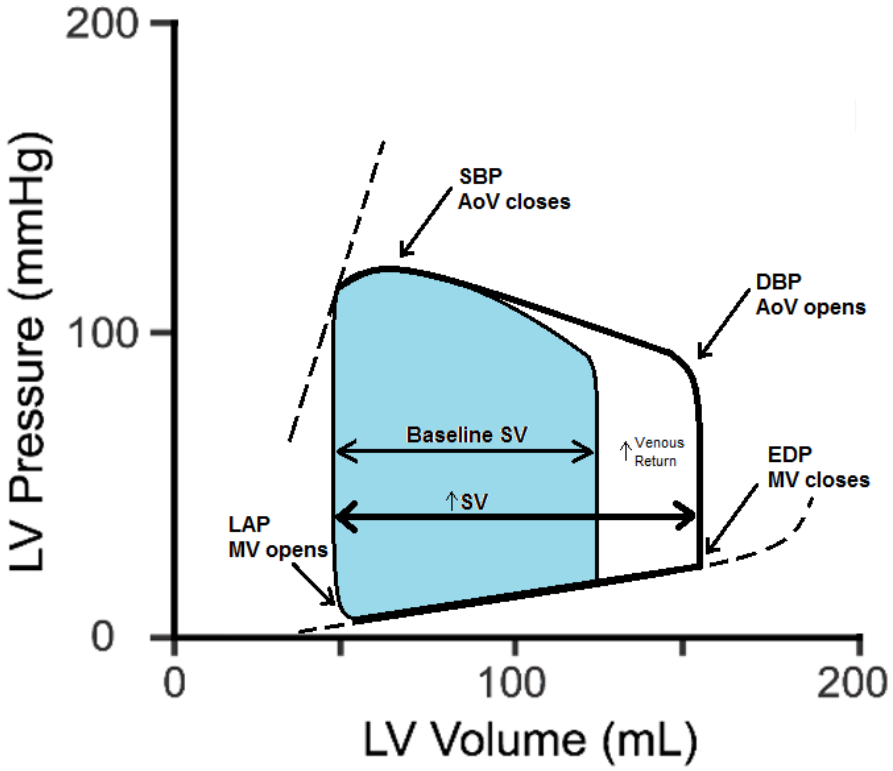
Abbreviations: LVEDP: Left Ventricular End Diastolic Pressure, SV: Stroke Volume.

Figure 2.2. Frank-Starling graph to show effects of inotrope on stroke volume relative to left ventricular filling pressures



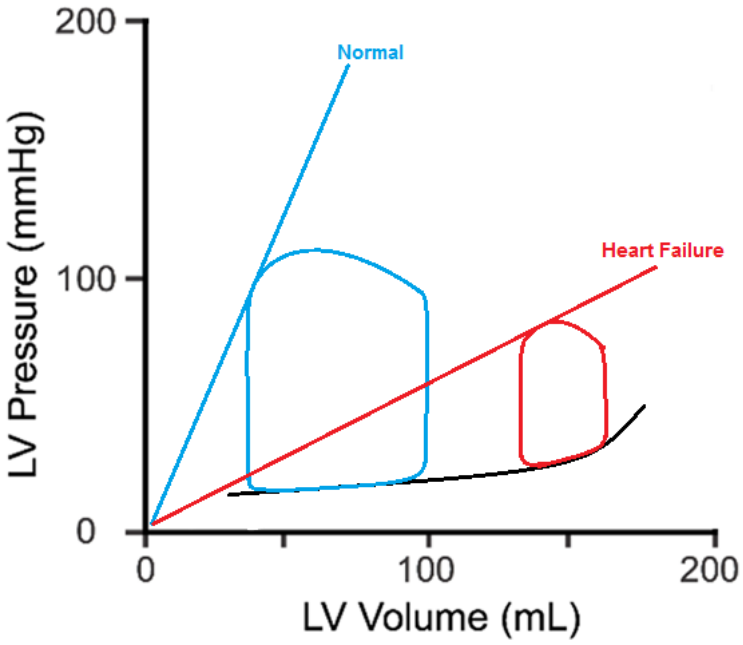
A) normal contractility *B*) increased contractility *C*) Decrease contractility

Figure 2.3. Pressure-volume loop as it relates to increased preload (venous return) and left ventricular function (stroke volume).



Abbreviations: EDP: End Diastolic Pressure, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, AoV: Aortic Valve, LAP: Left Atrial Pressure, SV: Stroke Volume.

Figure 2.4. Pressure-Volume loop representing results of heart failure



Box 1

Indications for Heart Transplant:

- Significant life, limiting heart failure:
    - Persistent NYHA class III or IV symptoms despite maximal guideline directed medical therapy.
    - decreased exercise tolerance (peak $V_{O2} \leq$ 14mL/kg/min for patients not on beta blockers and peak $V_{O2} \leq$ 12mL/kg/min for patients on beta blockers).
- Recurrent life-threatening LV arrhythmias despite optimized medical antiarrhythmic therapy.
- Refractory cardiogenic shock requiring mechanical circulatory support (LVAD, TAH).
- Cardiogenic shock requiring continuous parenteral inotropic therapy.
- End-stage congenital heart patient with heart failure.
- Refractory angina despite maximal medical therapy and not amenable to percutaneous or surgical revascularization.
- Severe hypertrophic or restrictive cardiomyopathy with end-stage heart failure symptoms.
- Severe cardiac allograft vasculopathy in transplanted patients with evidence of graft failure.

Contraindications for Heart Transplant:

- Age > 70 years old
- BMI > 35 kg/m

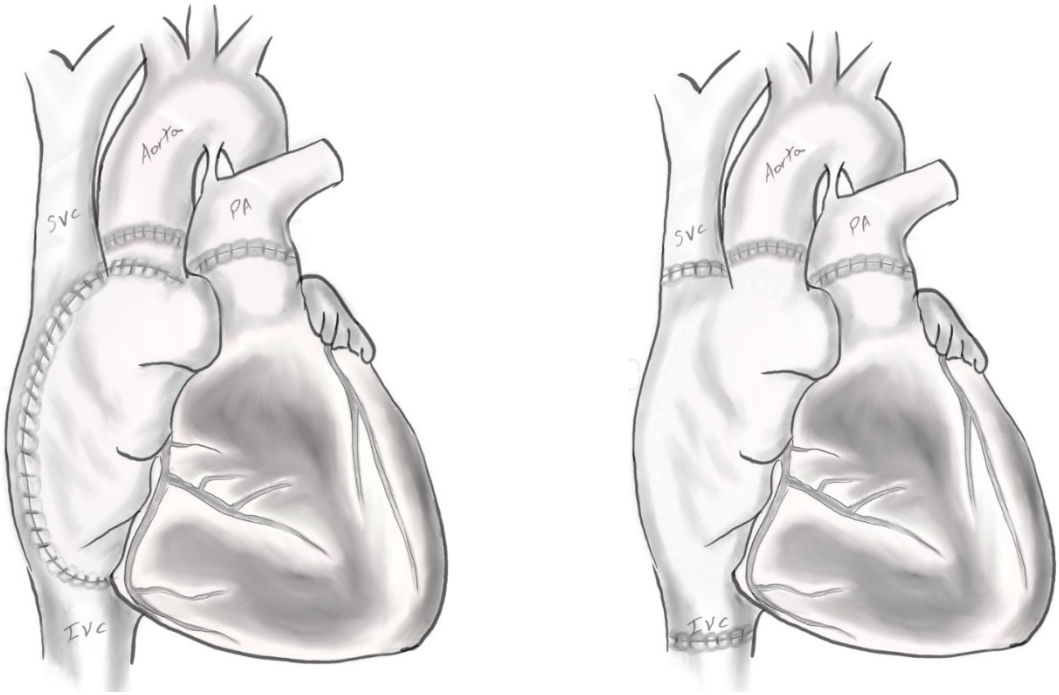
- TPG > 15 mmHg, PVR > 5 Wood units or pulmonary artery pressure > 60 mmHg with one of the above or the inability to achieve PVR < 2.5 Wood units with vasodilator or inotropic therapy
- Primary Lung disease with impaired pulmonary function tests (FEV_1 < 40% or predicted, FVC < 50% or normal DL < 40%)
- Uncontrolled diabetes (HgbA1C > 7.5%)
- eGFR < 30
- Hepatic Cirrhosis
- Severe peripheral vascular disease not amenable to revascularization
- Active infections except LVAD related infections (HIV, Hepatitis B and Hepatitis C)
- Active drug use: must be abstinent 6 months
- Non-compliance or lack of caregiver or social support
- Dementia or mental retardation

Abbreviations: *BMI* body mass index, *TPG* transpulmonary gradient, *PVR* pulmonary vascular resistance, *FEV* forced expiratory volume, *FVC* forced vital capacity, *DLCO* lung diffusion capacity, *HbA1C* glycosylated hemoglobin, mmol millimoles, mol moles, *eGFR* estimated glomerular filtration rate, *mg* milligrams, *dl* deciliters, *HIV* human immunodeficiency virus, *TB* tuberculosis

(Data *From* Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant 2016;35(!):1-23.

Figure 2.5. (A, B) Two different approaches for anastomosis during orthotropic heart transplant.

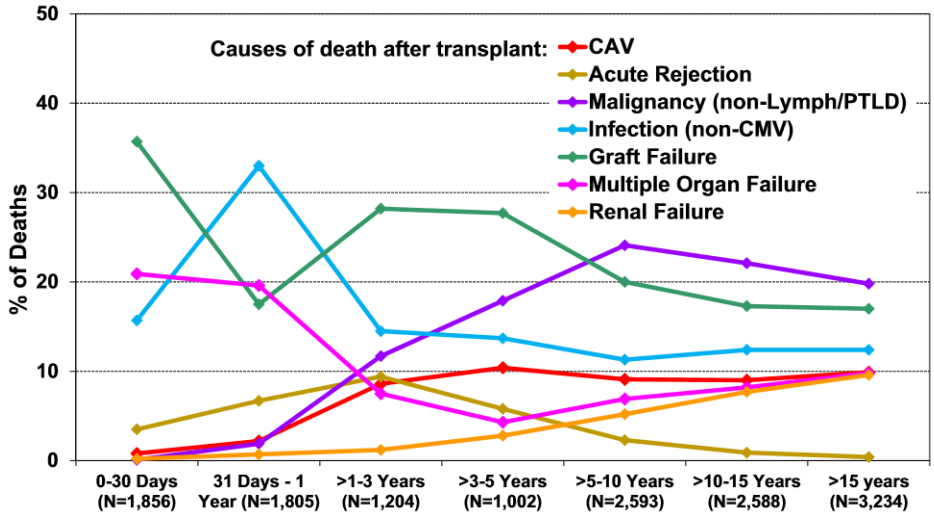
A **B**



Biatrial Technique **Bicaval Technique**

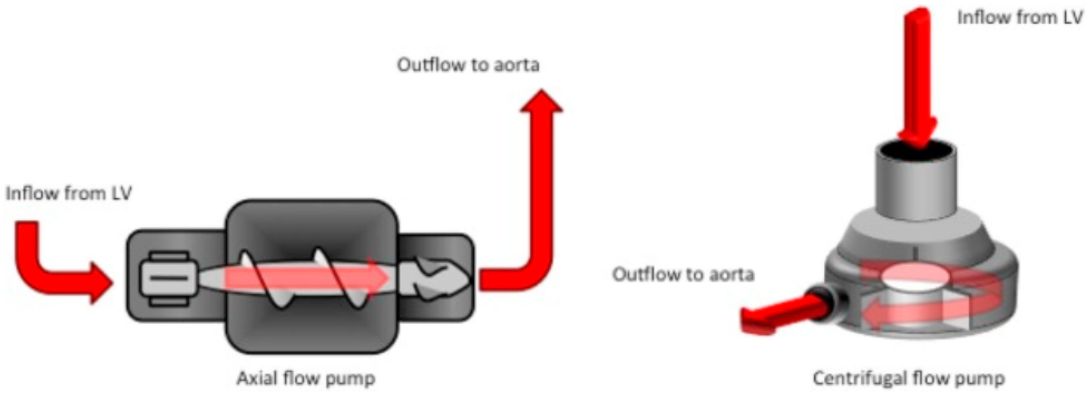
IVC: Inferior Vena Cava, SVC Superior Vena Cava, PA Pulmonary Artery

Figure 2.6. Relative incidence of leading causes of death for adult heart transplants (deaths: January 2009–June 2016). CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus; PTLD, post- transplant lymphoproliferative disorder.



(*From* Kirlkin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36(10): 1080-6: with permission).

Figure 2.7. The mechanism of axial (eg, HeartMate II) versus centrifugal (HeartWare, HeartMate III) pump hemodynamics.



(From Lim HS, Howell N, & Ranasinghe A. The physiology of continuous-flow left ventricular assist devices. J Card Fail. 2017;23(2):170; with permission.)

Box 2

Indications for mechanical support:

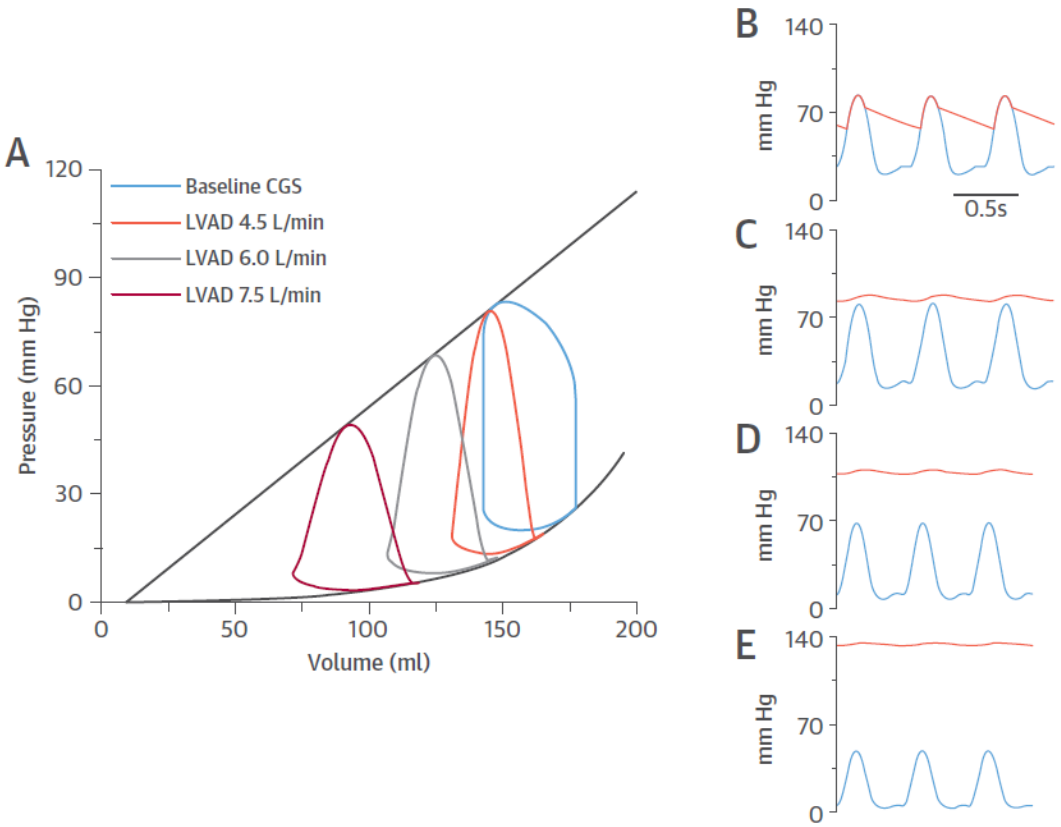
- Severe symptomatic heart failure despite optimal medical therapy
- Left Ventricular Ejection Fraction (LVEF) that is less than or equal to 25 percent.
- Exercise VO2 that is less than or equal to 12 ml/kg/min
- Continuous intravenous inotropes or IABP therapy to prevent symptomatic hypotension, decreasing renal function or worsening pulmonary congestion.

Contraindications for mechanical support:

- blood clotting disorders
- severe cirrhotic liver disease
- severe lung disease
- other co-morbid conditions that result in < 1 year survival

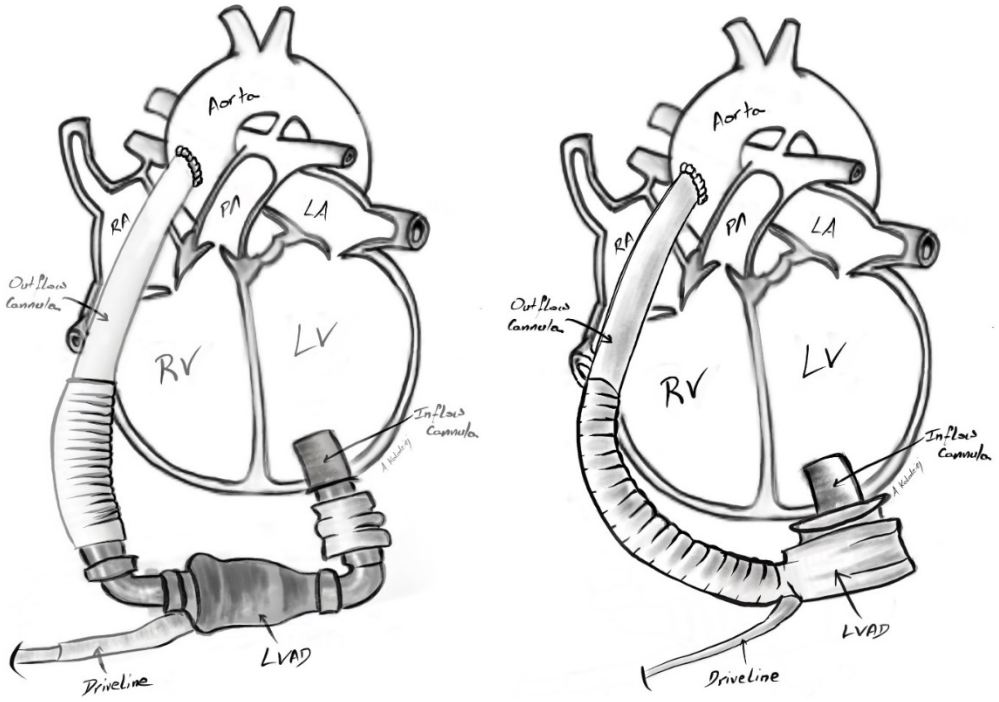
(Data *From* Miller LW, Guglin M. Patient selection for ventricular assist devices: a moving target. J Am Coll Cardiol. 2013;61(12):1209-21.

Figure 2.8. Flow-dependent changes of the pressure-volume loop



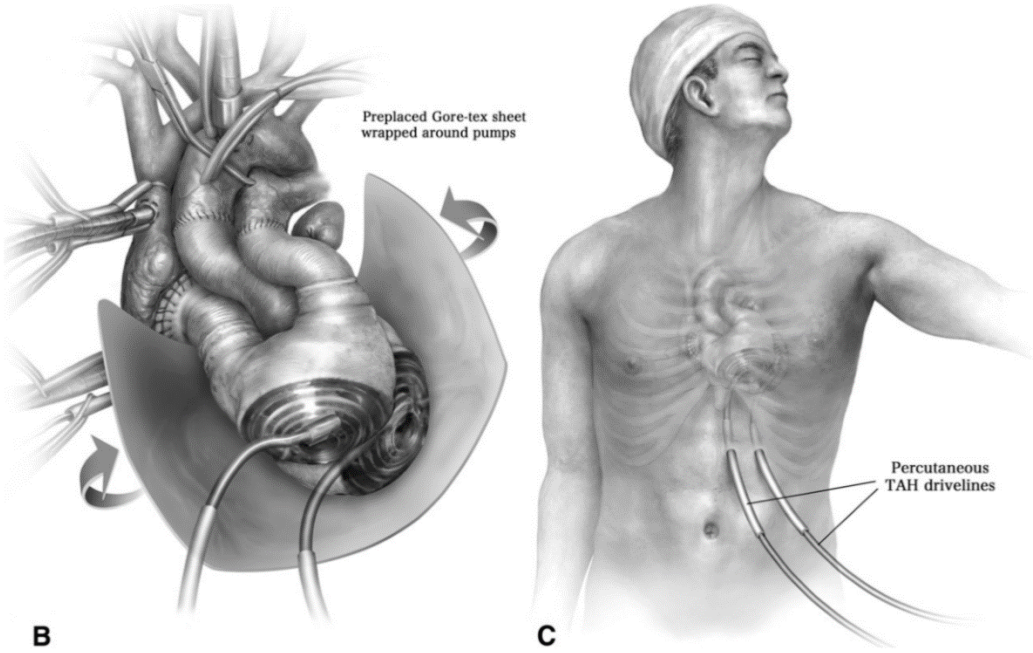
(A) Flow-dependent changes of the pressure-volume loop with LV-to-aortic pumping. The loop becomes triangular and shifts progressively leftward (indicating increasing degrees of LV unloading). Corresponding LV and aortic pressure waveforms at baseline (B), 4.5 l/min (C), 6.0 l/min (D) and 7.5 l/min (E). With increased flow, there are greater degrees of LV unloading and uncoupling between aortic and peak LV pressure generation. CGS, cardiogenic shock.
(*From* Burkhoff D, Sayer G, Doshi D, et al. Hemodynamics of mechanical circulatory support. J Am Coll Cardiol 2015;66-2671; with permission)

Figure 2.9. Types of LVAD device



(A) Axial Flow Device (B) Centrifugal Device RA, right atrium; RV, right ventricle

Figure 2.10. Total artificial heart



(A) Gore-tex (Gore Medical, Flagstaff, AZ) sheets are sewn into the pericardial well with a few 4-0 prolene sutures. After coming off bypass, and hemostasis is achieved, the sheets can be wrapped around the ventricles to prevent harm on reentry. (B) Percutaneous lines exit 6-8 cm from left subcostal margin.
(*From* Morris RJ. The Syncardia total artificial heart; implantation technique. Oper Tech Thorac Cardiovasc Surg 2012;17(@):164; with permission).

Box 3:

Indications:

- Patients who are heart transplant candidates with severe biventricular failure and imminent risk of death (INTERMACS profiles 1 and 2) in setting where suitable donor is not available.
- Bridge to transplant in patients in need of re-transplantation experiencing graft failure not responding to conventional therapy: Severe and diffuse coronary artery vasculopathy.
- Patient's with infiltrative or hypertrophic cardiomyopathy and associated low output failure versus cardiogenic shock. Knees are patients not amenable to left ventricular systolic devices
- Patient's who experienced ventricular tachycardia storm or malignant arrhythmias despite multiple ablations and medical therapy.

Contraindications:

- Patients for ultimately not deemed to be transplant candidates

(Data *From* Arabia F. Total artificial heart. In: Kobashigawa JA, editor. Clinical guide to heart transplantation. Cham, Switzerland: Springer; 2017. P. 227-236.)

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Chapter Three: Markers of Frailty in Patients Undergoing Left Ventricular Assist Device Implantation

Abstract

Background: Frailty has been linked to adverse clinical outcomes, disability, increased hospital length of stay (LOS), readmissions and increased mortality. Several markers of frailty are associated with aging and other co-morbid conditions leading to uncertainty about their applicability to patients undergoing evaluation for Left Ventricular Assist Device (LVAD) implantation. The purpose of the study was to identify a feasible frailty measure in adults with end-stage HF who underwent LVAD implantation. In order to determine the best marker of frailty in LVAD patients, we tested the hypothesis that frailty would predict 30 day rehospitalization rates using Fried's criteria, SPPB, handgrip strength, serum albumin and 6MWT in patients undergoing LVAD implantation.

Methods: A total of 23 patients were recruited and enrolled between January 2015 and May 2016. This was an observational cohort study in which Fried's criteria, SPPB, handgrip strength, serum albumin levels, and 6MWT were measured prior to LVAD implantation. Hospital readmissions was measured to examine the relationship between measures of frailty and 30-day rehospitalization rates.

Results: A total of 23 patients met eligibility criteria and were included in the analysis. Patients were labeled as frail or non-frail for each measurement of frailty. The vast majority of patients were labeled as frail. All patients were frail as measured by self-reported exhaustion. Albumin, low physical activity and 6MWT were similar with approximately 91% of patients being measured as frail. Fried's criteria labeled 87% as frail followed by gait speed (69.6%), Chair sit to stand (69.6%), Weight loss (65.2%),

Short Performance Physical Battery (60.9%) and Balance (56.5%). Handgrip was least likely to measure one as frail (52.2%). During the 30-day follow-up period, 7 patients were readmitted to the hospital. Handgrip strength and 6MWT were the only two frailty indicators differed between those who were readmitted and not readmitted within 30-days. Handgrip strength was the only marker predictive of hospital readmission and it had a negative association. Compared to those who were not frail, frail patients by handgrip criteria were 93.4% less likely to be admitted ($p = 0.033$).

Conclusion: Changes associated with the disease process of patients with end stage heart failure undergoing LVAD implantation makes it difficult to identify markers of frailty in this population. The findings of our study indicate that none of the markers are good predictors of frailty in patients with advanced heart failure with LVADs because they all identify a vast majority of the patients as frail.

Introduction

Chronic heart failure is a devastating and progressive condition affecting over 5.7 million Americans, and demands enormous resources which together account for 2-3% of the national health care budget.[-] The number of adults with heart failure is expected to exceed 8 million and the annual costs is expected to increase from $30.7 billion to $69.7 billion by 2030. Readmission rates remain a burden with approximately 50% of all patients being readmitted within six months and 25% being readmitted within 30 days. As heart failure progresses and becomes advanced, morbidity and mortality increase even further.

The high rate of morbidity and mortality combined with increased costs for readmissions associated with advanced heart failure has led to the development of

advanced treatments such as implantable left ventricular assist devices (LVADs). While the use of LVADS is associated with a significant reduction in morbidity and mortality among patients with advanced heart failure compared to medical treatment alone, the costs associated with this technology remain high with an estimated cost per quality-adjusted years of over > $400,000. Moreover, despite advances in technology, complications associated with LVADs such as infection, bleeding and stroke remain high. Minimizing complications in this population is essential to reducing rehospitalization rates and healthcare costs. It is important to identify those who are most likely to benefit from an LVAD and also identify those who are most likely to have complications associated with LVAD implantation. General guidelines and criteria for patient eligibility have been established and include the following: 1) severe symptomatic end-stage heart failure despite optimal medical therapy; 2) left ventricular ejection fraction (LVEF) less than or equal to 25 percent; 3) exercise VO2 less than or equal to 12 ml/kg/min; and 4) continuous intravenous inotropes or intra-aortic balloon pump therapy to prevent symptomatic hypotension, decreasing renal function or worsening pulmonary congestion.[,] Choosing patients for LVAD remains a challenge because these patients are often deconditioned and unstable due to the progression of their disease with a high risk of adverse events after cardiac surgery., Additionally, the overall physical condition of the patient is an important consideration particularly with respect to the capacity of the patient to participate in their own physical rehabilitation following LVAD implantation. Consequently, the concept of frailty has emerged as an important factor for appropriate patient selection.

Frailty is defined as an increased vulnerability due to age or physical condition because of decline in physiological reserves or function that compromises the ability of the patient to adjust to acute stressors.[illegible] In the Cardiovascular Health Study, frailty was defined according to Fried's Criteria: 1) poor grip strength; 2) slow gait; 3) low level of physical activity; 4) low energy or self-reported exhaustion; and 5) unintentional weight loss. Meeting a minimum of 3 criteria was defined as frail.

Frailty has been linked to adverse clinical outcomes, disability, increased hospital length of stay (LOS), readmissions and increased mortality.[illegible] Frailty has been studied in the elderly population and in patients undergoing cardiac surgery but not well studied in patients undergoing LVAD implantation.[illegible] Fried's criteria is the most commonly used measurement of frailty in patients with LVADs. Several components of Fried's frailty score including decreased gait speed, self-reported exhaustion, low physical activity and weight loss are associated with aging and other co-morbid conditions leading to uncertainty about their applicability to patients undergoing evaluation for LVAD implantation.

Another commonly used validated measure of frailty is the short physical performance battery test (SPPB). The SPPB assesses gait speed, balance and lower extremity muscle strength to identify those who are frail. The SPPB has been well studied in other populations including those with heart failure and identifies patients who are at high risk for progressive disability, increased hospital length of stay and mortality.[illegible] The SPPB has not been used in patients with end-stage heart failure undergoing evaluation for LVAD implantation.

While Fried's criteria and the SPPB are common measures of frailty, they are complicated to administer because they include multiple components with different modes of assessment. Identifying a more suitable measure of frailty that is feasible and sensitive in patients with LVADs is essential. Single markers of frailty may be a better indicator of frailty in this population.[,,] Clinical evidence from the heart failure literature suggest that handgrip strength, albumin and six minute walk distance improve after LVAD placement, therefore these markers may be good measurements of frailty for this population.[,]

Handgrip strength is a simple and effective measure of frailty. Assessing handgrip strength prior to LVAD implantation may aid in determining LVAD candidacy, as reduced handgrip strength identifies those at risk for increased LOS following LVAD implantation. Reduced handgrip strength is a predictor of reduced survival after VAD implantation, in addition to post-operative outcomes including bleeding and infection. Thus, handgrip strength may be a good individual marker for frailty in LVAD patients.

Serum albumin is an indicator of disease severity in patients with heart failure and has been shown to be associated with increased mortality and morbidity.[,] Up to 49% of patients with heart failure have hypoalbuminemia and serum albumin is an inexpensive marker recently proposed for the identification of patients with heart failure at risk of adverse outcomes. In patients with LVADs, pre-implantation albumin was identified as a indicator of 3 month mortality post LVAD implantation and is associated with prolonged hospitalization in patients undergoing LVAD implantation.[,] In addition, post-implantation normalization of albumin levels is associated with improved survival.

Based in these findings, serum albumin may be a good single marker of frailty in LVAD patients.

The Six Minute Walk Test (6MWT) is associated with frailty and predicts mortality in older patients with heart failure. Furthermore, changes in 6MWT distance predict rehospitalizations. In patients with LVADs, the 6MWT is associated with functional decline and patients walking less than 300 meters have increased mortality. The 6MWT is feasible for patients with acute heart failure and can be used to assess baseline status and response to therapy, [and] thus might be a good single marker for frailty in LVAD patients.

It is anticipated that identification of frailty in patients would enhance patient selection for LVAD implantation and potentially identify patients whose frailty is likely to reverse following successful implantation of LVAD. The purpose of the study was to identify a feasible frailty measure in adults with end-stage HF who underwent LVAD implantation. In order to determine the best marker of frailty in LVAD patients, we tested the hypothesis that frailty would predict 30 day rehospitalization rates using Fried's criteria, SPPB, handgrip strength, serum albumin and 6MWT, in patients undergoing LVAD implantation.

Methods

Study design

This was an observational cohort study conducted at a major academic medical center in which Fried's criteria, SPPB, handgrip strength, serum albumin levels, and 6MWT were measured prior to LVAD implantation. Hospital readmissions were

measured to examine the relationship between measures of frailty and 30-day rehospitalization rates.

Sample and setting

After receiving Institutional Review Board approval for the study, a total of 23 patients were recruited and enrolled between January 2015 and May 2016 from a hospital associated with a major academic health center. Eligible participants were patients with a diagnosis of end-stage heart failure with reduced ejection fraction < 25% who were classified as New York Heart Association (NHYA) Class IV and who were scheduled to undergo LVAD implantation. All eligible patients during the enrollment time period agreed to participate and provided signed informed consent. Patients who could not complete the physical tests (n = 1) or who died before discharge (n = 1) were not eligible for the study.

Measurement of variables

These variables were measured in the patient's room prior to LVAD implantation. All data were collected within 1 week prior to implantation.

Fried's Criteria

Fried's Criteria includes the following domains: 1) self-reported exhaustion; 2) physical activity; 3) weight loss; 4) strength; and 5) gait speed.

Self reported exhaustion was measured by asking the patient the following 2 questions from the Center for Epidemiologic Studies Depression Scale (CES-D): How often in the past week did you feel like everything you did was an effort and how often in the past week did you feel like you could not get up and going? Answers were categorized into 2 groups: Often (> 3 days) or not often (0-2 days). Those who answered

often were labeled as frail. The CES-D scale is the most common instrument used in the Fried's criteria to examine self-reported exhaustion.

Low physical activity was measured by asking the patient a single question to identify self-reported physical activity: Over the past week (even if it was not a typical week), how much time did you exercise or were you physically active (included both exercise and your usual activities of daily living)? The answers were categorized into (1) None; (2) Less than 30 minutes/week; (3) 30-60 minutes/week; (4) More than 60 minutes/week. More than 60 minutes a week was defined as being physically active, less than 60 minutes was defined as having low physical activity. The single-item question that was used was easy to complete and construct and validity have previously been established and have been used in several previous populations including patients with heart failure.

Weight loss was self-reported by asking the patient if they had ≥ 10 pound weight loss in the prior year. This is the most commonly utilized way of measuring weight loss for Fried's criteria.

Strength was measured using handgrip strength, which is associated with increased mortality, bleeding and infection after LVAD implantation. It was measured in the dominant hand using a Jamar Hydraulic Hand Dynamometer (JLW Instruments, Chicago, IL), which is an accessible, widely used device. Handgrip strength was measured by a nurse practitioner who was trained by an exercise physiologist. Patients were asked to perform a maximal isometric contraction for 5 seconds with their dominant hand three times with a 30 second rest period between each contraction. Strength was defined as the average of the 3 contractions. Patients whose handgrip was less than 25 %

of their body weight in kilograms were labeled as frail. Those with a handgrip strength greater than 25% of their body weight in kilograms were labeled as non-frail.

Gait speed was measured as follows by the nurse practitioner. A cone was placed at the starting point and at the end point with a distance of 4 meters measured by a tape measure in between the starting and end point. Gait speed was measured with a stop watch and was defined as the time required for the participant to walk from the beginning to the end. Gait speed is identified as a predictor of mortality and morbidity in patients undergoing cardiac surgery and has been identified as a frailty indicator in patients with advanced heart failure.

Short performance battery test

The short physical performance battery test (SPPB) was used to measure lower extremity functional ability. The SPPB was conducted by a physical therapist. The SPPB is used to evaluate frailty using a series of three physical performance tests (gait speed, chair rises and tandem balance). Gait speed was measured as described above. Chair raises were conducted in the participant's room. The participant was asked to go from sitting to standing position with arms were folded across chest 5 times as quickly as possible without stopping and was timed. Tandem balance was measured with feet positioned in 3 different positions (feet together, semi tandem with the heel of one foot placed by the big toe of the other foot and full tandem with feet directly in front of each other). The participant was asked to stand in each position for 10 seconds and was allowed to use arms, bend knees or move their body to maintain balance. Each tandem position was scored with a range of 0 to 4 (0= couldn't perform, 1 = needed assistance to perform, 2 = performed with great difficulty by themselves, 3 = performed with some

discomfort, 4 = performed without difficulty or discomfort). After each tandem position was scored, the three measures were added together for a total score that ranged from 0 (worst performance) to 12 (best performance). Patients were classified as frail (SPPB score < 6), borderline frail (SPPB score 7-9) or non-frail (SPPB score ≥ 10). The SPPB has been shown to have predictive validity for mortality, increased hospitalization and disability in older adults.

Serum Albumin

Hypoalbuminemia is a prognostic indicator in patients with heart failure and is associated with increased mortality and unfavorable outcomes. Serum albumin levels (g/dl) were measured by standard laboratory techniques. Serum albumin levels were collected at the time of the patients pre-operative routine laboratory work on the day of surgery and analyzed in the clinical laboratory at the hospital. Patient were categorized according to serum albumin level (frail < 3.5 g/dl and as non-frail > 3.5 g/dl).

Six minute walk test

The 6MWT has been identified as an important outcome measure of functional capacity in people with severe heart failure and is a marker of frailty. The 6MWT is safe, easy to administer and has been found to be reliable predictor of post-LVAD mortality. A nurse practitioner or physical therapist instructed the patients to walk for 6 minutes down a hallway free of obstacles at a pace at which they felt comfortable. Patients were permitted to use a walker or cane if needed and rest breaks were permitted, although time recording does not stop with any break. The hospital hallway was marked in 1 meter increments and the total distance in meters walked in 6 minutes was recorded. Patients

walking less than 300 meters were classified as frail. Those walking greater than 300 meters were classified as non-frail.

Sociodemographic and Clinical Variables

Gender, age, marital status, body mass index, comorbidities, and heart failure etiology (ischemic vs non-ischemic) were obtained from the medical record. Comorbidity data included diabetes, coronary artery disease and chronic kidney disease.

Hospital Readmission

Hospital readmission data was obtained from the medical record. Time to hospital readmission was defined as time from date of discharge to the date of rehospitalization for any cause.

Data analysis

Demographic and clinical characteristics were reported using frequencies and percentages for categorical variables and mean ± standard deviation for continuous variables. Frequencies were used to determine frailty for each measure. Chi-square analysis was used to determine if the measures of frailty were predictive of 30 day. All analysis was conducted using SPSS software.

Results

A total of 23 patients met eligibility criteria and were included in the analysis. Patient characteristics are presented in Table 3.1. The average age of patients was 59 ± 9 years. Almost all participants were male and married. The primary etiology of heart failure for this population was ischemic cardiomyopathy. Over two-thirds of the patients had coronary artery disease and over half of the patients had diabetes mellitus. Chronic kidney disease was prevalent in nearly half of the patients.

Patients were labeled as frail or non-frail for each measurement of frailty which is presented in Table 3.2. All patients were frail as measured by self-reported exhaustion. Albumin, low physical activity and 6MWT were similar with approximately 91% of patients being measured as frail. Handgrip was least likely to measure one as frail.

During the 30-day follow-up period, 7 patients were readmitted to the hospital. Median hospital length of stay was 19 days and median length of stay in the intensive care unit was 8 days. The most common cause for readmission was acute heart failure symptoms (n = 6). Only two frailty indicators differed between those who were readmitted and not readmitted within 30-days. These were handgrip strength and 6MWT. Of those admitted within 30 days of discharge, 14.3% were frail by handgrip criteria, while of those not admitted, 68.8% were frail by handgrip criteria. Of those admitted within 30 days of discharge, 71.4% were frail by 6MWT criteria, while of those not admitted, 100% were frail by 6MWT criteria. (Table 3.3). With the exception of handgrip strength, none of the criteria were predictive of hospital readmission (Table 3.4). Compared to those who were not frail, frail patients by handgrip criteria were 93.4% less likely to be admitted ($p = 0.033$).

Discussion

The study demonstrated several indicators of frailty in patients with advanced heart failure undergoing LVAD implantation and which measurements were predictive of 30 day re-hospitalization. The findings of our study indicate that measures of frailty that contain multiple components such as Fried's criteria and SPPB, and measures that are single markers such as handgrip, 6MWT and albumin are not good predictors of frailty in patients with advanced heart failure with LVADs.

We found that nearly 87% of patients with advanced heart failure undergoing LVAD implantation were frail according to Fried's criteria and 85% of those patients were readmitted within 30 days. While the Fried's criteria is the most commonly used measurement of frailty in patients with HF and those with LVAD's, it has been suggested that Fried's criteria may not be applicable in patients with advanced heart failure undergoing LVAD implantation. The Fried criteria was originally developed to define frailty in a population of ambulatory adults. Due to the progression of disease and inflammatory response leading to deconditioning and debilitation, these measurements may not accurately reflect frailty in patients with advanced heart failure undergoing LVAD implantation.

Some criteria such as self-reported exhaustion, self-reported physical activity, and weight loss may not be accurate in this population. Weight loss may be masked by volume overload in the setting of end-stage HF leading to inaccurate assessment of weight loss in the past year. Most patients with end-stage heart failure are not able to perform activity of daily living and have limited ambulation due to symptoms associated with heart failure including fatigue, shortness of breath and weakness. Therefore, self-reported exhaustion and self-reported physical activity may not accurately reflect frailty, but may be only associated with disease progression of heart failure.

The SPPB has been identified as a frailty indicator in patients with advanced heart failure and are predictive of outcomes. However, this was not found in our study. The SPPB is sensitive to the physiological decline associated with aging and is influenced by cognition and motivation which play a role in determining prognosis in frail patients with HF. The SPPB integrates the effects of physiological decline, malnutrition and

comorbidities. However, the SPPB is influence by severity of illness and symptoms and may not be feasible for many hospitalized patients. By comparing individual components of this integration will allow for the possibility of markers of frailty that are easier to administer.

One component of the SPBB and Fried's criteria is gait speed. Our study did not support the findings of other investigators.[,] Gait speed in patients with advanced heart failure undergoing LVAD implantation was not predictive of readmission and identified frailty in about two-thirds of the patients. Gait speed has been identified as a single measure of frailty and was found to be predictive of 6 month mortality when compared to Fried's criteria in other populations.[,] It is a preferred measure of frailty compared to SPPB and Fried's criteria because it is quick to administer and practical and provides useful prognostic information.[,] However, its applicability to patients undergoing LVAD implantation may be limited. There is a significant minority of patients who are not ambulatory or are unable to perform the activity. Alternative measures such as handgrip strength may be more feasible in this population.

Handgrip was not a good measurement of frailty based on our findings. It identified few patients as frail. This contradicts other studies that support handgrip strength as a good predictor of frailty.[,] To my knowledge no studies have examined length of stay to handgrip strength or prediction of handgrip strength to 30 day readmission. Our study found that handgrip strength was the only measure that predicted 30 day readmission but the relationship was a negative association. For those who were frail by handgrip strength, they were more likely to not be admitted. The wide confidence interval indicates that this is not a precise measurement which may due to the small

sample size. Handgrip has been linked to increased length of stay when examined as part of Fried's criteria in relation to outcomes and hospitalization.

Measures such as gait speed, and 6MWT mainly use lower extremity strength to assess functional ability, handgrip strength is performed with minimal exertion using upper body strength, which could account for the difference of frailty classification.

Post-LVAD implantation 6MWT has been examined and is associated with increased mortality. It has been validated to measure functional capacity and outcomes in heart failure, but its utility in patients with LVADs in the context of frailty is unknown. The 6MWT identified over 90% of our patients as frail and is not a good measure of frailty in patients with advanced HF undergoing LVAD implantation. This is the only study to examine the 6MWT as an indicator of frailty in comparison to multiple other measures and to assess if 6MWT predicts re-hospitalization.

Albumin identified over 91% of our patients as frail, yet it was not predictive of 30 day readmission. It is not a good indicator of frailty in patients with advanced HF undergoing LVAD implantation. It is well understood that patients with heart failure often have cardiac cachexia so the likelihood of unintentional weight loss is prevalent in most of the population reaching end stage heart failure. As a result, malnutrition is inevitable and is associated with postoperative complications, prolonged hospitalizations and poor outcomes. Furthermore, hypoalbuminemia, as a marker of malnutrition, is associated with morbidity and mortality and low albumin levels (<2.5 mg/dl) are associated with mortality and morbidity after LVAD implant. In addition, pro-longed post-operative length of stay is also associated with low albumin levels.

To my knowledge this is the first study to compare these measures of frailty in patients with LVADs. Identification of patients at high risk for functional decline and poor outcomes is crucial when considering LVAD and patient selection is important to attain a favorable outcome. One of the most difficult challenges is differentiating between underlying conditions such as inflammatory, malnutrition, low activity levels that can occur with both frailty and heart failure.

There are some limitations that should be acknowledged in the interpretation of the present data. This was a single-center study and the results may not be generalizable to other patients at other centers. The number of patients in the study was small and we were limited in the number of factors we could adjust for in the analysis. Heterogeneity among groups of patients should be considered in future research and indicate which fraction of patients are bridge to transplant versus destination therapy. Patients considered for destination LVAD tend to be older and have more comorbid illnesses. Future research should also focus on broader range of outcomes and include a larger sample size. In addition, future research should focus on additional predictors of frailty and interventions or changes in management that will improve frailty prior to LVAD implantation.

Conclusion

Changes associated with the disease process of patients with end stage heart failure undergoing LVAD implantation makes it difficult to identify markers of frailty in this population. The findings of our study indicate that none of the markers are good predictors of frailty in patients with advanced heart failure with LVADs because they all identify a vast majority of the patients as frail. Given these findings, it may be more beneficial to focus on which measures of frailty improve post-implantation.

Table 3.1: Patient demographic and clinical characteristics N = 23

Characteristics	Mean ± SD or N (%)
Sociodemographics	
Age, years	59.61 ± 9.58
Gender Male Female	 21 (91.3) 2 (8.7)
Marital stats Married or cohabiting Living with other family	 22 (95.7) 1 (4.3)
Readmitted within 30 days No Readmitted Readmitted	 16 (69.6) 7 (30.4)
Clinical Characteristics	
Body mass index, m^2/kg	29.22 ± 5.70
6 minute walk, meters	189.04 ± 84.163
Albumin, mg/dl	2.75 ± 0.43
Etiology of Heart Failure Non-ischemic cardiomyopathy Ischemic cardiomyopathy	 8 (34.8) 15 (65.2)
Coronary artery disease (CAD) Do not have CAD Have CAD	 7 (30.4) 16 (69.6)
Diabetes mellitus (DM) Do not have DM Have DM	 10 (43.5) 13 (56.5)
Chronic kidney disease (CKD) Do not have CKD Have CKD	 12 (52.2) 11 (47.8)

Table 3.2: Comparison of Left Ventricular Assist Device Patient Characteristics Between Patients Readmitted Within 30 Days and Those not Readmitted, N = 23

Characteristics	Not Readmitted, n = 16 Mean ± SD or N (%)	Readmitted, n = 7 Mean ± SD or N (%)	P
Sociodemographics			
Age, years	59.7 ± 10.8	59.4 ±6.7	0.95
Gender Male Female	 15 (93.8) 1 (6.3)	 6 (85.7) 1 (14.3)	0.56
Marital stats Married or cohabiting Living with other family	 15 (93.8) 1 (6.3)	 7 (100) 0	0.39
Clinical Characteristics			
Body mass index, m^2/kg	30.2 ± 4.7	26.9 ± 7.5	0.20
Albumin, mg/dl	2.75 ±.50	2.76 ± .21	0.97
6 minute walk, meters	177.1 ± 74.6	216.3 ± 104	0.31
Non-ischemic cardiomyopathy	7 (47.8)	1 (14.3)	0.15
Coronary artery disease	10 (62.5)	6 (85.7)	0.24
Diabetes mellitus	8 (50.0)	5 (71.4)	0.33
Chronic kidney disease	11 (68.8)	0 (0)	0.001
Frailty Characteristics			
Fried Criteria, yes frail	14 (87.5)	6 (85.7)	0.91
Short Performance Physical Battery, yes frail	11 (68.8)	3 (42.9)	0.25
Hand grip, yes frail	11 (68.8)	1 (14.3)	0.01
Albumin, yes frail	14 (87.5)	7 (100)	0.22
6 minute walk test, yes frail	16 (100.0)	5 (71.4)	0.02
Low physical activity, yes frail	15 (93.8)	6 (85.7)	0.55
Gait speed, yes frail	12 (75.0)	4 (57.1)	0.40
Weight loss, yes frail	10 (62.5)	5 (71.4)	0.68
Balance, yes frail	10 (62.5)	3 (42.9)	0.38
Chair sit to stand, yes frail	11 (68.8)	5 (71.4)	0.90
Self-reported exhaustion, yes frail	16 (100)	7 (100)	n/a

Table 3.3: Categorization of Left Ventricular Assist Device Patients as Not Frail or Frail for Each Individual Frailty Measure, N = 23

Measure	Not frail N (%)	Frail N (%)
Fried Criteria	3 (13)	20 (87)
Short Performance Physical Battery	9 (39.1)	14 (60.9)
Hand grip	11 (47.8)	12 (52.2)
Albumin	2 (8.7)	21 (91.3)
6 minute walk test	2 (8.7)	21 (91.3)
Low physical activity	2 (8.7)	21 (91.3)
Gait speed	7 (30.4)	16 (69.6)
Self-Reported exhaustion	0	23 (100)
Weight loss	8 (34.8)	15 (65.2)
Balance	10 (43.5)	13 (56.5)
Chair sit to stand	7 (30.4)	16 (69.6)

Table 3.4: Frailty Predictors of 30 day Readmission

	B	Odds Ratio	95% Confidence Interval	P
Fried's Criteria	-.154	.857	.065-11.357	.91
SPPB	-1.076	.341	.055-2.131	.250
Handgrip	-2.580	.076	.007-.807	.033
Albumin	.040	1.041	.126-8.598	.970
6MWT	0.006	1.006	.995-1.017	.304
Legend: Short Physical Performance Battery (SPPB), Six Minute Walk Test (6MWT)				

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Chapter Four: Factors of Frailty That Improve Post VAD

Abstract

Background: Frailty has been identified as a prognostic marker for adverse outcomes in patient with heart failure and patients undergoing cardiac intervention and surgery. There is minimal information regarding outcomes and short-term improvement in frailty post Left Ventricular Assist Device (LVAD) implantation. Three objective measures that reflect frailty and that have been used by others to measures frailty in patients with heart failure but not in LVAD patients or to predict outcomes include handgrip strength, the six minute walk test (6MWT) and serum albumin. Thus, we chose these three measures to reflect frailty and the purpose of the study was to determine whether frailty measures improve 3 months post LVAD implantation and to compare sensitivity of these three measures to change in frailty.

Methods: This was a 3 month longitudinal cohort study of 23 patients with advanced heart failure who underwent LVAD implantation. Patients were enrolled between January 2015 to May 2016 and within 1 week of scheduled date of LVAD implantation. Patients of all ages and implantation strategy were included. Frailty was reflected by handgrip strength, 6MWT and serum albumin.

Results: Prior to LVAD implantation, frailty measurements by handgrip strength identified 12 patients as frail compared to 22 patients by 6MWT and 21 patients by albumin. Post LVAD measurements of frailty identified 13 as frail by handgrip, 11 by 6MWT and 9 by albumin. There was no difference in handgrip strength from pre-implantation and post-implantation. Only 8% of patient walked 300 meters or more in 6 minutes prior to LVAD implantation. In contrast, 53% of patients were able to walk more

than 300 meters at 3 months post-implantation with an average 47% improvement in 6MWT distance ($p = 0.002$). Mean distance walked increased significantly from pre- to post-implantation ($p < 0.001$). Pre-operatively 21 (91.3%) patients met criteria for frailty based on serum albumin cut-point and post-operatively 9 (39.1%) met frailty criteria ($p = 0.002$). Mean serum albumin increased significantly pre- to post-implantation ($p < 0.001$).

Conclusion: In patients with heart failure who undergo LVAD implantation, the 6MWT and serum albumin measurements are reflect short-term improvement in frailty and these simple measures may be used to determine those patients who are responsive to LVAD implantation. Frailty by select markers is likely to improve in most people after LVAD implantation, and thus frailty should not preclude candidate selection for an LVAD.

Introduction

Heart failure is a progressive condition that affects 5.7 million Americans with more than 670,000 new cases each year. Approximately 100,000 patients with heart failure in the United States are unresponsive to maximal medical therapy resulting in further deterioration, rehospitalization, and death. The high rate of morbidity and mortality, and poor quality of life associated with heart failure has led to exploration of additional treatments for those with advanced heart failure that include left ventricular assist devices (LVADs).

Despite improvement in morbidity and mortality with LVADs, multiple complications such as stroke, bleeding and device-related infections occur. The cost associated with these treatments is extensive. ‹‹‹ Consequently, it is crucial to identify

patients who are most likely to benefit from a LVAD. One potential factor that may be important to patient selection is frailty.

Frailty has been identified as a prognostic marker for adverse outcomes including death, disability and rehospitalization in patient with heart failure and patients undergoing cardiac intervention and surgery.[,,,,,] Frailty reflects physiological changes across many organ systems due to a decrease in physiological reserve and to vulnerability caused by physical and psychological stressors such as acute or chronic illness. When exposed to stressors, patients who are frail are at risk for further decompensation, adverse events, complications, longer recovery, functional decline and mortality.[,,,]

Frailty in the elderly community and in patients undergoing cardiac surgery leads to adverse outcomes and increased mortality and morbidity.[,,,] Recently, there has been a growing interest in the effect of frailty on patients undergoing LVAD. Frailty is prevalent in 21% of patients with advanced heart failure who undergo LVAD implantation and is associated with increased hospital length of stay, higher risk of hospital readmission and increased hospital length of stay.

Little is known about frailty in patients with an LVAD and most of the research has focused on how frailty may impact prognosis and outcomes after LVAD implantation. There is minimal information regarding short-term improvement in frailty post LVAD implantation. Clarification of how frailty improves post LVAD will allow for better patient selection to ensure that those undergoing LVAD implantation benefit from the device with minimum complications and are most likely to recover. It typically takes approximately 3 months for patients to recover from post-surgical changes, undergo

rehabilitation, and adapt to their new lifestyle. Further information is warranted to determine if short-term measures in frailty improve during this time frame also.

To date, there is no gold standard definition of frailty. In order to attempt to operationalize the definition of frailty, Fried proposed a clinical phenotype which defines frailty as meeting three out of five phenotypic criteria: 1) slowness; 2) unintended weight loss; 3) inactivity; 4) exhaustion; and 5) decreased grip strength." The subjectivity of some of these indicators and their universality among individuals with advanced heart failure suggest that use of Fried's criteria may be inappropriate with patients with end-stage heart failure. Three objective measures that reflect frailty and that have been used by others to measures frailty in patients with heart failure but not in LVAD patients or to predict outcomes include handgrip strength, the six minute walk test (6MWT) and serum albumin. Thus, we chose these three measures to reflect frailty and the purpose of the study was to determine whether frailty measures improve 3 months post LVAD implantation and to compare sensitivity of these three measures to change in frailty.

Methods

This was a 3 month longitudinal (from one week pre-implant to 3 months post LVAD implant) cohort study of 25 patients with advanced heart failure who underwent LVAD implantation.

Subjects

Patients were enrolled between January 2015 to May 2016 at a major medical center and within 1 week of scheduled date of LVAD implantation. Patients of all ages and implantation strategy (i.e., bridge to transplant or destination therapy) were eligible for the study if they (1) had a physician diagnosis of advanced heart failure as

documented in the hospital medical records with a confirmed left ventricular ejection fraction (LVEF) < 25% by echocardiography and (2) were able to complete required physical tests (i.e., handgrip strength and 6MWT). A total of 25 eligible patients agreed to participate in the study during the enrollment period. One patient was physically unable to perform the 6MWT at 3 months post-implantation and one patient died prior to 3 month follow-up resulting in a final sample of 23 patients.

Measures

Frailty was reflected by handgrip strength, 6MWT and serum albumin.

Handgrip strength. Handgrip strength was measured in the dominant hand using a hydraulic hand dynamometer by Jamar Hydraulic Hand Dynamometer (JLW Instruments, Chicago, IL). The patient was permitted to stand or sit with arms at their side not touching their body and elbow bent slightly. They were instructed to squeeze the dynamometer with as much force as possible for five seconds. Handgrip strength was recorded as the average force to the nearest kilograms of 3 trials spaced 30 seconds apart to avoid muscle fatigue. Patients whose handgrip force was < 25% of their body weight in kilograms were categorized as frail. The pre-LVAD handgrip strength was measured by a nurse practitioner in the patient's hospital room within 1 day of LVAD implantation. Post- LVAD handgrip strength was measured in the clinic room at each patients' 3 month routine follow-up visit by the same nurse practitioner.

Six minute walk test. Patients were instructed to walk down a hallway free of obstacles at a comfortable pace for 6 minutes. They were permitted to use a walker or cane if needed and take rest break although timing continued. To improve accuracy of measured distance, 100 meters of the hallway was marked in 1 meter intervals. A stop

watch was used to time the test. The total distance walked after 6 minutes was documented. Patients walking < 300 meters were categorized as frail. The 6MWT was conducted by a nurse practitioner or physical therapist. The pre-LVAD implantation 6MWT was conducted in a hospital hallway. The post LVAD implantation 6MWT was conducted in the clinic hallway at the 3 month routine follow-up visit.

Albumin. Blood for serum albumin levels was collected as part of the patients' routine pre-operative laboratory work and as part of their routine 3 month post-implantation laboratory work. Serum was analyzed in the clinical laboratory. Patients were classified as frail if they had an albumin level < 3.5 g/dl.

Procedure

Approval to conduct the study was received from the Institutional Review Board. Patients admitted for LVAD implantation were recruited for the study by the advanced heart failure team. The nurse practitioner for the team explained the study to patients and asked them to participate in the study. If they agreed, the nurse practitioner obtained written consent while the patient was in the hospital prior to LVAD implantation. Demographic and clinical data were retrieved from hospital medical records at baseline and 3 months post LVAD implantation. These data were age, gender, albumin, body mass index (BMI in kg/m2), etiology of cardiomyopathy (ischemic vs non-ischemic), living arrangements and comorbidities (i.e., coronary artery disease [CAD], diabetes mellitus [DM] and chronic kidney disease [CKD]). Heart failure related data included diagnosis documented by physician from echocardiogram with LVEF < 25%. The 6MWT and handgrip were measured at baseline and at 3 months post LVAD implantation per study protocol.

Data Analysis

Demographic and clinical characteristics were reported using frequencies and percentages for categorical variables and mean ± standard deviation for continuous variables. Frequencies were used to determine frailty for each measure. Paired t-tests were used to determine differences between pre- and post- 6MWT, handgrip strength, and serum albumin levels. McNemar's chi-square tests were used to compare proportions of individuals within each frailty category from pre- to post-implantation.

Results

Patient characteristics. The majority of patients were male (88%), over 40% were under the age of 60 years, and 96% were married or cohabitating (Table 4.1). The body mass index range was 16 kg/m to 44 kg/m pre-implant compared to 20 kg/m -39 kg/m post-implant. Only one patient was underweight with a BMI less than 20 kg/m prior to LVAD implant. Over 60% of patients had a BMI > 30 kg/m pre-operatively. Post-operatively 58% had a BMI > 30 kg/m and no patients had a BMI < 20 kg/m. The primary etiology of heart failure for this population was ischemic cardiomyopathy (60%). The most common comorbidity was CKD (52%), followed by DM (40%) and CAD (36%).

Frailty measures. Frequencies of each frailty measure are listed in Table 4.2. Prior to LVAD implantation, frailty measurements by handgrip strength identified 12 patients as frail compared to 22 patients by 6MWT and 21 patients by albumin. Post LVAD measurements of frailty identified 13 as frail by handgrip, 11 by 6MWT and 9 by albumin. Comparison of pre-implantation and 3 month post-implantation frailty measures are listed in Table 4.2. There was no difference in handgrip strength from pre-

implantation and post-implantation. Only 8% of patient walked 300 meters or more in 6 minutes prior to LVAD implantation. In contrast, 53% of patients were able to walk more than 300 meters at 3 months post-implantation with an average 47% improvement in 6MWT distance ($p = 0.002$). Mean distance walked increased significantly from pre- to post-implantation ($p < 0.001$). Pre-operatively 21 (91.3%) patients met criteria for frailty based on serum albumin cut-point and post-operatively 9 (39.1%) met frailty criteria ($p = 0.002$). Mean serum albumin increased significantly pre- to post-implantation ($p < 0.001$).

Discussion

Using three single objective markers for frailty, we identified two markers sensitive to improvement after LVAD implantation. Both serum albumin and 6MWT improved significantly from pre-implantation to 3 months after LVAD implantation. There was no change in handgrip strength at 3 months after LVAD implantation. Alone or together these two markers could be used to determine improvement in frailty after LVAD implantation. These objective markers have advantages over self-reported markers, such as exhaustion and physical activity, that are commonly used to reflect frailty and that are subject to patient bias in reporting. Other, longer measures such as Fried's criteria are longer and can over-identify frailty.

Although there is no gold standard to measure frailty in patients undergoing VAD implantation, it is important to assess for frailty in the patient selection process and assess for improvement in frailty post implant because of increased risk of post-operative complications, and increased morbidity and mortality with frailty. Our findings on frailty measures that improve post-LVAD implantation are consistent with those of prior studies

in which an improvement in 6MWT was found. Albumin levels have not been used as markers of frailty, but has been found to predict outcomes. Our findings suggest serum albumin may also be useful as a marker of frailty.

Hypoalbuminemia is a prognostic indicator in patients with heart failure and is associated with poor prognosis after LVAD surgery. [illegible] Low albumin levels are reported to be present in patients with heart failure but are most prevalent in patients with end stage heart failure who are undergoing LVAD implantation. 2, [illegible] Our study findings were similar to previous studies concluding 91% of patients having low albumin levels prior to LVAD implantation and significant improvement in serum albumin levels post LVAD implantation. This is consistent with previous findings that report improvement in serum albumin levels post-LVAD implantation. Guvenc, et al (2107) supported that low albumin levels are corrected within six months after LVAD implantation and Go et al (2015) reported improvement in serum albumin in 94% of patients post LVAD at 1 year. Patients in our study had improvement in serum albumin levels 3 months after LVAD implantation suggesting that frailty as measured by serum albumin normalized in a majority of patients.

We used the 6MWT based on findings from others studies of 6MWT and frailty. Boxer et al. (2010) noted a high correlation between the 6MWT and frailty (as defined by Fried Criteria) in patients with heart failure. In a recent study, Hasin et al. (2017) reported that the 6MWT was the strongest predictor of post LVAD survival. Hasin et al. (2012) assessed frailty by 6MWT, and their study did show an improvement in 6MWT after LVAD implantation at 3 months but approximately 20-30% of patients in their study failed to improve. In addition, they measured frailty at 3 months and 1 year and noted that

after 3 months patients remained stable with very little improvement at 1 year. Our study is consistent with these findings and we found that the 6MWT improved in 50% of patient by 3 months.

In our study, handgrip strength did not change from baseline to 3 months post LVAD implantation. Chung et al. (2014) studied monthly handgrip strength from baseline to 36 months after LVAD implantation. They saw improvement at 3 months that was sustained at 6 month where it plateaued. Our failure to show an improvement at 3 months may have been a result of our smaller sample size or the fact that 3 months seems to be the point at which handgrip strength begins markedly improving. These findings suggest that handgrip strength measured at 3 months may not be a good short-term marker,

This study has several limitations. It was a single-center study with a small study cohort. Because the cohort studied was homogenous, this limits generalizability to a larger, more diverse population of patients undergoing LVAD implantation. The short term nature of the study does not allow any conclusions regarding long-term improvement in frailty.

Conclusion

In patients with heart failure who undergo LVAD implantation, the 6MWT and serum albumin measurements reflect short-term improvement in frailty and these simple measures may be used to determine those patients who are responsive to LVAD implantation. Frailty by select markers is likely to improve in most people after LVAD implantation, and thus frailty should not preclude candidate selection for an LVAD.

Table 4.1: Patient Demographic and Clinic Characteristics, n = 23

Characteristic	N (%) or mean ± SD
Age, years	59 ±9.4
Sex	
Male	21 (91.3)
Female	2 (8.7)
Marital status	
Married	22 (91.3)
Not Married	1 (4.3)
Body Mass Index, m^2/kg	
Pre-Implantation	29.2±5.7
Post-Implantation	29.9 ±4.9
Etiology	
Ischemic	15 (65.2)
Non-ischemic	8 (34.8)
Comorbidities	
Coronary Artery Disease	16 (69.6)
Diabetes	13 (56.5)
Chronic kidney Disease	11 (47.8)
LVAD for destination therapy	15 (65.2%)

Table 4.2: Comparison of Pre-Implantation and Post-Implantation Frailty Measures

Frailty Measure	Pre-operative mean ± SD	Post-operative mean ± SD	p-value
Handgrip Strength (kg)	22.8 ± 10.7	24.7 ± 11.1	0.060
Frail, n (%)	12 (52.2%)	13 (56.5)	1.00
Six Minute Walk (meters)	186 ±83.2	275 ± 121.1	<0.001
Frail, n (%)	22 (95.7%)	11 (47.8%)	**0.002**
Albumin (g/dl)	2.7 ± .4	3.5 ±.4	<0.001
Frail, n (%)	21 (91.3%)	9 (39.1%)	**0.002**

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Chapter Five: Summary and Integration

The overall purpose of this dissertation was to determine which measures of frailty were most likely to predict frailty in patients with end stage heart failure who were undergoing LVAD implantation and to determine if measures of frailty improved post LVAD implantation. The studies were conducted for the following aims: 1) determine which measures of frailty measure frailty in patients with LVAD 2) determine if measures of frailty improved post LVAD implantation 3) determine which measures of frailty are predictive of 30 day readmission.

Frailty is an emerging concept that has gained interest over the last 30 years. Initially, clinicians and researchers started examining frailty in older adults and for the past decade, frailty has been an upcoming topic across many spectrums of disease, especially in the field of cardiovascular medicine. Due to conflicting ideas about the definition of frailty, researchers started focusing on recognition and relationship of attributes between aging, disability and chronic disease in hopes of conceptualizing frailty.

After a joint effort between multiple investigators, a general agreement described the core definition of frailty as an "increase vulnerability to stressors due to impairments in multiple, inter-related systems that lead to a decline in homeostatic reserve and resilience." This definition served as a foundation to explore distinct concepts and ways to measure and distinguish frailty from deterioration due to chronic disease. Although an agreement on the main core of frailty was established, a comprehensive definition was lacking. Unique characteristics of frailty that spread across a continuum of frailty

remained in question, especially when establishing criteria and the most commonly used measures to label one as frail.

In an attempt to conceptualize frailty, Fried established 5 criteria to measure frailty. The Cardiovascular Health Study validated the construct validity of these five measures which include weight loss, weakness, exhaustion, slowness, and low activity. Fried's criteria is the most commonly used measure of frailty for most populations in current research. However, most research validating Fried's criteria has been conducted in older, aging adults and not in populations with chronic disease so the validity in these populations remains uncertain. Due to the severity of illness, overlap of physiological responses and decrease in physical function associated with chronic disease, the question of applicability of Fried's criteria to patients with chronic heart failure remains. Subsequently, this leads to the exploration of other measures that may be more appropriate and easier to administer or measure in this population.

Patients with end stage heart failure suffer from physical deterioration, malnutrition and chronic inflammatory response which all overlap with components of frailty. Research has demonstrated that patients with HF who are frail are more likely to die or have adverse outcomes compared to those without frailty. Given the mortality rates of those with end stage heart failure, advanced therapies including surgical options are on the rise for treatment.

Chapter two discusses the epidemiology and pathophysiology of heart failure and surgical approaches for those with end stage heart failure. As discussed, heart failure continues to increase in both incidence and prevelance and 5 year mortality is 80%.

Heart failure is most common cause of re-hospitalization and is related to symptoms caused by congestive exacerbations. Guideline directed therapy is essential to treating heart failure but for those who are refractory to medication therapy surgical approaches including heart transplant or LVADs are available to those who are candidates.

Heart transplant remains the gold standard with a 1 year survival rate of 90%. Approximately 3500 heart transplants are performed annually in the United States. The most common cause of post-transplant complications is early graft failure which can lead to death. With advancements in immunosuppression, acute rejection rates trend downward. Long term complications are mostly related to cardiac allograft vasculopathy in addition to malignancy.

Despite promising results with heart transplantation, challenges remain due to a shortage of donor organs in comparison to those listed. The use of mechanical circulatory support, including LVADs, emerged and is used to offer patients an option for destination therapy or bridge to transplant pending candidacy. Initially, pulsatile pumps were used as a bridge to transplant and noted a 48% reduction in mortality compared with optimal medical therapy. Durability of pulsatile pumps was an issue and continuous flow pumps evolved. A recent analysis of the INTERMACS registry revealed an 89% 1 year survival rate with the use of continuous flow pumps.

Due to the increasing number of patients with advanced heart failure, the current strategy for screening patients for heart transplantation and LVAD is gaining acceptance. Regardless of which surgical option is decided upon, the benefits of transplant and ventricular assist devices outweighs pharmacological treatment for heart failure alone.

Frailty impacts outcomes in patients undergoing cardiac surgery and should be identified in patients with advanced heart failure undergoing surgical options, especially those undergoing LVAD. It is important to recognize those who are frail and those more likely to benefit from LVAD and have positive outcomes. Recent studies have demonstrated that patient selection is essential to ensure positive results with less adverse events following LVAD implantation. However, in order to recognize those who will most likely benefit, more research is needed to determine the best way to select these candidates. Identifying those who are frail, is gaining interest for patient selection and while frailty has been extensively studied in other populations, limited research has been conducted in patients undergoing LVAD.

Chapter three is a data analysis on measures of frailty in patients with LVADs and identifies measures of frailty in patients with heart failure scheduled for LVAD implantation and which measures of frailty are predictive of 30 day readmissions. I identify a subset of 23 patients with end stage heart failure enrolled in a study at a university medical center. Baseline measures of Fried's criteria (gait speed, exhaustion, weight loss, strength, physical activity), albumin, 6 MWT, handgrip and SPBB were entered into the model along with covariates identified from the literature (age, gender, BMI, heart failure etiology, diabetes, coronary artery disease and chronic kidney disease). Demographic and clinical characteristics were reported using frequencies and percentages for categorical variables and mean ± standard deviation for continuous variables. Frequencies were used to determine frailty for each measure. Chi-square analysis was used to determine if the measures of frailty were predictive of 30 day readmission. All analysis was conducted using SPSS software.

The study concluded that none of the markers examined were good predictors of frailty in patients with advanced heart failure with LVADs. The only marker that was predictive of 30 day readmission rates was handgrip strength. This was a negative association indicating that compared to not frail, frail patients by handgrip criteria were 93.4% less likely to be admitted. Over 85% of the patients were frail as measured by Fried's criteria, 6MWT, Low Physical Activity, Self-reported exhaustion, and albumin. The other markers of frailty measured frailty in over 50% of the patients. These findings indicate that these measures of frailty are not precise measurements of frailty and some markers such as self-reported exhaustion may be overly sensitive to measuring frailty in patients with LVADs.

The results from my study may be due to the fact that measures of frailty such as Fried's and SPPB that are devised of several components that may not accurately identify frailty in patients with end stage heart failure with LVADs because some of these components may be influenced by chronic disease. Chronic inflammation which is associated with heart failure is also a linked to cognitive impairment which affects physical performance measure such as gait speed which is a part of both the Fried's and SPBB criteria. In addition, our study did not recognize hand grip strength as a measure of frailty, whereas other studies have found that hand grip strength is an independent predictor of frailty. Our small sample size is likely the culprit to the difference in these findings. In addition, discrepancies may be attributed to the degree of illness in the cohort. Some patients were severely ill requiring more emergent LVAD implantation, while others were stable at home and scheduled for LVAD implantation.

Once measures of frailty have been identified, it is important to determine which measures may improve over time after an intervention. Previous findings support that those who have improvement in measures of frailty, have fewer complications and better outcomes. To further expand on this concept, we examined which measures of frailty improved over time after LVAD implantation.

Chapter Four is an analysis of albumin, 6MWT and handgrip and whether these measures of frailty improve over 3 months. Longitudinal data was collected at baseline (pre-implantation) and at 3 months (post-implantation). Data from 23 patients with HF who underwent LVAD implantation was used in the analysis. Demographic and clinical characteristics were reported using frequencies and percentages for categorical variables and mean ± standard deviation for continuous variables. Frequencies were used to determine frailty for each measure. Paired t-tests were used to determine differences between pre- and post- 6MWT, handgrip strength, and serum albumin levels. McNemar's chi-square tests were used to compare proportions of individuals within each frailty category from pre- to post-implantation. Results of the study demonstrated the 6MWT and albumin improved post LVAD implantation at 3 months while handgrip strength did not change.

Our findings on frailty measures that improve post-LVAD implantation are consistent with prior studies who have examined improvement in 6MWT and albumin levels prior and post implantation but differ from previous investigations regarding frailty as defined by handgrip strength. Again, our small sample size likely contributes to the difference in findings regarding handgrip strength. Also, longitudinal studies have the ability to demonstrate progress and change over time. Chung et al found that handgrip

was an independent predictor of frailty, but their study measured changes in handgrip over 6 months. Additionally, Maurer et al reported that is took at least 3 months to start seeing improvement in frailty with significant improvement at 6 months. We only compared 2 time points which included baseline and 3 months post implantation. Based on previous the previous finding, more long term follow-up is needed to identify reversibility of frailty.

Impact of Dissertation on the State of Science

This dissertation represents an important contribution to the literature as little is known about frailty in patients with LVADs. The findings of this dissertation filled some gaps in understanding which measures of frailty including Fried's criteria, SPPB, albumin, 6MWT and handgrip strength measured frailty in patient with end stage HF undergoing LVAD implantation and which measures of frailty predict 30 day readmission. In addition, the findings support which measures of frailty improve post LVAD implantation.

Fried's criteria is the most commonly used frailty measure in patients with LVADs and is highly predictive of adverse outcomes. Multidimensional frailty measures such as Fried's criteria, include multiple domains that may vary from one measure to another and may be difficult to apply in certain settings and in patients that are severely ill. Single item measures may be successful in measuring frailty and may be more practical in patients with LVADs. While several studies have examined gait speed as a single measure and a couple of studies have examined handgrip as a single measure, other specific measures that can help identify frailty are unknown.

In Chapter three, I evaluate if single measures of frailty and measurement tools that utilize several components to measure frailty measure frailty in patients with LVADs and if these markers of frailty predict 30 day readmission rates. No studies in the literature evaluating frailty have examined all these tools and no studies have looked at frailty measures that predict 30 day readmission rates. Prior studies have examined how frailty impacts length of stay, time to extubation and adverse outcomes but the results are inconsistent. Whether single objective measures of frailty are valid in determining frailty, more research is needed but my study findings provide a strong beginning foundation.

Additionally, prior studies that measure frailty in older adults have demonstrated that some measures of frailty can improve. Very few studies have examined this in patients with LVADs. There are limited longitudinal studies examining the reversal of frailty measures in patients receiving LVADs Improvement in frailty measures after 6 months has been examined by some investigators but specific measures that support reversibility of frailty are unknown. Improvement in handgrip strength and gait speed post LVAD implantation has been investigated. Additional measures of frailty in patients with LVADs that support reversibility of frailty have not been examined.

The results described in chapter 4 advances the state of science in evaluating how baseline measures of albumin, 6MWT and handgrip strength improve from baseline to 3 months. My study supports that albumin and 6MWT improved 3 months post LVAD. While handgrip strength did not improve at 3 months, other investigators found that at 6 months, handgrip strength did improve and more long-term analysis should be considered in future studies.

Recommendations for future research

Frailty is an important predictor of adverse outcomes in patients with HF undergoing LVAD such as 30 day readmission, increased hospital LOS, mortality and post-operative complications. Frailty is more common in patients with chronic disease such as those with end-stage heart failure. As a result, frailty should be routinely assessed in patients with end stage heart failure approaching LVAD implantation to detect the presence of frailty, need for early intervention to slow the progression and improve outcomes and assist with patient selection for LVAD implantation.

In order to assess the presence of frailty, clinicians need to be able to use sound measures that are easy to administer and brief without being burdensome to the patients. There are tools available to measure frailty but some measures are lengthy and burdensome making it difficult to complete. More studies need to be conducted in order to replicate the results of this study and support the reliability in patients with HF undergoing LVAD implantation. In addition, measurement tools with multiple components may over diagnose frailty whereas single measures may be prone to missing frailty. However, the underlying assumption would be that because components of the pathologic process of frailty are associated with each other, not all are necessary to be labeled as frail and single measures may be adequate. Addition research is needed to test this assumption.

Heart failure is a dynamic illness and future research should focus on long-term follow-up to determine how frailty impacts outcomes and which measures of frailty are reversed following LVAD implantation. Patients with end-stage heart failure are often

deconditioned, malnourished, and have a chronic inflammatory response. Due to their condition they may not seek and utilize available resources appropriately such as attending cardiac rehabilitation, nutrition counseling, or clinic appointments. As a result, their condition further deteriorates and frailty is exacerbated. Focusing on earlier identification of frailty in the ambulatory setting and early intervention for physical rehabilitation and nutritional supplementation should also be a focus in this population to slow the progression of frailty. A small randomized trial found that patients who were enrolled in cardiac rehabilitation after LVAD implantation had promising results with improvements in frailty. Additional research including longitudinal data are needed to further support these findings.

Limitations

Limitations of these studies include that these were single-centered studies and each of the studies reported in this dissertation had a small sample size. In addition, patients with end stage heart failure who underwent LVAD implantation participated in the study which limits heterogeneity. Additional potential limitations include the use of self-reported measures of exhaustion and physical activity and in some patients self-reported weight loss in the past year. We did not have access to all patients' information from previous medical records to verify weight loss. Additionally, the fact that many of these patients were very ill resulted in limitations of the applicability of some of the frailty measures. The relatively short-term follow-up does not allow any conclusions to be made about long-term outcomes and reversibility.

There are barriers to engaging in some measures of frailty. Patients who have marked physical limitations are unable to complete some measures such as 6 MWT and previously reported gait speed test. Utilizing weight loss as a measure of frailty may underestimate the prevalence of frailty in obese patients and it is also difficult to discern true weight loss in patients with heart failure due to variability secondary to volume status. Chronic inflammation associated with chronic disease is also associated with cognitive impairment which is associated with a decline in psychomotor activities such as gait speed. This may lead to inconsistencies with identifying those who are frail because it is often difficult to differentiate between frailty and the effects of the disease itself.

Conclusion

In summary, implications of this dissertation include the importance of monitoring frailty over time as well as the need for further longitudinal studies that examine the relationships between frailty and early intervention to slow the progression of frailty. A better understanding how frailty changes over time will allow clinicians the opportunity for timely interventions designed to reduce the progression and improve outcomes. In addition, identifying those that are frail will allow for better patient selection to avoid unnecessary LVAD implantation on those likely to not survive or have post-operative complications and adverse events and will identify markers of frailty that will likely improve in patients post LVAD implantation.

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Professional Experience

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August 2009 – April 2010	Sahetya Medical Group Bowling Green, KY	Acute Care Nurse Practitioner Critical Care/Pulmonary
November 2007 – July 2009	Paragon Family Practice Lexington, KY	Acute Care Nurse Practitioner Internal Medicine
June 2008 – December 2008	Cardiology Associates Lexington, KY	Acute Care Nurse Practitioner Cardiology
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October 2005 – December 2006	Nashville General Hospital Nashville, TN	Registered Nurse Emergency Room
September 2004 – October 2005	Vanderbilt University Hospital Nashville, TN	Registered Nurse Emergency Room
June 2003 – August 2004	Lifeline Home Health Bowling Green, KY	Physician/Community Educator
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Publications

*Falls, Candice, Kolodziej, Andrew (2019). Surgical Approaches in Heart Failure. Critical Care Nursing Clinics 907, Volume 31, Issue 3