DECISION AID TO DETERMINE THE NECESSITY OF RIGHT VENTRICULAR SUPPORT FOR PATIENTS RECEIVING A LEFT VENTRICULAR ASSIST DEVICE

by

Bronwyn E. Uber

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This thesis was presented

by

Bronwyn E. Uber

It was defended on

March 29, 2006

and approved by

Harvey S. Borovetz, Ph.D., Professor, Bioengineering Department

Marwan A. Simaan, Ph.D., Professor, Electrical and Computer Engineering Department

James F. Antaki, Ph.D., Professor, Department of Bioengineering
Thesis Advisor

DECISION AID FOR RIGHT VENTRICULAR SUPPORT

OF PATIENTS RECEIVING A LEFT VENTRICULAR ASSIST DEVICE

Bronwyn Uber, M.S.

University of Pittsburgh, 2006

The purpose of this study was to improve the efficacy of VAD therapy for patients intended for VAD insertion. The study focused on the specific decision whether an LVAD or BiVAD is appropriate. A hierarchical decision model was constructed using an influence diagram of clinical risk factors derived through interviews with expert cardiologists and cardiac surgeons. Most of the variables are summarized by two independent criteria: risk of surgery and risk of right ventricular (RV) failure. These risks are computed from various patient demographics, tests, and hemodynamics using expert physician-selected weighted linear and weighted non-linear relationships.

The model was validated with retrospective data from patient records at University of Pittsburgh Medical Center (UPMC) for patients implanted after 1990 and explanted before 2006. In total 239 patients were implanted and explanted during this time, of those 168 had sufficient information to be used in this analysis. 48 patients received biventricular assistance (BiVADs), 119 patients received only left ventricular assistance (LVADs). Of these 119 LVAD patients, 19 subsequently received an RVAD due to unanticipated RV dysfunction. Pre-implant data were used as input to the model.

The model parameters were derived from two different physicians. The models based on individual physician's weightings predicted 63% (47%) of the patients who required an RVAD after implant. However, these decision models also recommended BiVAD implantation for 40% (43%) of patients who were treated successfully with an LVAD alone.

A nonlinear numerical optimizer was used to improve the model parameters to optimize the agreement with eventual outcomes. The optimized model predicted 74% of the patients who required an RVAD post-implant and recommended the implantation of BiVADs in 21% of patients who were treated successfully with an LVAD alone. In conclusion, the decision model provided a more aggressive use of biventricular assistance, which retrospectively would have benefited patients who required an RVAD at a later date, but would have unnecessarily implanted RVADs in some patients that survived with an LVAD alone. However the model also identified that 48% of the patients who initially received BiVADs to be candidates for LVAD alone.

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PREFACE

DEDICATION

Dedicated to my Mother (1948-2003)

Who is always proud of me no matter what I do

And who believes that I can accomplish anything.

ACKNOWLEDGEMENTS

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1.0 INTRODUCTION

In the early era of artificial heart development, it was believed that patients suffering from end-stage heart disease could be salvaged by substituting a prosthetic heart in place of the failing heart. In 1984 it was demonstrated that some patients could be treated through a far less invasive procedure entailing the circulatory support of just the left ventricle. Today, ventricular assist devices (VADs) are striving to become a routine therapy for treating patients of severe heart failure. In cases where both ventricles are unable to support their respective loads, or cases of pulmonary hypertension, a right-ventricular assist device (RVAD) is often indicated. However the decision to insert an additional RVAD at the time of LVAD insertion is not always obvious. The consequence of making the wrong decision could be catastrophic. Choosing to forgo RVAD insertion in a patient with deteriorating right ventricular function could require re-operation to insert a RVAD at later time. In acute cases of failure, there is risk of mortality and morbidity. Conversely the decision to insert an RVAD proactively in a patient without symptoms may expose the patient to unnecessary surgical trauma and additional device-related complications.

Retrospective studies based solely on pre-operative patient characteristics, hemodynamics, echo parameters or other specific measures have not been able to clearly discern the appropriate criteria for this decision. The lack of consensus has resulted in different medical centers having significantly different methods. Consequently, there is a wide variation amongst centers of the proportion of VAD patients who receive bi-ventricular support (BiVAD), ranging from 15% to 60% internationally. [1, 2] At the University of Pittsburgh Medical Center approximately 40% of the patients who received a VAD between 2000 and 2005 were also supported, either acutely or chronically with an RVAD. The obvious advantage of definitively identifying the criteria that indicate the need for RVAD is the motivation of this study. Not only would this lead to improved overall outcomes, it would serve to transmit expertise between centers, and provide more homogenous treatment amongst centers.

2.0 BACKGROUND

2.1 ROLE OF VAD SUPPORT IN END-STAGE HEART FAILURE

Heart Failure is a large and growing problem in the Western World. Currently it affects approximately 5 million people in the United States, and the direct and indirect cost associated with heart failure is expected to be $29.6 billion in 2006 alone. Based on a 44-year follow-up of the National Heart, Lung, and Blood Institute (NHLBIs Institute's, (NHLBI) Framington Heart Study it was found that 80% of men and 70% of women under the age of 65 who have HF will die within 8 years. [3] There are currently three broad treatment categories for congestive heart failure. The first level of treatment is medical (drugs and lifestyle changes), the second level is surgical and the third level is either mechanical circulatory support and/or cardiac replacement. Currently, cardiac transplantation is considered the preferred treatment for end-stage failure; however, the availability of donor organs has limited the number of transplants to approximately 3000 for the past decade. Consequently, the waiting time for the few patients fortunate to be listed for a transplant can be very long. In 2002 the average wait for a heart by an adult between 35 and 49 years old was 299 days**.** [4] For patients who cannot survive to transplant mechanical circulatory support has been become a common treatment option. [5] Ventricular Assist Devices, commonly known as VADs, have been used to provide circulatory support to patients who cannot survive the waiting time to transplantation. This "bridge-to-transplant" role however does not solve the problem of limited supply. More recently two other roles have evolved: bridge-to-recovery (BTR) and destination therapy (DT). BTR is obviously considered the ideal outcome, enabling the patient live a normal live untethered by mechanical devices and not dependent on anti-rejection drugs. However if mechanical circulatory support is to receive the widespread application that has been hoped for, the preponderance of the 40,000-200,000 prospective patients will be implanted with a device "permanently." Currently BiVADs are not reimbursed by insurance for destination therapy and few VAD patients are bridge-to-recovery so the main indication for BiVAD patients is bridge-to-transplant.

2.2 LVAD VERSUS BIVAD

A left ventricular assist device (LVAD) is typically inserted in the thorax or abdomen. Usually the inflow cannula is connected to the apex of the left ventricle and the outflow cannula is connected to the aorta, so it works to augment (either completely or partially) left ventricular function. Figure 1 illustrates an implanted intra-corporeal LVAD: the device is implanted in the body. Other LVAD devices are extra-corporeal, residing outside of the body. An LVAD only supports the systemic circulation; dependent upon the right ventricle to supply blood through the pulmonary circuit. If the right ventricle is either dysfunctional or the pulmonary resistance excessive, the cardiac output can be severely diminished unless an RVAD is inserted. When applied together, the procedure is referred to as BiVAD, shown in Figure 2

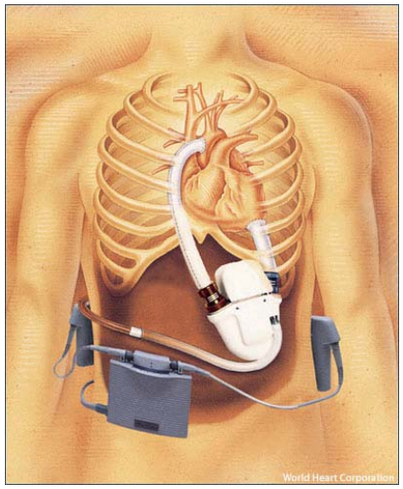

Figure 1: Implanted LVAD [6]

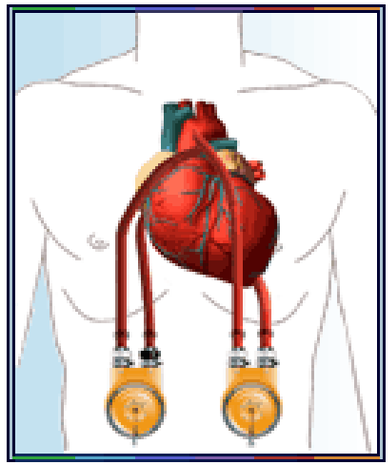

Figure 2: Paracorporeal BiVAD [7]

While the implantation of an LVAD can improve RV function by decreasing the pulmonary pressure and congestion, the RV may not be able to keep up with the (suddenly) significantly increased flows. Also, the shift of the intraventricular septum due to LV unloading can contribute to RV dysfunction as can the trauma caused by the implantation surgery. Severe cases of RV failure can result in death or may require a subsequent implantation of a VAD to support the pulmonary circulation (RVAD). Unfortunately, subsequent RVAD implantation has been associated to lower survival rates. [5, 8] Ochiai et al. found that only 24% patients that were re-operated to insert an

RVAD survived to transplant, as compared to 74% survival of patients receiving LVAD alone. Incidence of bleeding was also more common in the RVAD group, 54% versus 27%. [5]

Figure 3 graphically depicts the survival of LVAD, BiVAD, and LVAD with subsequent RVAD patients based on data from the University of Pittsburgh Medical Center. [9] LVAD survival is the highest, over 80% survival at three years, followed by BiVAD with just under 50% and LVAD followed by RVAD is the lowest with only 25% survival at three years.

While it is important to avoid RV failure it is certainly not ideal to implant all patients with BiVADs. The added implantation of an RVAD increases (effectively doubles) many of the risk factors associated with a single VAD such as thrombosis, infection, and mechanical failure. The surgery for implantation naturally takes longer, dictating that a patient be on cardiopulmonary bypass and anesthetized for more time, which also is associated with numerous side-effects. [10] El-Banayosy et al. found that 60.8% of LVAD patients were discharged from the hospital, while only 50.9% of BiVAD patients were discharged. Post-transplant survival for both groups was fairly high, LVAD 96.9%, BiVAD 87.1%. [10]

In addition to the risk of morbidity and mortality, it is significantly more cumbersome for the patients to care for two devices - particularly if they desire to return home. Furthermore, the only clinically approved RVAD is a pneumatically actuated extracorporeal device, which is far less “forgettable” than the implantable LVADs. The controller and batteries for current LVAD systems can easily be carried in a backpack, which is not true for the current RVAD devices.

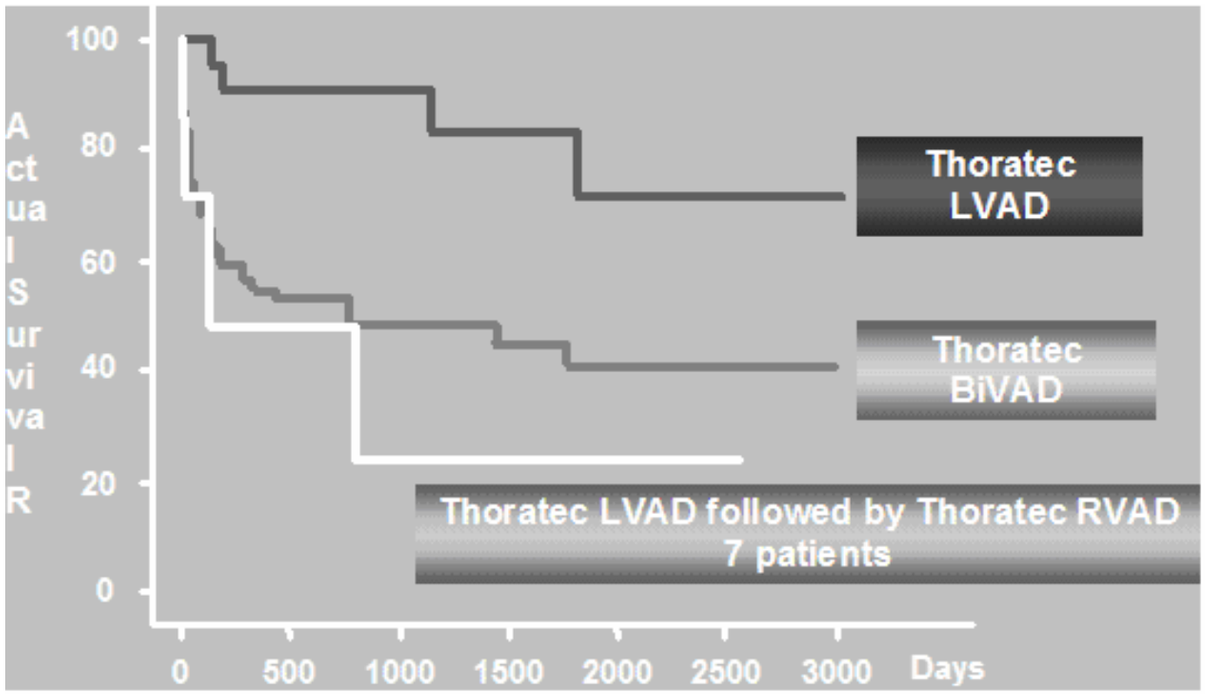

Figure 3: Actual survival for patients implanted with an LVAD, BiVAD or LVAD followed by RVAD

2.3 PATIENT SELECTION FOR VADS

Patient selection is crucial to the success of VAD treatment. Selection for LVADs are now well established, mostly because the indications for left-ventricular support are very similar to the criteria for selecting heart transplant candidates, which has evolved over several decades. [2] Many studies have identified the variables that play a significant role in the decision [11, 12] and some studies have developed simple scoring systems to assist the physicians. [11] For example, the factors used at Colombia Presbyterian by Oz et al. include: urine output <30mL/hr (weight of 3), central venous pressure >16mmHg (weight of 2), mechanical ventilation (weight of 2), prothrombin time >16s (weight of 2), and reoperation (weight of 1).

There has yet to be consensus among centers and even individual physicians at the same institution regarding the decision between implanting an LVAD or BiVAD. [8, 13] The lack of agreement has resulted in different centers having significantly different methods that result in varying percentages of BiVADs implanted with varying rates of success. The percentage of BiVADs implanted ranges from 60% to 15% in centers across the United States. [1, 2] At

the University of Pittsburgh approximately 40% of the VAD patients that were implanted between 2000 and 2005 received BiVADs.

Some studies simply compare pre-implant criteria of LVAD patients versus BiVAD patients [10]. These studies are not useful in identifying the criteria for future treatment. It is important to know the outcomes of the decision, and not merely compare the enrollment values from the two different implant groups – which tacitly assume that every decision (to implant an LVAD or BiVAD) was correct. The small number of VAD patients makes statistical analysis difficult and sometimes multivariate analysis impossible. [5]

While pre-operative values are used to predict RV failure, there is another factor, independent of pre-operative assessment which will influence the probability or RV Failure. This factor is the post-operative care. Centers use different strategies to help prevent RV failure [13] such as careful fluid management and the use of nitric oxide. [5] This variation in strategies can partially explain the variation of success between centers.

2.4 RV DYSFUNCTION POST-LVAD

Right ventricular failure is significantly less common than left ventricular failure. It rarely occurs without LV failure. [2] If it occurs in conjunction with LV failure it is called Bi-ventricular failure. The pumping function of the right ventricle (RV) can also be impaired as a result of an LVAD implantation. This is associated with higher mortality. Morgan et al. found that survival to transplant was significantly lower in the patients who needed an RVAD post-LVAD, 64.7% versus 72.1%. [14] Naturally, because of its importance, the prediction of post-LVAD RV failure has been intensely studied. Table 1 summarizes the findings from thirteen different studies. [1, 5, 9-11, 14-21] The table reveals contradictory conclusions. Many of the variables were not found to be significant, and for almost every variable found significant in one study, there was a different study that found it not to be significant. The summary table also highlights six variables (identified with red boxes) for which the number of studies where they were found to be significant outnumbered those studies where they were found to be insignificant. Those variables are: emergency implant, ventilator pre-implant, degree of inotropic support, prothrombin time (PT) central vascular pressure (CVP), mixed venous oxygen saturation and intra-operative bleeding. Kavarana et al. did not find any of the preoperative hemodynamic data significant in predicting right ventricular dysfunction, and the only significant intraoperative variable was percent bleeding. [20] This issue has stimulated a broader debate regarding the relative dependence of the need for biventricular support on hemodynamic parameters and clinical status parameters. [1, 15]

In summary, while the importance of avoiding RV failure is without debate, numerous studies on the subject have failed to deliver definitive criteria to predict RV dysfunction in patients with LVAD support.

Table 1: Summary of multiple studies examining predictions for RV failure

Rightmost column indicates the number of studies finding each independent variable to be significant (sig) or not significant (ns). Variables which had more significant than insignificant results are highlighted with a red square. (See Nomenclature section for description of variables)

	Summary				Summary	
	sig ++	ns -			sig ++	ns -
Patient Characteristics and history				**Preoperative Hemodynamics**		
Female	2	9		CO	1	3
Age	2	10		CI	1	9
BSA	2	4		HR		4
Diagnosis	3	6		LVEF		3
Race		1		RVEF at rest	1	2
NYHA	1	2		RAP		4
Emergency Implant	2			LAP		2
Preoperative IABP (%)	1	6		MAP		2
Preoperative ventilator (%)	6	2		CVP	4	2
Preoperative ECMO (%)	1	4		TPG		3
Febrile days before implant	1	1		PVR		7
Duration of inotropic support (preimplant)		2		SVR		2
Degree of inotropic support (preimplant)	1			SVRI		1
Preoperative bloodwork				RVSW	2	
Total bilirubin	2	5		mean PAP	3	6
Albumin		1		systolic PAP	1	1
AST	1	4		diastolic PAP	1	1
BUN		7		PCWP	1	3
Creatinine	2	6		Mixed venous oxygen saturation	1	
hemoglobin		2				
platelet count		1				
PT	3	1				
PTT		1				
Intraoperative						
CPB time		1				
Bleeding (%)	1					
PRBC		1				
PLT		1				
FFP		1				

2.5 DECISION TOOLS

Decisions play an important part in each of our lives. Some decisions are easy and take very little thought. Other decisions are significantly more difficult and can occur at different places and times. Many tools and strategies have been created to aid in the decision making process. This section discusses *difficult* decisions, and the associated decision analysis that defines important concepts related to decision making and describes modeling techniques. Finally decision-making in healthcare, where these difficult decisions are extremely prevalent, is discussed.

2.5.1 Difficult Decisions

A difficult decision is characterized by having one or more of the following factors: complexity, inherent uncertainty, conflicting objectives, and different perspectives. A complex decision is difficult to fully analyze because it contains many more factors than a person can process in their consciousness at one time. Difficulty can occur as a result of inherent uncertainty in the inputs to the decision. Every medical test, for example, contains inherent uncertainty; if the same test is repeated a different answer may result. This uncertainty is greater for some tests than others. A decision may have multiple, conflicting objectives which necessitates trade-offs. This is common in engineering, where a designer must strive to make a product which is simultaneously safe, effective, and low cost. Finally, additional difficulty may be a result of different perspectives leading to different conclusions. Groups or committees sometimes cannot arrive at a consensus as a result of their different perspectives. [22]

The decision between implanting an LVAD or BiVAD possesses all four of the basic sources of decision difficulty. As a result it is understandable that the establishment of clear criteria has been evasive. The decision is very complex; there are numerous factors including hemodynamics parameters and various signs and symptoms of clinical status. The inherent uncertainties about whether the RV will fail are not only influenced by pre-implant values but also by post-implant management. Multiple objectives are present: optimizing the patient’s survival, optimizing quality of life and minimizing complications and morbidity. Finally, physicians have their own experiences and biases that lead to subjective decisions.

2.5.2 Decision Analysis

Each person's perceptions and subjective preferences can lead to bad decisions; in the medical field these bad decisions can have catastrophic consequences. This has been the motivation for development of Decision Analysis techniques, which can be used to eliminate the effects of those imperfections and make better decisions.

A flowchart depicting the decision-analysis process is shown in Figure 4. The initial step in the process is to clearly and thoroughly define the decision. A common mistake in all decisions is finding the right solution to the wrong problem.

Also clearly identifying the objectives is crucial. Many times one decision has multiple, conflicting objectives; if that is the case the most critical objectives need to be identified. The overall objective of a decision may be a combination of multiple different objectives – which can be related in equation format. One example is trying to maximize both survival and quality-of-life; for different people the relative weight of two objectives may vary.

Once the objectives are obtained, they need to be closely examined to ensure that all alternatives have been identified. The actual modeling of the decision can be partitioned into three areas: the problem structure, the uncertainty and the preferences. Obviously, the model is essential for decision-analysis and provides the most quantitative and analytical approaches to a decision. The problem should be decomposed and modeled in several different ways. From these different models the best one is chosen. This entire process is iterative, once an alternative is chosen the sensitivity analysis is performed to determine how dramatically the decision changes due to small adjustments in the criteria. If the alternative is very sensitive it may be decided that further analysis is needed, in which case the decision, objectives, alternatives and the model may all be subject to reevaluation. [22]

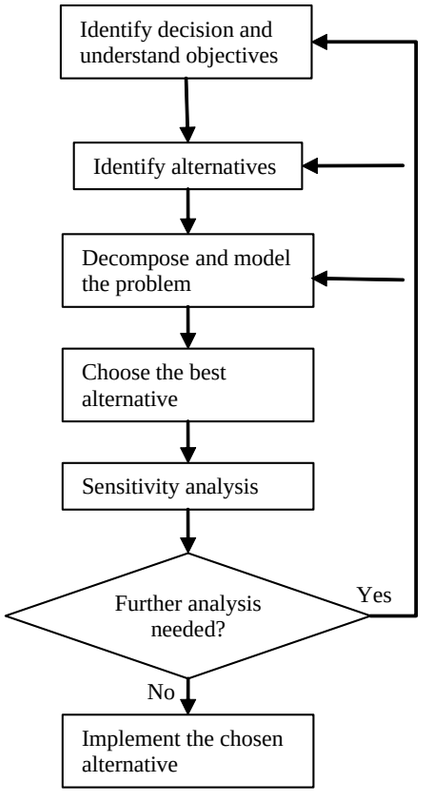

Figure 4: Decision-Analysis Process [22]

2.5.3 Important Concepts Applicable to Decision Models

To fully understand and analyze the models, several fundamental concepts must be understood. The sensitivity of a model is one such concept, and refers to the dependence of the decision outcome upon particular aspects of the model. For example input variable values, variable weights and model structure all can impact the outcome of the model. Ideally, a model should not be overly sensitive: small changes in the model should not have a dramatic impact on the results. *[Note: This is not to be confused with sensitivity of a medical test, which refers to the probability that an infected individual will test positive.]*

Decision bias is another important concept which describes a factor that can skew a decision. There are many different types of bias which can affect all aspects of a decision. When judging the probability of a particular event a physician may be biased due to experience or regret from past cases. Preferences and values of both the physicians and

patients can be affected by bias, and can affect the treatment plan. Bias can be evident in how a physician presents treatment options to a patient. The use of a decision-analysis aims to minimize these and other types of bias.

Outcomes for each decision must be identified. In some decisions the outcome is very simple such as an investment decision in which is commonly accepted that the decision yielding more money is better. Decisions related to health care have more complex outcomes which must consider not only life and death, but also quality of life. There have been different measures created to address this problem. One of which is *Quality Adjusted Life Years* (QALY) taking into account both quantity and the quality of life that would result from a particular health-related decision. [23]

2.5.4 Modeling Techniques

A decision ***model*** refers to any type of mathematical representation of a decision process. There are numerous modeling techniques available, and the selection of an appropriate model is critical to its effectiveness. When evaluating various decision models, the end users must be considered. The current decision model is aimed at physicians (as opposed to patients, care-givers, or clinical engineers). This bears upon the complexity of the model, which must account for all the critical factors, but not be so complex that it becomes unwieldy and impractical to implement. Complexity is well explained by a famous Einstein quote, “Make everything as simple as possible, but not simpler.” [24] The time horizon also needs to be considered, namely the period of time over which the intervention and outcomes are recorded. This study examines patients the day before their VAD implant and the outcomes are measured for one month after implant based on the premise that VAD related right ventricular failure usually occurs within the first week after implantation.

2.5.4.1 Decision Tree

The simplest decision models are basic decision trees. These are made up of three components: the structure of the problem, the probabilities of events in the structure, and values of the possible outcomes. Figure 5 illustrates this using a simple investment decision. The decision maker has a choice between three options, choice 1 is a risky investment with a higher pay-out (the outcome), choice 2 is a less risky investment, and choice 3 bears the least risk - such as putting the money in a bank account, and earning a small, yet fixed interest rate with less overall payout. The expected value of each choice can be determined by multiplying the probability (p) by the outcome, and summing the values for each choice. These expected outcomes can then be used to decide where to invest the money. Decision trees can become much more complicated, particularly for healthcare decisions which do not have such quantifiable outcomes. [23]

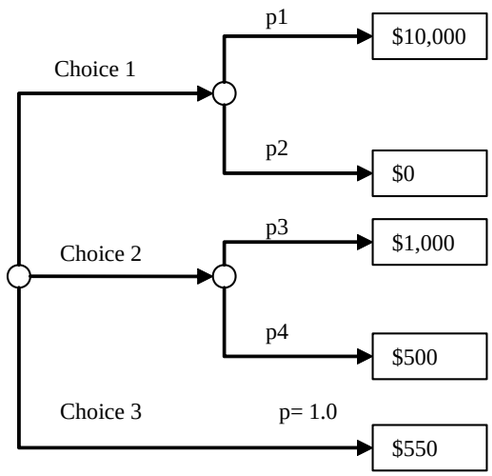

Figure 5: Example of simple decision tree.

2.5.4.2 Influence Diagrams

Influence diagrams are a common alternative way to graphically represent a decision model. Decision nodes are represented as squares; chance nodes used to represent any chance events are depicted as circles; and final utility, the final consequence or payoff, is depicted as a diamond. Relationships between nodes are depicted using arrows. The direction of the arrows represents the direction of influence, the node at the beginning of an arc is a predecessor and the node at the end of the arc is a successor. The simple medical example shown in Figure 6 represents the decisions for screening and treating cancer. There are two decisions to be made: whether to get a breast cancer screening and whether to get treatment for cancer. The relationship between getting screened for breast cancer and getting treatment is represented by an arrow. The test result, depicted as a chance node due the inherent uncertainty, will also influence the decision to get treatment. Cancer status, another uncertainty, will affect both the test result and the life expectancy (which represent the overall utility). Furthermore, the decision to get treatment will also affect life expectancy, while the decision to get screened will not directly affect life expectancy.

Influence diagrams are useful models, but they also have some drawbacks. The chance nodes can become extremely complex when many variables are being considered, because the probability of every combination needs to be determined. For each chance node and decision node with precursors, the probability table must include a separate column and then also a row for each combination of results from the precursor nodes. [23] This makes them less useful in complex healthcare decisions, where the analysis of influence diagrams is arduous and often impractical.

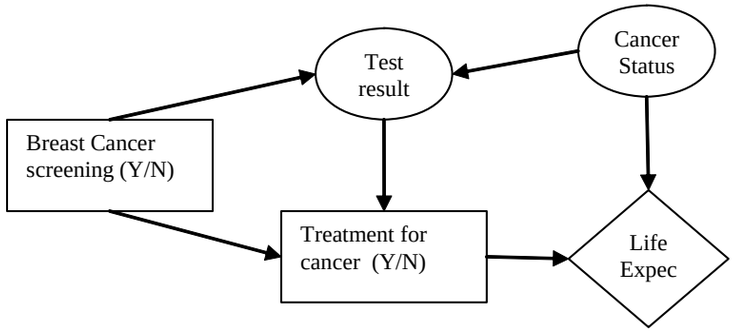

Figure 6: Influence Diagram (adapted from figure by Chapman et al. [23])

2.6 DECISION MAKING IN HEALTHCARE

Medical decisions are particularly difficult because of the high stakes and the complexity involved. Often these decisions need to be made quickly, and without complete information. As healthcare spending continues to rise, cost is also becoming increasingly important. The growing number of diagnostic tests available, while useful, continues to make decisions even more complex. Considering more variables does not necessarily equate with a better decision. The human brain can only consider 7±2 variables at a time. [25] While computers can be used as an aid, sometimes simplification is the answer. The following is a story about diagnosing heart attacks at Cook County Hospital, paraphrased from the book Blink by Malcolm Gladwell. [25]

> *When Brendan Reilly became the chairman of Cook County Hospital in Chicago he inherited a mess. Resources were running low, there were not enough beds or nurses and the hospital cared for many patients without any health insurance. The emergency department was especially bad; often it was difficult to even walk through the emergency department because of the overwhelming number the patients. With low resources and a large number of patients it is especially important to correctly predict which patients needs what, especially who needs to be admitted (which takes up a bed and costs roughly $2,000-a-night). A large part of the problem seemed to be patients who thought they were having a heart attack – approximately thirty a day. Reilly compiled twenty typical case studies and gave them to the physicians, asking them to estimate on a scale of zero to one hundred whether or not each patient was going to have a heart attach in the next three days. The results were all over the place, there*

was no consensus, for each case the answers pretty much ranged from zero to one hundred. There was no standardized, rational way of making the decision of whether a patient was or was not having a heart attack. In the 1970's a cardiologist by the name of Lee Goldman had retrospectively analyzed hundreds of cases from which he derived an algorithm for predicting a heart attack. The algorithm is simple, using only a minimal amount of information. It emphasized the point that more information is not necessarily good, it can actually be harmful. When Reilly tested this algorithm in the ER, it correctly predicted the serious cases 95 percent of the time, while the physicians were only right 75 to 89 percent of the time. [25]

As a result of the proportion of decisions in healthcare which fit this profile, evidence-based medicine - a type of decision analysis - is a rapidly growing area. Evidence-based medicine is defined as explicitly applying the best data and scientific results possible to the health care decisions for individual patients. Application of evidence-based medicine has produced some computer-based decision support systems. The goal of these decision support systems is not to take the place of a physician. They are to aid in the decision making process by managing complexity, looking objectively at decisions, and eliminating inherent bias.

2.7 PREVIOUS DECISION MODELING FOR VAD PATIENTS

The literature does not contain any reference to formalized decision modeling related to patients with VADs. The only research on this topic, to our best knowledge, was recently reported by Santelices, Drudzdel, and Antaki in 2004 and 2005. They applied decision analysis to assess the readiness of VAD patients for ventricular recovery, particularly aimed at weaning and removal of their device. Expert interviews resulted in an algorithm with two main phases: a multi-parameter health status screening followed by three weaning studies involving different cardiac capacity exams. The algorithm was represented both as a flow chart and influence diagram using GeNIe 2.0 software, a Bayesian inference engine available as freeware, developed by Drudzdel.

In this model, each node was binary and the probabilities were assigned by experts. The preliminary application of the algorithm was able to predict 90% of the cases that were successfully weaned, and 100% of the cases proceeding to transplantation. However, limited data – due to the small number of VAD implants and even smaller number of weaned patients -prevented any definitive conclusions from being drawn. Only 11 total patients comprised this study. [26]

3.0 METHODS

The scope of this study includes patients for whom a VAD has already been identified as the preferred intervention. The specific decision examined is whether an LVAD or BiVAD is appropriate.

Prior studies from the literature addressing the RV failure after LVAD implant have been limited to statistical analyses of individual variables and were not successful in identifying appropriate patient selection criteria. This current study aimed to fill this need by constructing a decision model to better understand, and provide an opportunity to optimize, the decision. The model was constructed using data from interviews with physician and evaluated using retrospective data from University of Pittsburgh Medical Center (UPMC). It was optimized by changing the model parameters and reevaluating, as described in the subsequent sections.

3.1 IDENTIFICATION OF RELEVANT VARIABLES

A literature review was conducted to understand the lack of or disagreement between significant variables found in previous studies and to provide an initial list of variables that could be considered in constructing a model. Interviews were then conducted with physicians at UPMC. The physicians were chosen to represent a range of different specialties that play a role in the decision between implanting an LVAD and BiVAD. Heart failure cardiologists (Dr. Jeffrey Teuteberg, Dr. Marc Simon, Dr. Linda Cadaret, Dr. Srinivas Murali) cardiothoracic surgeons (Dr. Robert Kormos and Dr. Hiroyuki Tsukui), and critical care physicians (Dr. G. Daniel Martich and Dr. Penny Sappington) comprised the expert pool. The goal of the first interview was to obtain an initial, comprehensive list of the variables that the physicians consider important when evaluating a patient for an LVAD or BiVAD.

3.2 INFLUENCE DIAGRAM

Using the physician's description of the decision process an influence diagram was constructed. (See Figure 7) The influence diagram was structured in a hierarchal fashion. The first tier clusters specific measures to define categories, represented by the dashed bordered ovals: *Hepatic Function*, *Renal Function*, *Pulmonary Function*, *Coagulopathy*, *Hemodynamics*, *Infection*, *Co-morbidities*, *Pulmonary Hypertension*, *RV Function*, and *Other Assessment*. The fully detailed list of all the variables associated with the different categories, grouped by tier is provided in Table 2. The second tier, shown as solid bordered oval combines the first tier categories into *Risk of Surgery* and *Risk of RV Failure*. *Risk of Surgery* represents the current clinical status of the patient, the sicker the patient is the more likely a physician will implant a BiVAD. *Risk of RV Failure* is self-explanatory, it is a measure of the current RV function, the more dysfunction the more likely a physician will implant a BiVAD. The third tier, indicated by a triple boarder, combines the *Risk of Surgery* and *Risk of RV Failure*. The fourth and final tier, depicted as the square decision node, combines the result of the third tier with *Estimated Waiting Time* and *Emergency Implant* to determine the L/B Index (the final result).

The diagram was constructed with multiple tiers in effort to mimic the schemata of the physician's decisions. It was difficult for any of the physicians to relate an individual variable to the probability of needing an LVAD or BiVAD. However, relating individual variables to categories such as "Liver Function" and then using those to determine a "risk of surgery" are relationships that physicians make routinely. The end result is determining the relationships between individual variables and the final decision. The overall utility function is a combination of mortality, morbidity, and quality of life summarized in a simple algebraic equation. A BiVAD is associated with higher morbidity due to higher complications and a lower quality of life due to additional constraints of having two pumps. However if a patient receives just an LVAD and then their RV fails (implying that a BiVAD should have been prescribed) they experience a higher mortality. The actual equation used to represent utility is further described in relation to Equation 1 (page 25) which is used in the optimization.

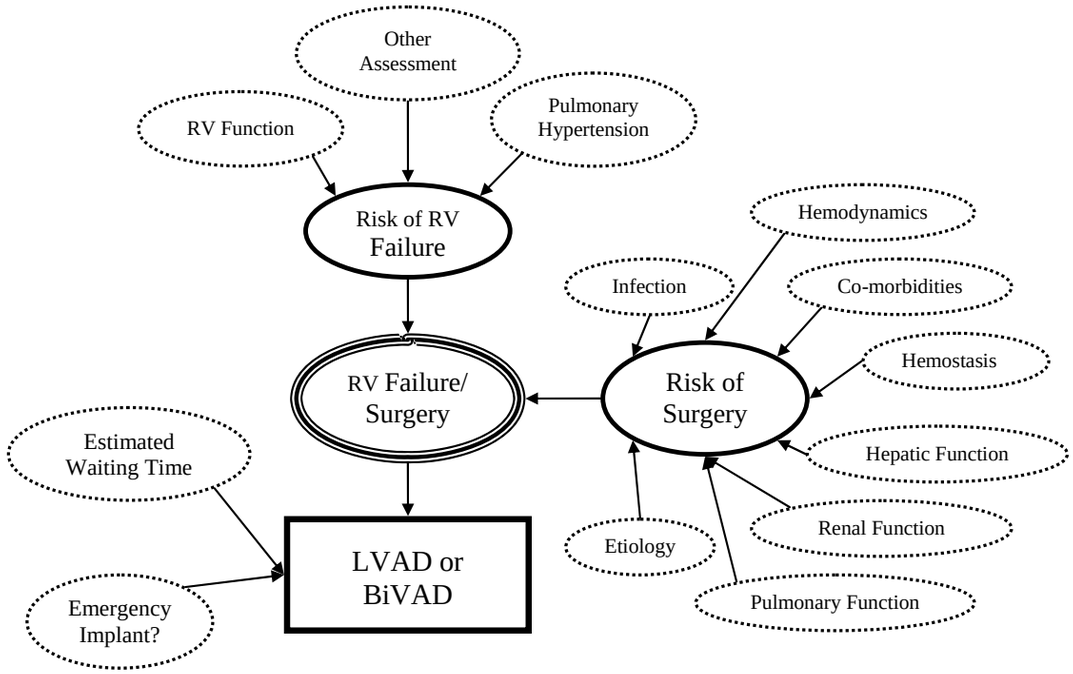

Figure 7: Simplified Influence Diagram illustrates the decision to implant an LVAD or BiVAD

Table 2: Table containing variables and categories used in the decision model according to tiers

Tier 1	
Hepatic Function	**Infection**
Total Bilirubin	WBC count
ALT	**Etiology**
AST	Ischemic acute
Renal Function	Ischemic non-acute
Creatinine	Non-ischemic acute
Renal Dysfunction	Non-ischemic non-acute
On Dialysis ?	
Pulmonary Function	**Pulmonary Hypertension**
Mech. Vent?	PA - systolic
ECMO support?	PA - mean
Pulmonary disease	TPG
Hemostasis	PVR (woods units)
PTT	**RV Function**
INR	RAP
Platelet count	RVED
Hematocrit	RV systolic
Hemodynamics	TR (>=mod-sev)
NYHA class	**Other Assessment**
# of inotropes	RAP
PCW	mean PAP
PA sat	CI
CI	CPB time (mins)
IABP support?	
ECMO support?	**Estimated Waiting Time**
Co-morbidities	blood type
PVD	weight (kg)
Diabetes	**Emergency Implant?**
Previous sternotomy	
Pulmonary disease	
Smoker	
Albumin < 3	
Renal Dysfunction	

Tier 2
Overall Risk of Surgery
Hepatic Function
Renal Function
Pulmonary Function
Hemostasis
Hemodynamics
Co-morbidities
Infection
Etiology
Overall Risk of RV Failure
Pulmonary Hypertension
RV function (pre-op)
Other Assessment

Tier 3
RV Failure/surgery
Overall Risk of Surgery
Overall Risk of RV Failure

Tier 4
Final Result
RV failure/surgery
Estimated Waiting Time
Emergency Implant?

3.3 MODEL SELECTION AND DEVELOPMENT

Upon completion of the influence diagram and the list of variables, the type of model was chosen. The large number of variables dictated that the model could not be too complex, or it would be impossible to gather all the information necessary from physicians. For example if four leveled Bayesian networks, like those employed by Santelices et al. [26] were used for the entire model, over 4^8 (or 65,536) probabilities would need to be assigned by the physicians, which is impractical. Ultimately, the compromise was a model which aimed to balance complexity with practicality. The decision was broken into four tiers, which in turn broke the decision into different steps moving from individual variables to the final decision.

The first tier uses a linear relationship to combine individual variables into an assessment for each primary category. Each individual variable has physician defined intervals. Some variables were only True or False, but most were numerical intervals. Numerical intervals were broken into four categories representing normal values, mild dysfunction, moderate dysfunction, and severe dysfunction. The weights for each variable in this level were agreed upon by the cohort of physicians using a majority vote, although there was little disagreement at this level of the decision.

The second tier used the assessment for each primary category to define *Risk of RV Failure* and *Risk of Surgery*. A simple linear relationship is not sufficient to combine these primary categories to define the overall risk, because varying degrees of dysfunction for different categories can have significantly different effects on the risk of surgery of RV failure. For example mild kidney dysfunction does not have a significant impact on the risk of surgery while even mild pulmonary dysfunction is very significant. Two physicians, a cardiothoracic surgeon and a heart failure cardiologist, individually assigned weights to the primary categories and also chose from four different types of relationships: (A) linear, (B) sigmoidal, (C) convex (in which even mild dysfunction imparts serious risk) (D) concave (in which only severe dysfunction significantly impacts the risk). (See Figure 8) These figures relate the physician's perception of how the different category assessments (x-axis) relate to the next tier, *Risk of Surgery* or *Risk of RV Failure* (y-axis).

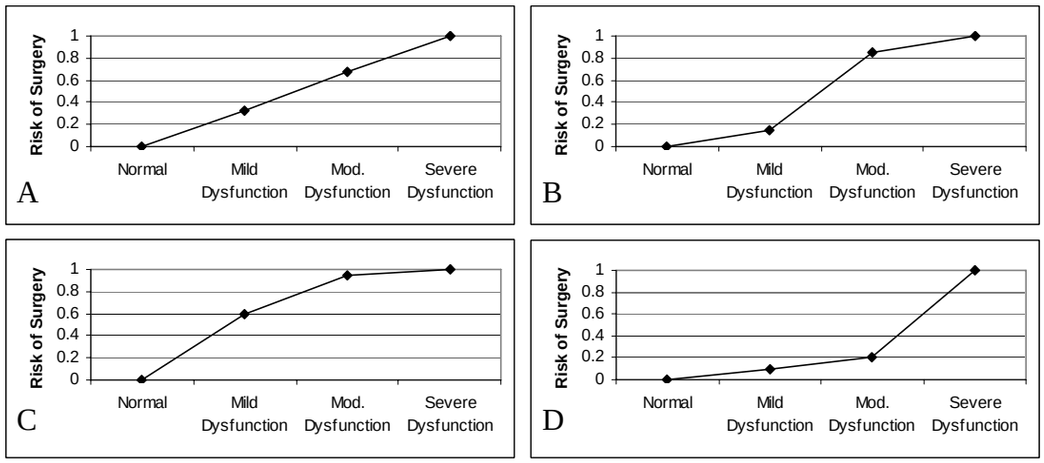

Figure 8: Graphs depict the four types of relationships the physicians could assign to each variable

The third tier combines *Risk of RV Failure* and *Risk of Surgery* using a probability table to define the results for each possible combination of risks.

The fourth tier linearly combines *Estimated Waiting Time* and *Timing of Implant* with the results from the table combining the *Risk of RV Failure* and *Risk of Surgery*. The result of the fourth tier, and therefore the final result is called the *L/B Index*. *L/B Index* is shortened from LVAD vs BiVAD Index and is a number between 0 and 1. An *L/B Index* result of 1 indicates that an LVAD should be implanted and a result of 0 indicates that a BiVAD should be implanted. Naturally results closer to 0 indicated that a BiVAD is preferred and results closer to 1 indicated that an LVAD is preferred.

The entire model was implemented in Microsoft Office Excel 2003 (11.5612.5606). This software was chosen because of the sophisticated optimizer, program-ability, popularity, and user-friendly interface which is greatly simplified using the forms function. The entire model was contained in one file. The first worksheet contained all of the weights that made up the model. Subsequent worksheets contained the modeling equations, with links to weights and the data from an individual patient. Further worksheets summarized the results of all the individual patient models as a whole and as sub-divided by patient outcomes.

As described above, the possible range of each individual variable was divided into intervals. Each interval was assigned a value for the tier-one computation, equally distributed from 1 to zero: normal = 1, mild dysfunction = 0.66, moderate dysfunction = 0.33 and severe dysfunction = 0. Thus each test result was converted into a number between 0 and 1 based on the interval onto which it falls. Binary tests were assigned a value based on severity, for example a *true* for *ECMO* is severe and was assigned a value of 0, while a *true* for *IABP*, which is less severe was assigned 0.33. A

false is 1 in both of these cases. For each category these results are combined as a weighted sum such that the result is a number between 0 and 1. An example of these calculations is shown in Figure 9. For the second tier the results of each category are again divided into intervals, in this case, defined by the type of relationship chosen. (See the four possible relationships, shown in Figure 8). The assigned values for these relationships are shown in Table 3. As with Tier-one, these values were combined using a weighted sum, which is depicted in Figure 10. As previously described the third tier employed a different method, where a probability is assigned for each possible combination of levels of *Risk of Surgery* and *Risk of RV Failure*. Finally the result of Tier-three is combined with the *Estimated Waiting Time* and *Emergency Implant* (a binary variable) to calculate the final result. The final result is always a number between 0 and 1, where 0 represents the greatest recommendation for BiVAD and 1 implies the greatest confidence that an LVAD should be sufficient.

Table 3: Assigned values for the intervals for each of the four relationships

	Normal	Mild Dysf.	Moderate Dysf.	Severe Dysf.
Linear	1	0.66	0.33	0
Sigmoidal	1	0.85	0.15	0
Convex	1	0.96	0.6	0
Concave	1	0.2	0.1	0

Hepatic Function	Test Value		Higher is Better	lowest	Range 1 end	range 2 end	range 3 end	index	Result	Present?	Weight	Weighted Result
Total Bilirubin	1.5	Present	0	0	1.2	1.6	4	4	0.66	1	1	0.66
ALT	74	Present	0	0	40	100	200	3	0.66	1	0	0
AST	48	Present	0	0	40	100	200	2	0.66	1	2	1.32
		lower is better		1	0.66	0.33	0					
											sum of weights	3
		all missing?		1							result	0.66
				Result of Hepatic function								
				0.66								

Renal Function	Test Value		Higher is Better	lowest	Range 1 end	range 2 end	range 3 end	index	Result	Present?	Weight	Weighted Result
Creatinine	3.8	Present	0	0	1.2	1.6	2.4	4	0	1	4	0
Renal Dysfunction	FALSE	Missing	0	FALSE		TRUE		3	1	0	2	0
On Dialysis ?	FALSE	Present	0	FALSE			TRUE	2	1	1	0	0
		lower is better		1	0.66	0.33	0					
											sum of weights	4
		all missing?		1							result	0
				Result of Renal function								
				0.00								

Figure 9: Example section of Tier-1 calculations, assessing hepatic and renal function, where 0 = severe dysfunction and 1 = normal function

Overall Risk of Surgery	result	missing?	weights	weighted result
Etiology	0.33	1	3	0.99
Hemodynamics	0.2	1	1	0.2
Hepatic Function	0.67	1	1	0.67
Renal Function	0.67	1	2	1.34
Pulmonary Function	1	1	2	2
Hemostasis	1	1	2	2
Infection	0.2	1	0	0
Co-morbidities	1	1	3.2	3.2
Sum of total values				10.4
Total weights:				14.2
Result				0.73

Figure 10: Example section of Tier-2 calculations, calculating the overall risk of surgery based on the assessments of each individual category

3.4 DATA ENTRY INTO THE MODEL

Retrospective patient data from the Artificial Heart Program at the University of Pittsburgh Medical Center were used to test the model and to allow for optimization. An IRB (#0509138), included in Appendix B, was obtained to allow researchers access to the data. All files including data with identifiers were password protected and kept in a secure place and were only viewed by researchers listed on the IRB. Each patient was given a numerical identifier known only to the investigator (Bronwyn Uber). Using these numerical identifiers allowed the data and the model to be viewed without comprising confidentiality. All patients over 18 years old, who were implanted at UPMC after January 1, 1990 and were explanted before January 1, 2006 were included in this study. There were 239 patients overall. Patients who did not have catheterization results one week prior to implant were not included; there were 57 of these patients. All data was required to be measured one week prior to the implant or the variable was identified as missing. The only exception to this rule was if moderate or severe tricuspid valve regurgitation was discovered on an echocardiogram, which was acceptable up to a month prior to implant. If there are multiple values for a variable from different days, the values from the day closest to the day of the implant were used. Data from the day of implant was not used because there was no way to distinguish whether it was before or after the implant.

Data for each individual variable was not available for every patient, so the model accounted for these missing data by automatically reducing the weighting coefficient to zero of a missing variable (or category) and rebalancing the remaining weights.

The accuracy of the program was evaluated by separating all patients according to outcome, as follows:

1. **“LVAD 0%”** or **“LVAD bad”**, which indicated that a BiVAD should have been implanted, was defined as any LVAD patient who needed RVAD or ECMO support post-implant. Patients who needed ECMO support purely for respiratory reasons were excluded from this group.
2. **“LVAD IS”** was defined as LVAD patients who needed inotropic support for more than 7 days post-implant.
3. **“LVAD RVF”** was defined as patients who have right ventricular failure listed as a complication post-implant, but neither a RVAD nor ECMO was inserted.
4. **“LVAD 100%”** or **“LVAD good”** which covers all the LVAD patients who did not have any of the complications listed for the above three groups.
5. **Other** was defined for the one patient who died in the operating room, and therefore conclusions about the necessity of an LVAD or BiVAD could not be determined.

BiVAD patients are difficult to differentiate on the basis of necessity for RV support, because there were no data to corroborate or refute the outcome if an RVAD had not been used. Therefore all of the BiVAD patients were grouped together. Each individual patient’s outcome was determined using data from the AHP (Artificial Heart Program) database and from medical records, and designated according to one of the four categories described above.

To assess the prediction accuracy of the model using different weights (from Physician #1, Physician #2 and optimization), an arbitrary cut-off of 0.5 was chosen to distinguish between the decision to implant an LVAD or BiVAD. An L/B Index less than 0.50 dictates that a BiVAD should be implanted. An L/B Index between 0.5 and 1.0 dictates that an LVAD should be implanted.

For patients in LVAD 0% and LVAD 100% outcome groups, the model prediction was compared to the outcome. The model decision was then identified as either a correct or incorrect decision. The patients in the LVAD IS or LVAD RVF groups were not included in this analysis because it is unclear whether these patients would have been better off as BiVADs, or as LVADs. Although the results from these groups were analyzed, they were not included in the optimization.

The initial guess for optimization was derived from the physician-supplied that produced the best initial results. The Objective Function used for optimization was a combination of the number of false positives and false negatives. It is important to consider the number of unnecessary BiVADs which would be implanted according the algorithm and the number of patients who would need RVAD support post-LVAD implant. Since the severity of needing RVAD support post-LVAD implant is greater than an unnecessary BiVAD, the subset of patients who incorrectly received an LVAD weighted two times greater than the subset of patients who incorrectly received a BiVAD. The equation for this variable is shown by Equation 1, where 73 is the number of LVAD patients without RV failure and 19 is the number of

LVAD patients who needed RVAD support post-implant. This optimization value was minimized, therefore looking for the least number of patients negatively affected (with RVAD support subset counting double due to the severity).

Equation 1

Optimization value = (1 - %correct “LVAD good”)*73 + 2*(1 - % correct “LVAD bad”)*19

The optimization was implemented using the SOLVER function within MS Excel™ (Microsoft, Inc.) based on the method of Generalized Reduced Gradient (GRG2) nonlinear optimization developed by Leon Lasdon, University of Texas at Austin, and Allan Waren, Cleveland State University. For linear and integer problems it uses the simplex method with bounds on the variables and the branch-and-bound method. Although the solver proved to be quite robust, it was not capable to accommodate the entire set of free variables at once. Therefore a two-stage approach was adopted wherein,each category and tier was evaluated separately and then combined. This maximizes the likelihood that it converges to the global minimum, and avoided being trapped in a local minimum. In the cases where there were only three variables weights, one variable was held constant at 1, and the other two were optimized for values between from 0 to 10. If there were more variables each variable was individually adjusted from 0 to 10 while keeping the others constant. If there were multiple values which resulted in the same optimization value preference was given to integers. In addition to optimizing the weights, each of the four relationships (Figure 8) was evaluated for each tier-two category and the one which resulted in the lowest objective function was chosen.

A sensitivity analysis was performed to identify variables that could be eliminated. This was achieved by individually reducing weight of each variable to zero and repeating the optimization. A negligible variable was defined as one which did not increase the optimal objective function greater 0.01%.

The entire data set was used to evaluate the model. The main reason for this choice was the relatively small number of patients, particularly in the “LVAD bad” group, which had only 19 patients. Ideally this model will be further validated in the future by prospective studies, in which it may be used in parallel with the physicians’ routine decision making.

4.0 RESULTS

Retrospective data from UPMC's Artificial Heart Program was obtained after gaining IRB approval. Using these data, the accuracy of the model using the weights from each of the two physicians was assessed. Neither of the results from the physician-derived model exactly matched the actual decisions that were made, which may be a result of the evolving decision process over the past decade and a half, or simply due to the inherent subjectivity by which the model was designed. These models predicted 63% (47%) of the patients who required an RVAD after implant. However these decision models would also have implanted BiVADs in 40% (43%) of patients who were treated successfully with just an LVAD. The model using the optimized weights had better results, predicting 74% of the patients who required an RVAD post-implant and only calling for implanting BiVADs in 21% of patients who were treated successfully with just an LVAD. Another result of the optimization was the identification of variables that were not important to the decision. The variables found to have a negligible effect (or even a negative affect) on the decision were: ALT, history of smoking, mean PAP, PVR, RVED, estimated waiting time and whether the emergent status of the implant.

4.1 PATIENT DATA

Data obtained after IRB approval, was received and systematically evaluated as described in the methods. Table 4 provides the breakdown of the total number of patients implanted with a VAD from 1987 to 2005 and explanted prior to 2006. Since medical methods including patient selection had evolved considerably over this period it was important to consider the outcome results broken down by individual years. Because data prior to 1990 was sparse, they were excluded from this study. The first BiVAD implanted at UPMC was in 1992, there were only two implants performed that year and then none until 1995. It is important to realize that as BiVADs became adopted as a standard of care, the decision process evolved over time. Therefore it would be inaccurate to homogenize the decision making process with one universal model. Nevertheless, the ultimate outcome of the current model is not to mimic the historical decisions

performed by the physician, but to develop a predictive tool that would most accurately correspond to the retrospective outcomes Therefore the data acquired before BiVADs were implanted are also useful for distinguishing those patients who can thrive on just an LVAD.

Table 5 summarizes the patients for whom sufficient data were available for this study. Table 6 provides the breakdown by year of implant according to device and outcome. The BiVAD patients were not further distinguished by by outcomes because of the rationale described previously.

Table 4: Number of patients with sufficient data

Total patients:	239
Before 1990:	14
Not enough data:	57
Total studied:	**168**

Table 5: Patient Breakdown by VAD type

BiVADs	48
Thoratec	45
Novacor+abiomed	1
Thoratec +IVAD	2
LVADs	119
Novacor	65
Thoratec LVAD	32
HM	19
HM II	3
Total	168

Table 6: Number of Patients for each LVAD Outcomes

Outcome	# of Patients
LVAD - 100%	73
LVAD - IS	18
LVAD - RVF	8
LVAD - 0%	19
Other	1

Figure 11 and Figure 12 illustrate the distribution of VAD type (LVAD or BiVAD) and outcome (the first four categories listed in Table 6) according to year. Figure 11 provides a bar graph in terms of number of patients and Figure 12 shows the same data as a percentage of all VADs implanted that year. Both figures are based on all VAD patients implanted during the specified time frame. It is interesting that the highest number of LVAD 0% in one year occurred the first year that BiVAD implants became commonplace (1996), likely due to the initial learning curve for patient selection. While the number has decreased since then, it still remains a significant issue. The number of BiVAD implants each year has been decreasing since 2002. The LVAD – IS group was only evaluated from 2000 – 2005, because data pertaining to length of inotropic support was not available for the earlier patients, which is why that category is only present from 2000 onwards. There is only a small number of LVAD- RVF data (n=8) however 50% of these patients were implanted in 2004. This parallels the decreasing number of BiVADs implanted.

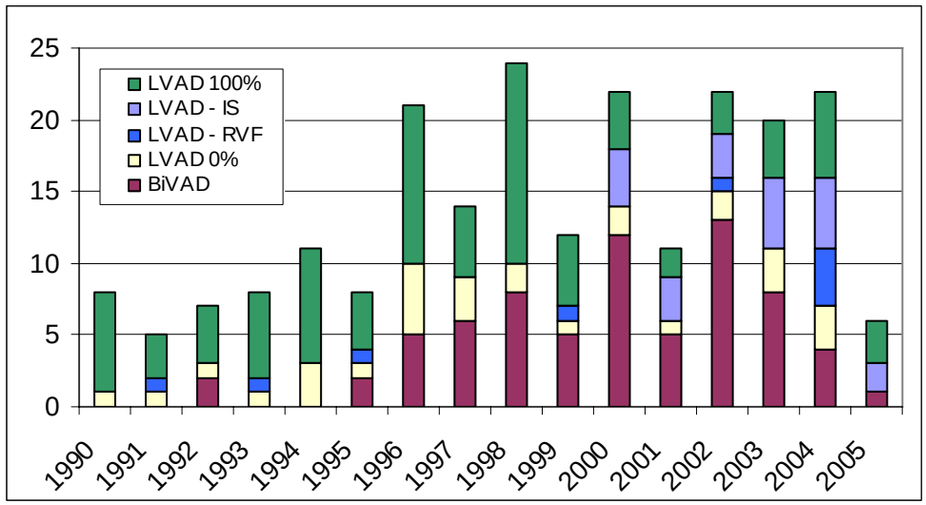

Figure 11: Number of VAD type and outcome by year

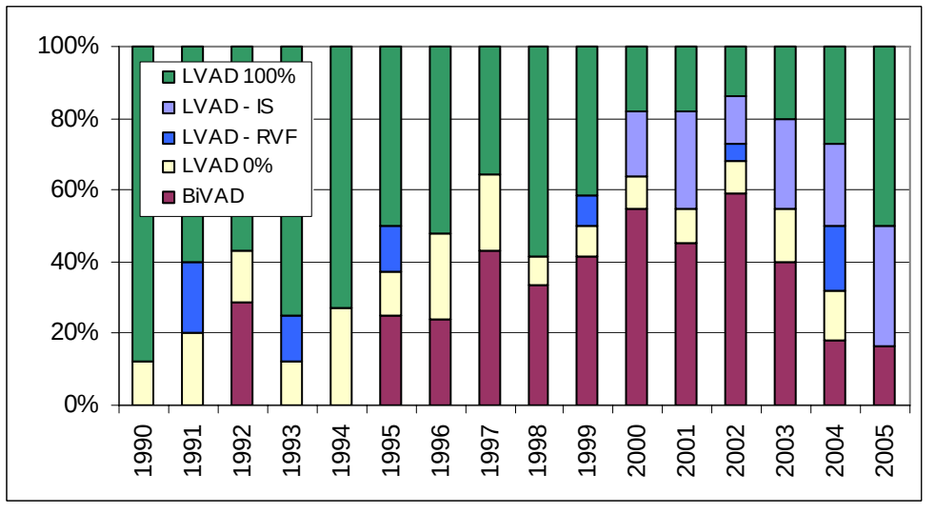

Figure 12: Percentage of each VAD type and outcome by year

Summary tables displaying average and standard deviation of age, weight, % female, % emergency implant, cardiopulmonary bypass time, days on ventilator post-implant and first and last implant date are available in Appendix C. Individual summaries are provided for all VAD patients, all BiVAD patients, all LVAD patients, LVAD – 100% patients (no RV failure) and LVAD 0% (RVAD post-implant).

Each continuous variable was individually compared using a two-sample unequal variance Student's t-test to determine significant differences between two groups. The groups compared were: BiVAD patients versus LVAD patients; BiVAD patients versus LVAD – 100% patients; and LVAD - 100% versus LVAD - 0% patients. Tabulations of these results are provided in Appendix C. When comparing the BiVAD patients with all LVAD patients the significant variables ($p<0.05$) were:

- cardiac index (CI)
- right atrial pressure (RAP), and
- cardio-pulmonary bypass time (CPB).

When comparing the BiVAD patients with the LVAD – 100% patients (those without RV failure) the cardiac index (CI), right atrial pressure (RAP), cardio-pulmonary bypass time (CPB) and creatinine levels were found to be significant. The comparison between LVAD – 100% patients and LVAD – 0% (RVAD post-implant) resulted in no significant differences in variables between the two groups, which can be used to explain why it is difficult to differentiate between those two groups based purely on individual variables.

Cut-off values for each variable and weights of individual variables were obtained from one physician. These were then reviewed by the other physicians and minor modifications were made as appropriate. There was little disagreement because these are common clinical variables with relatively well accepted normal ranges. Values from literature however were not sufficient for this four-level assessment because literature usually only indicates *normal* and *abnormal* values, as distinguished from the intermediate ranges adopted in this study. The weights and break points are summarized in Table 7.

Table 7: Variable weights and breakpoints obtained from physicians.

variable weight					
	Hepatic function				
		Normal	Mild Dysfunction	Moderate Dysfunction	Severe Dysfunction
1	Total Bilirubin	0 - 1.2	1.2 - 1.6	1.6 - 4.0	> 4.0
2	ALT	<40	40-100	100-200	>200
2	AST	<40	40-100	100-200	>200
	Renal function				
		Normal	Mild Dysfunction	Moderate Dysfunction	Severe Dysfunction
4	Creatinine	<1.2	1.2-1.6	1.6-2.4	>2.4
10000	Dialysis	FALSE			TRUE
2	Renal Dysfunction	FALSE		TRUE	
	Pulmonary function				
		Normal	Mild Dysfunction	Moderate Dysfunction	Severe Dysfunction
5	Mechanical Vent.	FALSE			TRUE
8	ECMO support	FALSE			TRUE
1	Pulmonary Disease	FALSE		TRUE	
	Hemostasis				
		normal			High
2	PTT	<40	40-60	60-80	> 80
3	INR	<1.4	1.4-1.7	1.7-2.0	>2
2	Platelet count	>150	150-100	100-50	0-50
1	Hematocrit	>35	30-35	15-30	0-15
	Hemodynamics				
		normal	mildly sick	moderately sick	severely sick
1	NYHA class		III		IV
3	Number of inotropes	0	1	2	>= 3
2	PCW	0-20	20-25	25-30	>30
3	PA sat	>50	45-50%		0-45%
3	CI	>2.3	2.0-2.3		0-2
5	IABP support	FALSE		TRUE	
8	ECMO support	FALSE			TRUE
	Infection				
		None	Mild	Severe	
1	WBC count	0-10	10-15	>15	
	Co-morbidities				
3	PVD				
3	Diabetes				
2	Previous sternotomy				
2	Pulmonary Disease				
1	Smoker				
3	Albumin < 3				
1	Renal Dysfunction				

Table 7 (continued)

variable weight					
	Pulmonary hypertension				
		Normal	Mild	Moderate	Severe
1	PA - systolic	<25	25-35	35-50	>50
1	PA - mean	<20	20-25	25-30	30+
2	TPG	<8	8-12	13-16	17+
2	PVR (Woods units)	<3	3-4	4-5	5+
	RV function				
		Normal function	Mild dysfunction	Moderate dysfunction	Severe dysfunction
3	RAP	<8	8-12	12-20	>20
1	RVED (echo)	Normal	Mild	Moderate	Severe
1	RVP systolic	0	35	50	60
2	TR (>= mod-sev)	FALSE			TRUE
	Other Assessment				
		Normal	Mild	Moderate	Severe
3	RAP	<8	8-12	12-20	>20
2	mean PAP	<20	20-25	25-30	>30
2	CI	>2.4	2.2-2.4	2.2-2.0	0-2.0
3	CPB time (mins)	0-100	100-150	150-200	>200
	Estimated Waiting Time				
		Short	Moderate	Long	
3	Blood Type	AB	B, A	O	
1	Weight (kg)	54.4 - 81.6	<54.4	>81.6	

4.2 RESULTS FROM PHYSICIAN #1

The additional weights necessary to complete the model, specifically those in Tier-2 to generate the weighted sums associated with the *Risk of Surgery* and *Risk of RV Failure*, and Tier-3 to complete the *Risk of Surgery* versus *Risk of RV Failure* table, was elicited from two different physicians. Due to the variability in the weights, which emphasizes the current disagreement about patient selection, the different sets of weights were evaluated separately. Table 8 shows the weights and results obtained from Physician 1. The relationships listed as A, B, C and D refer to the linear and non-linear choices of relationships described in the Methods Section, Figure 8.

Table 8: Model weights given by Physician #1

Physician 1				
Risk of Surgery	weight	relationship		
Etiology	3	A		
Hemodynamics	1	D		
Hepatic Function	1	B		
Renal Function	2	A		
Pulmonary Function	2	B		
Hemostasis	2	D		
Infection	3	D		
Co-morbidities	3	A		
Risk of RV Failure				
RV function (pre-op)	2	D		
Other Assessment	3	A		
Pulmonary Hypertension	1	D		
	Risk of Surgery			
	low	mod/low	mod	high
RV failure low risk	1	1	0.9	0.75
RV failure mod/low risk	1	0.8	0.75	0.5
RV failure mod risk	0.6	0.4	0.2	0
RV failure high risk	0	0	0	0
Final Result				
RV failure/surgery	3			
Waiting	1			
Timing	3			

The accuracy of the model using the weights from Physician #1 was evaluated as described in the Methods. These results from the model were then compared with actual medical decision that was made (BiVAD or LVAD) and their outcomes. These results are depicted in Table 9.

Recalling that the BiVAD patients could not be divided into outcome groups, the percentage of the "correct" BiVAD predictions is listed for reference only. It is not an indication of the accuracy of the model, because some of those BiVAD patients may not have ultimately needed a BiVAD. The percentage of "good decisions" is shown in Table 9. A good decision for LVAD-100% is implanting an LVAD and a good decision for LVAD - 0% is implantation of a BiVAD. Table 11 gives more detail about the L/B Index from the model and the result of sub-categories *Risk of Surgery* and *Risk of RV Failure* for each group. Using Student's t-test it was found that there was a significant difference between the overall results from the model for BiVAD and LVAD – 100% groups. This result is

understandable because the weights were derived from a physician who was primarily responsible for the historical decisions that divided those two groups. There was not a significant difference between the LVAD – 100% and LVAD – 0% groups. This also can be expected when modeling the decision that actually took place, because both of those groups were initially implanted with just a LVAD. The model however was found to outperform the actual decisions that were made in the LVAD – 0% group: capturing 63% of this group instead of 0% which was the actual decision. There were a large number (n=30) of "false LVADs" wherein the model predicted the need for a BiVAD yet the patients survived with an LVAD alone. There also were 7 "false BiVADs" predicted by the model, in which an LVAD was predicted, but the actual patients were found to require subsequent RVADs.

Table 9: Accuracy of model based on weights from Physician #1

Physician #1: Results	% good
BiVAD	82.0%
All LVAD	58.0%
LVAD- 100% (no RV Failure)	59.5%
LVAD 0% (RVAD needed)	63.2%

Table 10: Contingency table depicting the results of the model using the weights from Physician #1

		LVAD	
		good	fail
Prediction	LVAD	44	7
	BiVAD	29	12

Table 11: Model predictions based on Physician #1 (There is a significant difference p<0.00001 between the L/B Index for BiVAD versus LVAD-100% groups. There is not a significant difference between LVAD - 100% and LVAD - 0%. The difference between BiVAD and LVAD-0% was significant p=0.05)

Physician #1: Results	Risk Surgery		Risk RV		L/B Index	
	Avg	Stdev	Avg	Stdev	Avg	Stdev
BiVAD	0.59	0.20	0.31	0.26	0.31	0.23
All LVAD	0.68	0.13	0.43	0.25	0.53	0.29
LVAD- 100% (no RV Failure)	0.71	0.13	0.47	0.25	0.58	0.29
LVAD 0% (RVAD needed)	0.65	0.11	0.36	0.27	0.46	0.28

Another useful way to depict the data is to determine the number of LVAD – 100% (the successful LVADs) and LVAD – 0% (the failed LVADs) with each combination of *Risk of Surgery* and *Risk of RV Failure*. These results are shown in Table 12. While most of the LVAD – 0% patients were characterized as having moderate or severe risk of RV failure, there were six patients whom according to these weights and model were depicted as having low or mild risk of RV failure. Figure 13 provides a "cluster diagram" representing these same results shown in Table 12, where the highest risk is between 0 and 1, where 0 represents the highest risk. This diagram represents the number of patients in each category by the size (area) of the circle.

The distribution of BiVAD patients for each combination of Risk of Surgery and Risk of RV Failure is shown in Table 13. All of the patients determined to have a high risk of surgery were implanted with BiVADs. Similar to the LVAD 0% group while the majority of BiVAD patients had moderate to severe risk of RV failure, there was a significant subset which had low to mild risk of RV failure. The results give a clear indication that there is room for improvement in the model.

Table 12: Number of each LVAD outcome (No RV Failure and RVAD post-implant) in each category (based on weights from Physician #1)

		Risk of Surgery											
		1 (low)			2 (mild)			3 (moderate)			4 (high)		
Risk of RV failure	1 (low)	L-good	3	100%	L-good	8	80%	L-good	0		L-good	0	
		L-fail	0	0%	L-fail	2	20%	L-fail	0		L-fail	0	
	2 (mild)	L-good	11	100%	L-good	9	69%	L-good	3	100%	L-good	0	
		L-fail	0	0%	L-fail	4	31%	L-fail	0	0%	L-fail	0	
	3 (moderate)	L-good	9	90%	L-good	10	71%	L-good	5	83%	L-good	0	
		L-fail	1	10%	L-fail	4	29%	L-fail	1	17%	L-fail	0	
	4 (severe)	L-good	4	67%	L-good	11	73%	L-good	0	0%	L-good	0	
		L-fail	2	33%	L-fail	4	27%	L-fail	1	100%	L-fail	0	

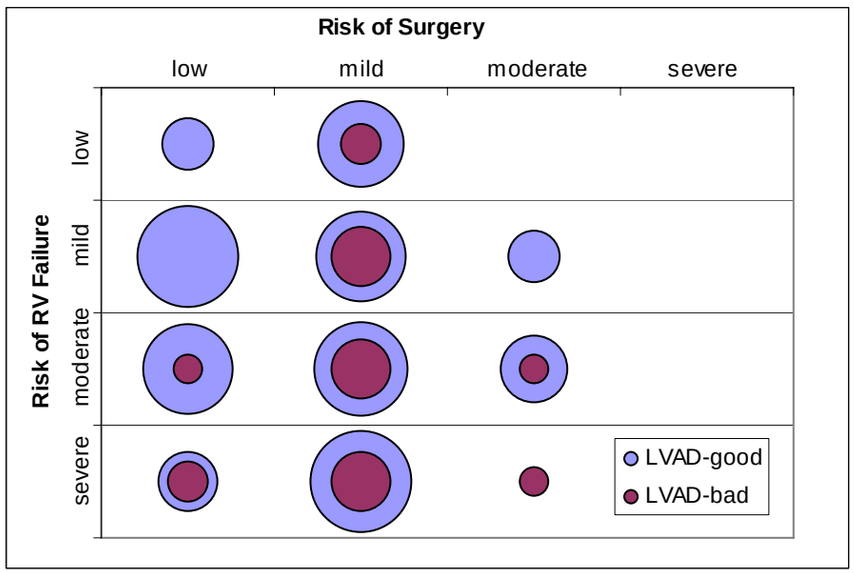

Figure 13: Cluster diagram of LVAD outcomes according to calculated Risk of RV Failure and Risk of Surgery (using weights from physician #1)

Table 13: Number of BiVADs in each category (based on weights from Physician #1)

All BiVADs					
		Risk of Surgery			
		1 (low)	2 (mild)	3 (moderate)	4 (high)
Risk of RV Failure	1 (low)	1	4	1	0
	2 (mild)	1	2	0	0
	3 (moderate)	0	7	3	3
	4 (severe)	4	13	7	2

Results from each sub-category (renal function, hemostasis etc.) can be found in Appendix D.1. Significant differences in indicators between BiVAD patients and all LVAD patients were: (1) *Hemodynamics*, (2) *Co-morbidities*, (3) *Overall Risk of Surgery*, (4) *RV Function*, (5) *Other Assessment*, (6) *Overall Risk of RV Failure*, (7) *RV Failure/ Surgery*, (8) *Emergency Implant*, (9) *L/B Index*.

Two important variables that were found NOT to be significant indicators of outcome were: (1) *Pulmonary Hypertension* and (2) *Estimated Waiting Time*. There were similar results for the BiVAD and LVAD – 100% group, the only difference was *Renal Function* which was also found to be significantly different. There was however no significant differences between any of the sub-categories or the L/B Index between the LVAD – 100% and LVAD – 0% groups, which emphasizes that these weights are not suitable for differentiating between these two groups.

As stated before, it is not possible to determine retrospectively based on the available data whether the preferential treatment for LVAD- IS (patients on extended inotropic support) and the LVAD- RVF (patients with RV failure, but no RVAD implanted) patients would have been an LVAD or BiVAD. But it is still informative to examine the model's predictions for these two groups. Using these weights the model strongly favors implanting BiVADs for both groups of patients.

Table 14: According to the weights from Physician #1, the percentage of BiVADs predicted for LVAD – IS and LVAD – RVF groups

	Predicted BiVAD
LVAD - IS	72.2%
LVAD - RVF	75.0%

4.3 RESULTS FROM PHYSICIAN #2

Weights were also obtained from Physician #2 shown in Table 15 and identical analyses were performed. The accuracy of the model based on Physician #2 is shown in Tables 16 - 18. When compared to the results using weights from Physician #1, the percentage of correct decisions is lower. However neither had significant differences in the overall result of LVAD – 100% and LVAD – 0%, which is central to the goal of this model. The breakdown of patients into categories based on *Risk of Surgery* and *Risk of RV Failure* is shown in Table 19, Figure 14 and Table 20. There were three more (total of nine) LVAD – 0% patients who were indicated as having low to mild risk of RV failure than there were based on weights from Physician #1.

Table 15: Model weights given by Physician #2

Physician 2				
Risk of Surgery	weight	relationship		
Etiology	1	A		
Hemodynamics	2	B		
Hepatic Function	4	B		
Renal Function	2	B		
Pulmonary Function	2	D		
Hemostasis	3	C		
Infection	5	B		
Co-morbidities	3	D		
Risk of RV Failure				
RV function (pre-op)	2	B		
Other Assessment	3	B		
Pulmonary Hypertension	1	D		
	Risk of Surgery			
	low	mod/low	mod	high
RV failure low risk	1	1	1	0.95
RV failure mod/low risk	1	0.9	0.8	0.75
RV failure mod risk	0.5	0.45	0.25	0.05
RV failure high risk	0.05	0	0	0
Final Result				
RV failure/surgery	3			
Waiting	1			
Timing	3			

Table 16: Accuracy of Model based on weights from Physician #2

Physician #2: Results	% good
BiVAD	68.0%
All LVAD	52.9%
LVAD- 100% (no RV Failure)	56.2%
LVAD 0% (RVAD needed)	47.4%

Table 17: Contingency table depicting the results of the model using the weights from Physician #2

		LVAD	
		good	fail
Prediction	LVAD	41	10
	BiVAD	32	9

Table 18: Model predictions based on Physician #2 (There is a significant difference $p<0.00001$ between Overall BiVAD and LVAD 100% results. There is not a significant difference between LVAD 100% and LVAD 0% and there is a significant difference between BiVAD and LVAD-0% $p<0.02$)

Physician #2: Results	Risk Surgery		Risk RV		L/B Index	
	Avg	Stdev	Avg	Stdev	Avg	Stdev
BiVAD	0.64	0.24	0.32	0.31	0.35	0.26
All LVAD	0.76	0.15	0.48	0.30	0.59	0.32
LVAD- 100% (no RV Failure)	0.79	0.12	0.51	0.31	0.60	0.32
LVAD 0% (RVAD needed)	0.75	0.15	0.45	0.31	0.57	0.32

Table 19: Number of each LVAD outcome (No RV Failure and RVAD post-implant) in each category (based on weights from Physician #2)

		Risk of Surgery											
			1 (low)			2 (mild)			3 (moderate)			4 (high)	
Risk of RV failure	1 (low)	L-good	11	86%	L-good	5	100%	L-good	1	100%	L-good	0	
		L-fail	2	14%	L-fail	0		L-fail	0		L-fail	0	
	2 (mild)	L-good	19	83%	L-good	4	57%	L-good	0		L-good	0	
		L-fail	4	17%	L-fail	3	43%	L-fail	0		L-fail	0	
	3 (moderate)	L-good	7	80%	L-good	3	67%	L-good	1	50%	L-good	0	
		L-fail	2	20%	L-fail	1	33%	L-fail	1	50%	L-fail	0	
	4 (severe)	L-good	14	78%	L-good	8	73%	L-good	0		L-good	0	
		L-fail	4	22%	L-fail	2	27%	L-fail	0		L-fail	0	

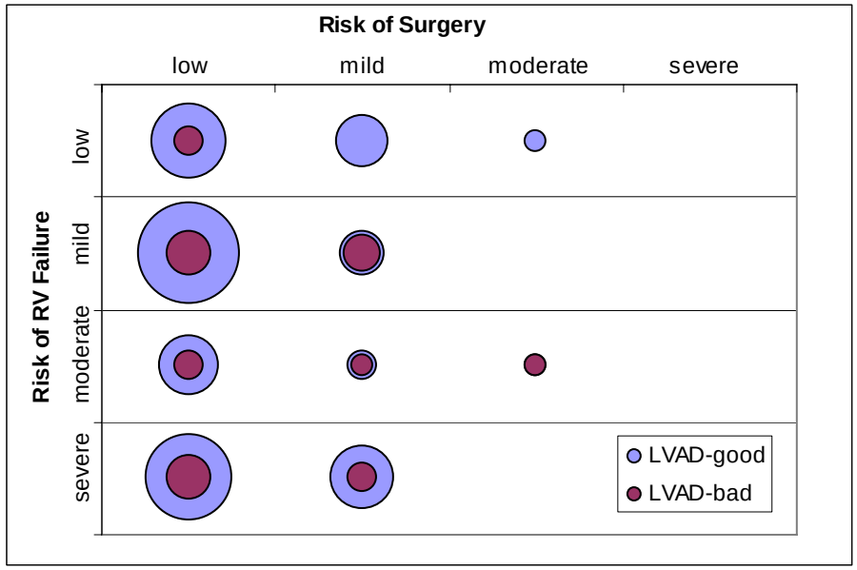

Figure 14: Cluster diagram of LVAD outcomes according to calculated Risk of RV Failure and Risk of Surgery (using weights from physician #2) , where the risk decreases from 4 to 0.

Table 20: Number of BiVADs in each category (based on weights from Physician #2)

BiVADs					
		Risk of Surgery			
		1 (low)	2 (mild)	3 (moderate)	4 (high)
Risk of RV Failure	1 (low)	5	1	0	0
	2 (mild)	3	4	1	0
	3 (moderate)	1	1	1	1
	4 (severe)	13	9	5	3

Results from each sub-category (renal function, hemostasis etc.) can be found in Appendix D.2. The difference in results between groups was also evaluated using a t-test. The significant differences between BiVAD patients and LVAD-100% patients were: *Hemodynamics*, *Co-morbidities*, *Overall Risk of Surgery*, *RV Function*, *Other Assessment*, *Emergency Implant*, and *L/B Index*. Once again there were no significant differences between any of the sub-categories or final results between the LVAD – 100% and LVAD – 0% groups.

Unlike the model using the weights from Physician #1, this model favors implanting LVADs for the LVAD- IS patients and is ambivalent for the LVAD- RVF patients (it predicts 50% LVAD and 50% BiVAD). (See Table 21)

Table 21: According to the weights from physician #2, the percentage of BiVADs predicted for LVAD – IS and LVAD – RVF groups

	Predicted BiVAD
LVAD - IS	33.3%
LVAD - RVF	50.0%

4.4 RESULTS FROM OPTIMIZATION

Because the model based on Physician #1 performed slightly better than the model of Physician #2, the corresponding weights were used as a starting point for the optimization. This was done based on the presumption that these weights were closest to the global minimum and therefore would facilitate convergence. Sensitivity analysis determined that ALT or AST (not both) could be eliminated without adversely affecting the optimization value. Two co-morbidities:

+smoker and +renal dysfunction were also eliminated. Mean pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) under pulmonary hypertension were also eliminated and the optimization value actually improved as a result. RV end-diastolic diameter, as determined by an echocardiogram was also eliminated; this was possibly due to the paucity of ECHO data. The elimination of infection under the Risk of Surgery also resulted in an increase in the optimization objective. Elimination of estimated waiting time and timing of implant (+/-emergency) from the final result further minimized the optimization value. Further optimization was performed for the individual weights and distributions. The resulting weights and distributions are shown in Table 22 and Table 23.

Table 22: Optimized variable weights with the same cut-offs obtained from the physicians

Optimized Weights		Intervals defined by physicians for continuous variables			
	Hepatic function				
		Normal	Mild Dysfunction	Moderate Dysfunction	Severe Dysfunction
1	Total Bilirubin	0 - 1.2	1.2 - 1.6	1.6 - 4.0	> 4.0
0	ALT	<40	40-100	100-200	>200
2	AST	<40	40-100	100-200	>200
	Renal function				
		Normal	Mild Dysfunction	Moderate Dysfunction	Severe Dysfunction
4	Creatinine	<1.2	1.2-1.6	1.6-2.4	>2.4
10000	Dialysis	FALSE			TRUE
2	Renal Dysfunction	FALSE		TRUE	
	Pulmonary function				
		Normal	Mild Dysfunction	Moderate Dysfunction	Severe Dysfunction
2	Mechanical Vent.	FALSE			TRUE
8	ECMO support	FALSE			TRUE
1	Pulmonary Disease	FALSE		TRUE	
	Hemostasis				
		normal			High
0.9	PTT	<40	40-60	60-80	> 80
1	INR	<1.4	1.4-1.7	1.7-2.0	>2
1	Platelet count	>150	150-100	100-50	0-50
1	Hematocrit	>35	30-35	15-30	0-15
	Hemodynamics				
		normal	mildly sick	moderately sick	severely sick
4	NYHA class		III		IV
4	Number of inotropes	0	1	2	>= 3
2	PCW	0-20	20-25	25-30	>30
2	PA sat	>50	45-50%		0-45%
2	CI	>2.3	2.0-2.3		0-2
5	IABP support	FALSE		TRUE	
8	ECMO support	FALSE			TRUE
	Infection				
		None	Mild	Severe	
0	WBC count	0-10	10-15	>15	
	Co-morbidities				
3	PVD				
1	Diabetes				
2	Previous sternotomy				
2	Pulmonary Disease				
0	Smoker				
1	Albumin < 3				
0	Renal Dysfunction				

Table 22 (continued)

Optimized Weights		Intervals defined by physicians for continuous variables			
	Pulmonary hypertension				
		Normal	Mild	Moderate	Severe
1	PA - systolic	<25	25-35	35-50	>50
0	PA - mean	<20	20-25	25-30	30+
2	TPG	<8	8-12	13-16	17+
0	PVR (Woods units)	<3	3-4	4-5	5+
	RV function				
		Normal function	Mild dysfunction	Moderate dysfunction	Severe dysfunction
1	RAP	<8	8-12	12-20	>20
0	RVED (echo)	Normal	Mild	Moderate	Severe
3	RVP systolic	0	35	50	60
3	TR (>= mod-sev)	FALSE			TRUE
	Other Assessment				
		Normal	Mild	Moderate	Severe
3	RAP	<8	8-12	12-20	>20
2	mean PAP	<20	20-25	25-30	>30
2	CI	>2.4	2.2-2.4	2.2-2.0	0-2.0
1	CPB time (mins)	0-100	100-150	150-200	>200
	Estimated Waiting Time				
		Short	Moderate	Long	
0	Blood Type	AB	B, A	O	
0	Weight (kg)	54.4 - 81.6	<54.4	>81.6	

Table 23: Model weights determined by the optimization

Optimization				
Risk of Surgery	weight	relationship		
Etiology	3	A		
Hemodynamics	1	D		
Hepatic Function	1	A		
Renal Function	2	A		
Pulmonary Function	2	B		
Hemostasis	2	B		
Infection	0			
Co-morbidities	3.2	A		
Risk of RV Failure				
RV function (pre-op)	1	D		
Other Assessment	1	A		
Pulmonary Hypertension	1	D		
	Risk of Surgery			
	low	mod/low	mod	high
RV failure low risk	1	1	0.9	0.75
RV failure mod/low risk	1	0.8	0.75	0.45
RV failure mod risk	0.6	0.4	0.2	0
RV failure high risk	0.55	0	0	0
Final Result				
RV failure/surgery	1			
Waiting	0			
Timing	0			

The results for the model using the weights from by the optimization are shown in Table 24 and Table 26. The percentages of LVAD – 100% and LVAD – 0% patients correctly identified were greater than those by either physician, both over 70% accurate. Only 5 LVAD- 0% patients were incorrectly identified (False BiVAD) and only 16 LVAD- 100% patients did not correspond to the historical decision to implant a BiVADs ("False" LVAD). (See Table 25.) Furthermore, unlike the previous weights there was a significant difference ($p < 0.003$) between the L/B Index of those two groups, which is a dramatic improvement over the previous weights that did not provide significant differences. There was no significant difference between the BiVAD and LVAD/0% groups, which is also a dramatic improvement because these two groups share the same outcome. It is interesting that this model concurs with just 56% of BiVADs decisions. These results can be interpreted that these new weights are not as accurate in predicting those patients who already received a BiVAD, or that historical clinical decisions were made more conservatively, chosing to err on the side of caution. This response might potentially be accommodated by the model through the selection of a more conservative cutoff value. Since the model was optimized using only LVAD patients, and there are no data to evaluate the necessity of post-implant BiVAD, the accuracy of the model cannot be verified in this respect.

Table 24: Accuracy of model based on optimized weights

Optimization: Results	% correct
BiVAD	54.2%
All LVAD	67.2%
LVAD- 100% (no RV Failure)	78.1%
LVAD - 0% (RVAD needed)	73.7%

Table 25: Contingency table depicting the results of the model using the optimized weights

		LVAD	
		good	fail
Prediction	LVAD	57	5
	BiVAD	16	14

Table 26: Individual model results from optimization (There is a significant difference p=0.0038 between the L/B Index for BiVAD and LVAD 100% Results. There is also a significant difference p=0.0022 between LVAD 100% and LVAD 0%. There is no significant difference between BiVAD and LVAD – 0%)

Optimization: Results	Risk Surgery		Risk RV		L/B Index	
	Avg	Stdev	Avg	Stdev	Avg	Stdev
BiVAD	0.63	0.20	0.34	0.29	0.41	0.38
All LVAD	0.71	0.13	0.36	0.27	0.50	0.35
LVAD- 100% (no RV Failure)	0.74	0.12	0.40	0.28	0.62	0.31
LVAD 0% (RVAD needed)	0.68	0.10	0.30	0.27	0.33	0.32

The separation of LVAD outcome groups into different categories also shows superior results with the optimization weights (see Table 27), with only two LVAD – 0% patients being categorized as having low to mild risk of RV failure. The distribution of BiVADs into the separate categories in Table 28 shows numerous BiVADs implanted in situations where it appears that they were not necessary, eleven implanted with low to mild risk of surgery and low to mild risk of RV failure. It is hoped that future research will be able to prove the veracity of this conclusion.

Table 27: Number of each LVAD outcome (No RV Failure and RVAD post-implant) in each category (based on weights from optimization)

		Risk of Surgery											
			1 (low)			2 (mild)			3 (moderate)			4 (high)	
Risk of RV failure	1 (low)	L-good	4	80%	L-good	5	83%	L-good	2	100%	L-good	0	
		L-fail	1	20%	L-fail	1	17%	L-fail	0	0%	L-fail	0	
	2 (mild)	L-good	7	100%	L-good	8	100%	L-good	0		L-good	0	
		L-fail	0	0%	L-fail	0	0%	L-fail	0		L-fail	0	
	3 (moderate)	L-good	17	94%	L-good	6	50%	L-good	2	67%	L-good	0	
		L-fail	1	6%	L-fail	6	50%	L-fail	1	33%	L-fail	0	
	4 (severe)	L-good	13	87%	L-good	9	56%	L-good	0		L-good	0	
		L-fail	2	13%	L-fail	7	44%	L-fail	0		L-fail	0	

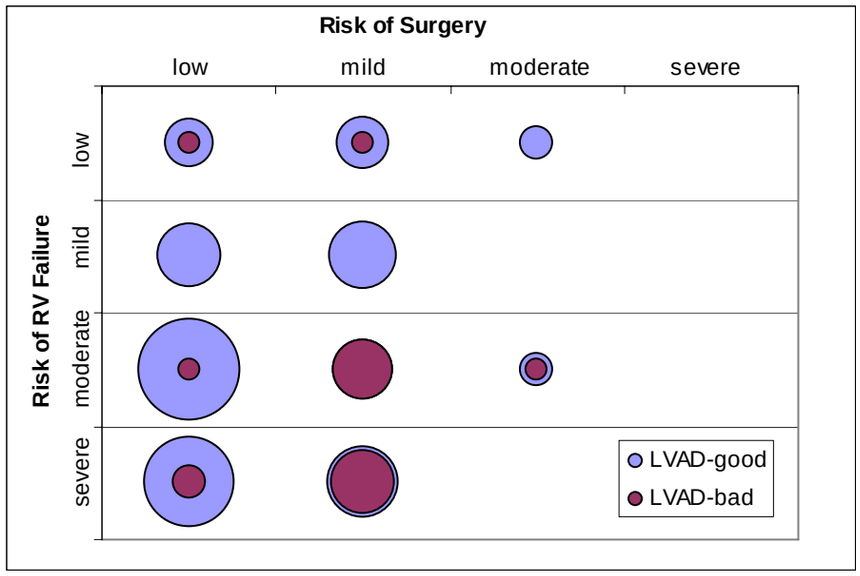

Figure 15: Cluster diagram of LVAD outcomes according to calculated Risk of RV Failure and Risk of Surgery (using weights the optimization) , where the risk decreases from 4 to 0.

Table 28: Number of BiVADs in each category (based on weights from optimization)

BiVADs

		Risk of Surgery			
		1 (low)	2 (mild)	3 (moderate)	4 (high)
Risk of RV Failure	1 (low)	2	5	0	0
	2 (mild)	1	3	1	2
	3 (moderate)	5	4	2	1
	4 (severe)	5	14	2	1

Results from each different sub-category (renal function, hemostasis etc.) using the optimized weights can be found in Appendix D.3. The significant differences between BiVAD patients and all LVAD patients (which includes LVAD- 100% and LVAD- 0%) were: *Hemodynamics*, *Overall Risk of Surgery*, *RV Function*, *Other Assessment*, *Pulmonary Hypertension*, and *Emergency Implant*. Interestingly there was no significant difference found between the final results of these two groups. This is not necessarily indicative of a defect in the model however, because it cannot be concluded that all LVAD patients would not have benefited from BiVAD, and conversely there is the potential that not all the patients who received BiVADs necessarily required RV support. For the BiVAD and LVAD – 100% group, a more valuable comparison, there were more significant differences. Notable amongst these are the combination of *RV*

Failure and Surgery and *L/B Index*. In addition, *Pulmonary Hypertension* was not found to be significantly different. Unlike the results based exclusively on the physicians-supplied weights, the optimized model produced significant difference between the *L/B Index* of the LVAD – 100% and LVAD – 0% groups. The sub-categories still were not significantly different, but the combination of categories resulted in a significant different between *Overall Risk of Surgery, Risk of RV Failure/ Surgery* and the *L/B Index.*

Similar to the results using the Physician #1's weights, the optimized weights also predicted BiVADs for the majority of the LVAD- IS and LVAD- RVF groups as shown in Table 29. When these two categories are grouped with the LVAD – 0%, which is reasonable due to adverse effects of extended inotropic support and the presence of RV failure, even if an RVAD is not implanted, the percentage of correct decisions is unchanged and therefore more BiVADs are correctly implanted. This can be seen in Table 30.

Table 29: According to optimized model the percentage of BiVADs predicted for LVAD – IS and LVAD – RVF groups

	Predicted BiVAD
LVAD - IS	77.8%
LVAD - RVF	62.5%

Table 30: Number of True and False LVADs and BiVADs predicted by the optimization, includes LVAD – RV and LVAD – IS

		LVAD	
		good	fail
Prediction	LVAD	57	12
	BiVAD	16	33

5.0 DISCUSSION

The decision between implanting an LVAD or BiVAD has yet to be definitively defined, despite numerous previous studies. It can be assumed that a simple, completely effective approach is improbable. However, the results of this research are extremely promising. An optimized multi-variate model, implemented in Excel was able to significantly differentiate between the LVAD- 100% and LVAD- 0% patients, and predict the correct outcome in over 70% of the cases. This is a significantly better result than the actual decisions made, where none of the patients in the LVAD-0% group were identified pre-implant.

The differences between physicians even at the same center can be seen by the contrasting weights supplied. Furthermore, the model using the physician-supplied weights did not completely predict the actual decisions that were historically made. This emphasizes the subjectivity by which these decisions are currently made. Although it is difficult for an individual to numerically quantify the criteria and weighting thereof that factors into a decision – as would a computer, one would have anticipated that the individual would be able to consistently adhere to similar guidelines – even while making intuitive decisions. The fact that this is not the case is further evidence of the potential value of a decision-support algorithm such as the one derived in this study. Accordingly, the physician-derived models were not as accurate in predicting outcomes, as compared to the mathematically optimized model. Hence they were more prone to make the "wrong" decisions.

It is important to point out that these conclusions are not necessarily an indictment of the judgment of the physicians who treat these patients. This study can only draw conclusions on the respective *models* of decision process. Not only are there inherent inaccuracies in extracting and uncoupling weighting functions from these individuals, the very structure of the model bears the bias of the engineer-scientist-mathematician who constructed it. Arguably a more accurate model of the decision structure could be created using a neural network approach, the simplicity and intuitiveness of the current approach outweighs the potential disadvantage of its topology.

Estimated waiting time on the transplant waiting list was found to be insignificant. This finding makes logical sense, because the chance of RV Failure is unaffected by the waiting time. However, the reason it is considered is because it affects the quality of life for the patient. In the optimization equation the quality of life was broadly taken

into account, but not individually adjusted for patients who are expected to remain on the device for an extended period of time. It is difficult to predict how much this would affect a particular patient's quality of life, and if mitigates the risk of placing an LVAD into a marginal patient.

Another variable found to be insignificant in the optimized model when differentiating the LVAD- 100% and LVAD- 0% groups is whether the implant is an emergency implant. However there was a significant difference due to this variable between the BiVAD and LVAD- 100% groups, which may simply indicate the physicians' thinking up to this point. It is possible that the physicians' natural bias that emergency implants require a BiVAD is not true. If further tests were done on BiVAD patients following implant this question could be eliminated. Protocols are needed to predict within a day or two after implant whether the RVAD was actually necessary. One way to evaluate this could be to reduce the RVAD flow by 50% and observe the corresponding change in RAP, RVP, PAP, TPG, PVR, and LVAD flows. Or, alternatively, the relationship of RVAD to LVAD flows might be used, although often these flows are manually set and therefore not necessarily a function of the actual need.

Another interesting result from the model is that using the optimized weights it is predicted that 46% of the patients who received BiVADs would have been adequately supported on an LVAD. As stated above, the data currently available does not allow for the assessment of truth in this statement. The collection of additional data needs to be collected in order to arrive at a concrete conclusion. Two conclusions could be drawn from the findings using the optimized model. Either some BiVAD patients could have gotten by with only an LVAD or this model should only be used for those patients for whom it is decided they only need a LVAD, leaving the initial separation between LVAD and BiVAD unchanged. The actual conclusion maybe a combination of those two, where some patients unnecessarily received BiVADs, and others are simply not captured by this model. The model was not designed to identify all of patients should receive a BiVAD, because it was optimized only using the patients who were initially implanted with LVADs.

The largest source of error was the missing data for many of the patients, which severely handicaps the model. For example, right atrial pressures were available for less than 40% of the patients. Therefore it would be advisable to collect an uniform set of data in any prospective study. Based on the sensitivity analysis performed in this model, it can be determined which variables are most valuable to record on a routine basis.

Another inherent source of error, virtually impossible to eliminate, is the non-uniformity of post operative care. For example, RV failure can result from poor fluid management or non-optimal LVAD settings. While patients expected to experienced RV failure can sometimes be carefully managed with inotropes, nitric oxide and other treatments, and avoid the need for an RVAD post LVAD implantation.

An additional source of error in construction of this model is the designation of cutoff value for the objective function. If the arbitrary cutoff (0.5) for the decision to implant an LVAD or BiVAD was shifted, the results would be different, however the overall success would not be improved. Likewise, the formulation of the objective function, which weights the implantation of an RVAD post-implant as twice as severe as an unnecessary BiVAD is open for debate.

Nevertheless, the cutoff may be adjusted to introduce a preference or tolerance of risk: a smaller number would favor implantation of an RVAD over the cost of an "unnecessary" procedure; a larger cutoff would weigh the cost, complexity, associated risk, and diminution of quality of life of RVAD insertion over the potential risk of returning to the OR to insert a device should failure ensue. This additional "adjustment" of the cutoff can be considered in terms of a "Factor of Safety" commonly used in engineering. For example, in spite of a model prediction that a specified structure is safe and will not fail, it is common to oversize the element to account for potential errors in the model, uncertainty in the conditions, and other random effects.

In the case of VAD support, there are additional factors that would affect bias or preference towards a more conservative decision. These would include the age and mobility of the patient, their tolerance of pain, psycholocial status, and other factors that all play into the "big picture."

Regardless of any change in threshold the distributions of LVAD/100% and LVAD/0% determined as a function of calculated *Risk of Surgery* and *Risk of RV Failure* show significant overlap, which explains the difficultly that has been experienced in prior attempts differentiate these two groups. This model based on the physicians' expertise was crucial as a starting point for the optimized model.

It is envisioned that this model will ultimately be developed into either a software tool, or handheld device that may be available to the medical and engineering staff. However further work will be required to completely implement this model in a clinically-acceptable system. A user friendly data entry form needs to be developed and a summary sheet of all the results which is automatically created for each individual patient. Also, additional prospective validation is clearly needed to determine the safety and efficacy of this algorithm. Ideally this should be based on multi-center data. While this model cannot immediately be used in the clinic, it is a promising start. The results with this data set clearly show that the model can differentiate between the LVAD "good" and LVAD "bad" groups, which was not possible simply using statistical analysis of individual variables. The model also gives more output than just the *L/B Index*, the division of the patients into different risk categories can show the physicians results from similar patients. The model could be validated with either a prospective study at UPMC, or retrospective data from other centers. The implementation in Excel™ allows for the model to easily be installed and used on either a personal computer or a handheld device. The decision between implant an LVAD or BiVAD is a complex decision, involving many variables.

This model is able to analytically consider all of the variables and arrive at a decision, which appears to be significantly more accurate that the current decision in the clinic. Furthermore the weights resulting from the optimization can be used independent of the model to elucidate which variables play an important role in the decision and which ones should not be considered.

APPENDIX A

LETTER FOR PHYSICIANS: DIRECTIONS FOR CHOOSING INTERVALS AND WEIGHTS

Dear Dr. _____

Last time we met we discussed assigning intervals and probabilities to all of the variables in the LVAD/BiVAD decision. This document is meant to clarify the information that I need to build this model.

Attached is an excel spreadsheet for collecting the information. It assumes that the probabilities for continuous variables are decided on separately (see below). All of the continuous variables need to filled in with measurement intervals (replace the bilirubin example). All of the risk factors (such as prolonged steroid use) need to be filled out with probability, see example in the sheet. “P” is written in the column to the right to denote that a probability is needed. The probabilities are written in terms of percents (100% = probability of 1.0), and the total of each row should add up to one hundred percent.

There are some variables that may need to be changed or clarified, such as ECHO which obviously in itself is not a measurement, so there is no interval and others like “days on inotropic support” which could be continuous (different intervals of days) or a risk factor for “over 5 days of inotropic support”.

The last two tables are compilation tables, risk of surgery which has some individual variables such as etiology and the other variables that we defined above, such as overall patient health. For those tables weights are needed for all of the variables (show in bold) and probabilities for the individual variables.

Look at this example and let me know if it makes sense to you and what adjustments you think should be made. As I was compiling this I realized how many variables there are and how much information is needed. It may be necessary to pare down the list some.

Step 1:

Break the continuous variable into intervals (the number can vary for different tests if that seems appropriate, the number of intervals shouldn't exceed 5). In this example I will use 4 intervals.

4 intervals (I am just making up these numbers)
Normal total bilirubin: < 1.2 mg/dl
Mild total bilirubin: 1.2 – 1.6 mg/dl
Moderate total bilirubin: 1.6 – 3.0 mg/dl
Severe total bilirubin: > 3.0 mg/dl

Risk factors such as "prolonged steroid use" does not have an interval, instead there will just be a probability distribution for if that risk factor is present.

	Liver dysfunction			
	Normal	Mild	Moderate	Severe
Prolonged steroid use	30%	30%	30%	10%

Step 2:

Each interval needs to be assigned a probability that represents the prediction of total liver function represented by that interval. The simplest would be that each interval corresponded directly to the corresponding category of liver function (there 100% probability), however that would not be realistic. The most complicated way to assign probabilities would be to assign them for each variable as show in table below. Just to explain in words the table: if a person has a value of total bilirubin in the normal range there is 95% chance that there liver function is normal, a 5% chance that he/she has mild liver dysfunction and 0% chance that he/she has moderate or severe dysfunction…

	Liver dysfunction			
Total Bilirubin	Normal	Mild	Moderate	Severe
Normal	95%	5%		
Mild	10%	80%	10%	
Moderate		10%	80%	10%
Severe		5%	20%	75%

I think that determining probabilities for each variable would take too much time and not be worth it. So I propose having one (or maybe two) standard probability distributions that you deem appropriate. Once the probabilities are decided the intervals just need to be determined and I will be able to automatically apply to the agreed upon probabilities to those intervals.

Step 3:

Each variable needs to be weighted according to the other variables in the group (ie group: liver dysfunction there is total bilirubin, liver enzymes and steroid use). I would recommend deciding which variable has the lowest weight, give that variable a weight of 1 and then decide how many times more important each other variable is and give it that number.

APPENDIX B

IRB PROTOCOL

TITLE: **CREATING AN IMPROVED MODEL OF THE DECISION BETWEEN IMPLANTING A LVAD OR A BIVAD**

OBJECTIVES AND SPECIFIC AIMS

Primary Objective:

The primary objective of this study is to design a computer model to analyze the clinical decision between a left ventricular assist device (LVAD) or a bi-ventricular assist device (Bi-VAD) in patients with end-stage heart failure and right ventricular dysfunction who require mechanical assistance. The model will be based on expert opinion and will be validated by data extracted from the Mechanical Circulatory Support Database.

Specific aims:

1. To operationalize the decision making process of choosing univentricular or biventricular support for patients with end-stage heart failure.
2. Incorporating expert opinion (including the significance of each variable) with clinical risk factors to build a computer program to model the LVAD/BiVAD decision.
3. Validate the model using data extracted from the Mechanical Circulatory Support Database and compare the outcomes predicted by the model to historical outcomes.

BACKGROUND AND SIGNIFICANCE

Heart failure secondary to systolic dysfunction is a disease of epidemic proportions in the U.S. with over 5 million effected individuals. Heart failure accounts for over one million hospitalizations, 400,000 deaths, and 40 billion dollars in health care expenses each year with a 5-year survival of less than 50%. Recent advances in therapy for patients with mild to moderate symptoms have improved symptoms, decreased hospitalizations and lengthened survival. Despite these advances, heart failure remains a progressive disease and many patients eventually progress to end-stage disease. Another group of patients with advanced heart failure are those with recent diagnoses, but with rapidly progressive cardiomyopathies. The definitive therapy for such patients is cardiac transplantation, however they may be too unstable to survive the wait for a suitable organ.

Ventricular assist devices have been increasingly utilized since they were first introduced over 20 years ago. **(1-4)** This has been largely due to the growing heart failure epidemic, which in turn has led to growing waiting lists and waiting time for cardiac transplantation. Furthermore, ventricular assist devices are now approved as "destination therapy" or permanent treatment, for end-stage heart failure patients who are not candidates for cardiac transplantation. In addition, there is a growing interest in using these devices for temporary support of a failing ventricle to allow for native recovery of function.

When approaching the patient in need of mechanical ventricular assistance an adequate preoperative assessment of the systolic function of the right ventricle (RV) is crucial to the proper choice of support device. Left ventricular assist (LVAD) function depends on sufficient residual RV function to move blood across the pulmonary circulation and hence provide proper LVAD filling and output. If the RV is deemed too dysfunctional for this task, then a biventricular support device (BiVAD) is required. As patients are surviving longer with and treated more effectively for heart failure their primary cardiomyopathic process eventually leads to some degree of RV dysfunction. There are potentially both beneficial and detrimental effects of left ventricular support on RV function. The RV usually benefits from the decrease in afterload and improvement in compliance mediated through a reduction of the left ventricular filling pressures by the LVAD. However, the increased preload as a result of increased cardiac output and shift of the interventricular septum to the left as a result of left ventricular (LV) decompression can result in RV dysfunction. Hence it is crucial to

adequately assess the RV, as patients with greater degrees of RV dysfunction tend to benefit less from and have a more negative response to LVAD support.

Despite the role for BiVADs in the setting of advanced RV dysfunction, biventricular support comes with higher attendant morbidities including a stroke rate of up to 11%, reoperation for bleeding in 26% and 41% mortality prior to transplantation. **(5)** However, one of the most serious complications after an LVAD is RV failure with a mortality of over 70% prior to transplantation. **(6,7)** Even if the patient survives, poor RV function post-operatively results in chronic volume overload and hence poor hepatic and renal function, diminished exercise capacity and potentially the prolonged need for inotropy. **(8)** There are few reliable clinical predictors in the literature for RV failure after LVAD. **(9-11)**

Significance:

This study will model and improve upon the current process for making the decision between a LVAD and a BiVAD, so that better universal protocols can be developed to match patients to appropriate VAD support, which in turn will improve patient outcomes.

RESEARCH DESIGN AND METHODS

Study Design:

Known risk factors for right ventricular failure or the need for BiVAD in the literature will be assembled. These will be combined with expert opinion to develop the decision making model. This model will then be validated using a retrospectively review of prospectively collected data on patients who have been supported with VAD. Two hundred eighty patients at the University of Pittsburgh Medical Center have been treated with VAD support over the last fifteen years. Of these, approximately 80% of patients have been successfully supported until cardiac transplantation, or in rare cases, device weaning. The data available from the medical records of these patients will be used in this study. In addition, data available in an existing database (IRB# 010134; Data Collection of Heart Transplant Evaluation and Heart Transplant With or Without Mechanical Circulatory Support**)** will be used.

Description:

The medical records and existing database information of patients supported with VAD will be reviewed and information recorded that includes demographics (age, race, ethnicity), past medical history, lab work, drug therapy, all cardiac testing the patient underwent prior and following implant. Status (alive, dead, transplanted, reimplanted on VAD, or VAD weaned), hospitalizations, medications, and all cardiac testing are recorded after initial implantation.

DATA COLLECTION

The protected health information collected on patients who have been supported with a ventricular assist device will be assigned a research code number and any obvious patient identifiers (name, social security number, hospital record number) will be removed from this information. Both the anonymized health information and the information linking the research code numbers to the patients' identities will be kept in a separate secure location. The information linking the research code numbers to the patients' identities will be stored separate from the anonymized health information. Dr. Robert Kormos will assume overall responsibility for the control of this storage area. Access to this information will be limited to investigators: Dr. Kormos, Dr. Teuteberg and Bronwyn Uber at the Cardiovascular Research Center of the University. The data from the existing database will be provided to the principal investigator by the database coordinator under IRB#0101034 and will be de-identified as above after correlation with additional data from the medical record. All the anonymized research information collected from both sources will be saved in a database that is password protected.

DATA ANALYSIS

The data from patients will be used to determine the success rate of the expert based LVAD/BiVAD decision. After the expert algorithm is created the individual cases will be put into the model and the model's decision will be compared to historical outcomes from the database. Regression analysis or other nonlinear approaches also will be used to derive optimal weights and variables from historical data which will then be compared the values determined from the expert opinions.

HUMAN SUBJECTS

***Recruitment Procedures**:*

The study will involve medical record review and database review (IRB#0101034) of up to 300 subjects who have been supported with a ventricular assist device. All patients will be over 18 years of age.

The racial and ethnic characteristics of the proposed subject population reflect the demographics of Pittsburgh and the surrounding area and/or the patient population of the University of Pittsburgh Medical Center. No exclusion criteria shall be based on race, ethnicity, or HIV status.

The Principal investigator, Dr. Robert Kormos, a heart failure cardiologist, Dr. Jeffrey Teuteberg, and bioengineering graduate student, Bronwyn Uber, are requesting a waiver of the informed consent/ HIPPA authorization to access, record and use protected health information/patient medical information of patients who have been implanted with a ventricular assist device.

HIPAA Waiver Criteria and Respective Justifications

Criterion: "The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals based on (a) an adequate plan to protect the identifiers from improper use and disclosure; (b) an adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research (unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law); and (c) adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by this subpart."

Justification: Access to and the use of protected health information by the research investigators who are also involved directly in the care of the respective patients involves no more than a minimal risk to the privacy of these patients since these investigators already have knowledge of and access to the patients' identifiable health information. Moreover, the protected health information that will be accessed, recorded and used by these investigators will be limited to that information which is related to the investigators' area of medical practice.

To further ensure that the risk to the privacy of the involved patients remains minimal the protected health information collected of patients supported with a ventricular assist device will be assigned a research code number and any obvious patient identifiers (name, social security number, hospital record number) will be removed from this information. Both the anonymized health information and the information linking the research code numbers to the patients' identities will be kept in a separate secure location. Dr. Robert Kormos will assume overall responsibility for the control of this storage area. Access to this information will be limited to investigators: Dr. Kormos, Dr. Teuteberg and Bronwyn Uber at the Cardiovascular Research Center of the University. The anonymized research information collected will be saved in a database that is password protected. The information linking the research code numbers to the patients' identities and the anonymized health information will be destroyed at 5 years following the publication of the respective research study in accordance with University policies.

We hereby provide our assurance that any protected health information recorded for the purpose of this research study will not be used by or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study.

Criterion: "The research could not practically be conducted without the waiver or alteration."

Justification: It is not possible to conduct this research study without access to and the use of protected health information. In accordance with the Federal Policy regulations governing human subject protections, the process of accessing identifiable medical record information for the purpose of identifying eligible patients for this research study so as to permit the subsequent obtaining of their HIPAA authorization, itself, requires the prior informed consent of the involved patients. The patients, whose protected health information will be accessed under this waiver request, have not previously provided informed consent for this research activity. Thus, obtaining the HIPAA authorization of these patients for the research use of their health information is impractical. In the absence of obtaining the HIPAA authorization of the patients for the use of their protected health information for research, the IRB and UPMC recommend the involvement of an honest broker system/process to perform an independent (i.e., independent of the research investigators) collection of the protected health information and its subsequent de-identification (in accordance with HIPAA "safe harbor" or "limited data set" standards) prior to providing the information to the research investigators. Such involvement of an independent honest broker system/process is cumbersome and adds expense to

the study, but is typically necessary so as to avoid a violation of the patients' privacy and medical record confidentiality by the research investigators. However, consistent with this waiver request, the research investigators who will access and use the protected health information are also involved directly in the care of the respective patients, thus obviating the privacy and confidentiality concerns. In summary, this research study could not practically be conducted without a waiver of the HIPAA authorization requirement.

Criterion: "The research could not practically be conducted without access to and use of the protected health information."

Justification*:* Access to and the collection and analysis of protected health information is necessary in order to conduct this research study. Consistent with the "minimum necessary standard" of the HIPAA privacy rule, we will only access and collect the specific health information necessary to complete this research study. This research study is limited to accessing, collecting and analyzing existing medical record information. There are no physical or psychological risks to the respective patients associated with the conduct of this research study.

Federal Policy Criteria and Respective Justifications

Criterion: **"The research involves no more than minimal risk."**

Justification*:* This research study is limited to accessing, collecting and analyzing existing medical record information. There are no physical or psychological risks to the human subjects (i.e., the respective patients) associated with the conduct of this research study.

Access to and the collection and analysis of identifiable medical record information for this research study involve no more than a minimal risk to the confidentiality of the respective patients private information based on (a) an adequate plan to protect the identifiers from improper use and disclosure; (b) an adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research; and (c) adequate written assurances that the recorded medical record information will not be reused or disclosed to any other person or entity, except as required by law or for authorized oversight of this research study

Criterion: "The waiver will not adversely affect the rights and welfare of the subjects."

Justification: Consistent with this waiver request, access to and the recording and use of identifiable medical record information for the purpose of this research study will be limited to investigators who are also involved directly in the care of the respective patients. The medical record information that will be accessed, recorded and used by these investigators will be limited to that information which is related to the investigators' area of medical practice. Since these investigators would already have knowledge of and access to such identifiable medical record information for their patient care responsibilities, granting of this waiver will not adversely affect the privacy of the involved patients or the confidentiality of their medical record information.

Criterion: "The research could not practicably be carried out without the waiver."

Justification: It is not possible to conduct this research study without access to and the use of the patients' medical record information. In accordance with the Federal Policy regulations governing human subject protections, the process of accessing identifiable medical record information for the purpose of identifying eligible patients for this research study so as to permit the subsequent obtaining of their informed consent, itself requires the prior informed consent of the involved patients. The patients, whose protected health information will be accessed under this waiver request, have not previously provided informed consent for this research activity. Thus, obtaining the informed consent of these patients for the collection and use of their identifiable medical record information for the purpose of this research study is impractical. In the absence of obtaining the informed consent of the patients for the use of their identifiable medical record information for research, the IRB and UPMC recommend the involvement of an honest broker system/ process to perform an independent (i.e., independent of the research investigators) collection of the requisite medical record information and its subsequent de-identification prior to providing the information to the research investigators. Such involvement of an independent honest broker system/process is cumbersome and adds expense to the study, but is typically necessary so as to avoid a violation of the patients' privacy and medical record confidentiality by the research investigators. However, consistent with this waiver request, the research investigator(s) who will access and use the patients' identifiable medical record information is (are) also involved directly in the care of the patients, thus obviating the privacy and confidentiality concerns. In summary, this research study could not practically be conducted without a waiver of the HIPAA authorization requirement

Criterion: “Whenever appropriate, the subjects will be provided with additional pertinent information after participation.”

Justification: Should the analysis of the medical record information collected for the purpose of this research study reveal a situation that may impact on the health of a patient, the investigators, who are also involved in the care of the respective patient, will promptly notify the patient and offer the availability of care.

RISKS AND BENEFITS

There is a small risk of breach in confidentiality

As a retrospective study, there is no potential benefit for the patients in this study. The results of the study should benefit future patients with this disorder.

Confidentiality

All clinical data will be coded to protect confidentiality and no participant will be identified in any publication. All research records will be kept separate from the participant’s medical records. Any information about the participant obtained from this research will be kept as confidential as possible.

All forms related to this research study will be stored in a locked file cabinet. Only the researchers involved in this retrospective study and the research coordinator will have access to the anonymized research records. Patients successfully weaned from VAD support will have their identity on these records indicated by a case number rather than by name, and the information linking these case numbers with their identity will be kept separate from the research records. Only Dr. Robert Kormos will have access to the linkage codes. The comparison data (age, sex, diagnosis, hemodynamics and evaluation of left ventricular function) from the existing database will be de-identified and provided to the principal investigator by the database coordinator under IRB#0101034. All the anonymized research information collected from both sources will be saved in a database that is password protected.

Data Safety Monitoring Board:

This is a retrospective study conducted by investigators at the University of Pittsburgh Medical Center. The Data Safety Monitoring Plan will consist of the Principal Investigator of this study, Dr. Robert Kormos, and the study coordinator. Breaches in confidentiality will be monitored every six months. All adverse events will be reported to the IRB as outlined in Chapter 30, Sections 3.4- 3.5 of the IRB reference manual. Reports from the Data and Safety Monitoring committee will be sent to the IRB at the time of annual renewal.

COST AND PAYMENTS

There is no cost to patient for inclusion into this retrospective study.

QUALIFICATIONS OF THE INVESTIGATORS

Dr. Robert Kormos is a Professor of Surgery and the Director of Heart Transplantation and the Artificial Heart Program.

Dr. Jeffrey Teuteberg is a faculty member of the Heart Failure Section at the University of Pittsburgh Medical Center.

Bronwyn Uber is a bioengineering graduate student at University of Pittsburgh.

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APPENDIX C

SUMMARIES OF PATIENT DATA

Table 31: Summary of all VAD Patients

	Average	STDV
Age (yr)	49.8	12
Weight (kg)	81.5	17.9
% Female	19.4%	
% Emergency Implant	23%	
CPB time (mins)	111	57.6
Ventilator post-implant (day)	4.5	7.6
Implant date	First: 2/05/90	
	Last: 7/1/2005	

Table 32: Summary of all Patients with a BiVAD

	Average	STDV
Age (yr)	48.3	12.3
Weight (kg)	78.4	16.6
% Female	31.4%	
% Emergency Implant	41%	
CPB time (mins)	149.58	59.6
Ventilator post-implant (day)	5.2	9
Implant date	First: 3/09/92	
	Last: 3/31/05	

Table 33: Summary of All Patients with an LVAD

	Average	STDV
Age (yr)	50.4	12
Weight (kg)	79.5	17.9
% Female	14.3%	
% Emergency Implant	11.1%	
CPB time (mins)	92.7	47.8
Ventilator post-implant (day)	4.3	7
Implant date	First: 2/05/90	
	Last: 7/01/05	

Table 34: Summary of LVAD - 100% Patients (No RV Failure)

	Average	STDV
Age (yr)	48	12.2
Weight (kg)	78.7	19
% Female	15.1%	
% Emergency Implant	9%	
CPB time (mins)	80.5	22.3
Ventilator post-implant (day)	3.5	6.9
Implant date	First: 2/05/90	
	Last: 8/17/04	

Table 35: Summary of LVAD - 0% (RVAD post-implant)

	Average	STDV
Age (yr)	54.2	8.9
Weight (kg)	81.2	15.4
% Female	10.5%	
% Emergency Implant	12.5%	
CPB time (mins)	100	33.5
Ventilator post-implant (day)	5.9	5.5
Implant date	First: 10/12/91	
	Last: 8/18/04	

Table 36: Comparison of data from all BiVAD and LVAD patients (If p<0.05 is not listed then difference in averages are not statistically different)

		All BiVADs		All LVADs	
	ttest	% TRUE	Average	% TRUE	Average
Hepatic Function					
Total Bilirubin			1.31		1.27
ALT			98.22		71.61
AST			80.04		63.92
Renal Function					
Creatinine			1.72		1.39
Renal Dysfunction		26.67% (n=30)		19.75% (n=81)	
On Dialysis ?		11.11% (n=9)		0% (n=28)	
Pulmonary Function					
Mech. Vent?		10.26% (n=39)		14.1% (n=78)	
ECMO support?		0% (n=9)		3.85% (n=26)	
Pulmonary disease		17.86% (n=28)		19.75% (n=81)	
Coagulopathy					
PTT			54.23		49.62
INR			1.26		1.30
Platelet count			182.63		209.08
Hematocrit			31.96		33.23
Hemodynamics					
NYHA class			3.53		3.35
# of inotropes			1.44		1.18
PCW			26.32		24.79
PA sat			48.11		51.91
CI	p<0.05		1.99		2.23
IABP support?		67.35% (n=49)		63.25% (n=117)	
ECMO support?		0% (n=8)		3.45% (n=29)	
Infection					
WBC count			10.30		10.24
Co-morbidities					
PVD		9.09% (n=33)		11% (n=100)	
Diabetes		40% (n=35)		18.45%(n=103)	
Previous sternotomy		40% (n=40)		25.77% (n=99)	
Pulmonary disease		17.86% (n=28)		20.99% (n=81)	
Smoker		64.52% (n=31)		64.71% (n=85)	
Albumin < 3		23.08% (n=13)		29.79% (n=47)	
Renal Dysfunction		26.67% (n=30)		17.72% (n=79)	
Pulmonary Hypertension					
PA - systolic			49.23		50.40
PA - mean			35.02		34.33
TPG			8.84		10.00
PVR (woods units)			2.41		2.81
RV Function					
RAP	p<0.05		15.41		11.85
RV systolic			47.54		52.22
TR (>=mod-sev)		100% (n=13)		59.26% (n=27)	
Operative Assessment					
RAP	p<0.05		15.41		11.85
mean PAP			35.02		34.33
CI	p<0.05		1.99		2.23
CPB time (mins)	p<0.05		149.78		92.67
Estimated Waiting Time					
blood type: A		18.37%		38.33%	
blood type: B		0		9.17%	
blood type: AB		4.08%		5.00%	
blood type: O		53.06%		47.50%	
weight (kg)			78.41		79.46
Etiology					
Ischemic acute		4.08%		3.33%	
Ischemic non-acute		46.94%		45.00%	
Non-ischemic acute		12.24%		1.67%	
Non-ischemic non-acute		40.82%		50.00%	

Table 37: Comparison of data from all BiVAD and LVAD patients without RV Failure (If $p<0.05$ is not listed then difference in averages are not statistically different)

		All BiVADs		LVAD 100%	
	ttest	% TRUE	Average	% TRUE	Average
Hepatic Function					
Total Bilirubin			1.31		1.40
ALT			98.22		61.11
AST			80.04		64.40
Renal Function					
Creatinine	p<0.05		1.72		1.28
Renal Dysfunction		26.67% (n=30)		12.24% (n=49)	
On Dialysis ?		11.11% (n=9)		0% (n=11)	
Pulmonary Function					
Mech. Vent?		10.26% (n=39)		11.36% (n=44)	
ECMO support?		0% (n=9)		8.33% (n=12)	
Pulmonary disease		17.86% (n=28)		12.24% (n=49)	
Coagulopathy					
PTT			54.23		49.66
INR			1.26		1.29
Platelet count			182.63		212.21
Hematocrit			31.96		33.01
Hemodynamics					
NYHA class			3.53		3.29
# of inotropes			1.44		1.19
PCW			26.32		24.11
PA sat			48.11		51.62
CI	p<0.05		1.99		2.31
IABP support?		67.35% (n=49)		62.5% (n=72)	
ECMO support?		0% (n=8)		6.67% (n=15)	
Infection					
WBC count			10.30		10.42
Co-morbidities					
PVD		9.09% (n=33)		6.45% (n=62)	
Diabetes		40% (n=35)		17.74% (n=62)	
Previous sternotomy		40% (n=40)		22.81% (n=57)	
Pulmonary disease		17.86% (n=28)		14.29% (n=49)	
Smoker		64.52% (n=31)		59.26% (n=54)	
Albumin < 3		23.08% (n=13)		23.53% (n=34)	
Renal Dysfunction		26.67% (n=30)		10.42% (n=48)	
Pulmonary Hypertension					
PA - systolic			49.23		48.48
PA - mean			35.02		32.82
TPG			8.84		9.30
PVR (woods units)			2.41		2.74
RV Function					
RAP	p<0.05		15.41		10.92
RV systolic			47.54		50.60
TR (>=mod-sev)		100% (n=13)		53.33% (n=15)	
Operative Assessment					
RAP	p<0.05		15.41		10.92
mean PAP			35.02		32.82
CI	p<0.05		1.99		2.31
CPB time (mins)	p<0.05		149.78		80.46
Estimated Waiting Time					
blood type: A		18.37%		43.84%	
blood type: B		0		6.85%	
blood type: AB		4.08%		5.48%	
blood type: O		53.06%		43.84%	
weight (kg)			78.41		78.67
Etiology					
Ischemic acute		4.08%		1.37%	
Ischemic non-acute		46.94%		45.21%	
Non-ischemic acute		12.24%		1.37%	
Non-ischemic non-acute		40.82%		52.05%	

Table 38: Comparison of data from LVAD patients without RV Failure and with RVAD post-implant (none of the averages are significantly different)

		LVAD 100%		LVAD 0%	
	ttest	% TRUE	Average	% TRUE	Average
Hepatic Function					
Total Bilirubin			1.40		1.39
ALT			61.11		98.00
AST			64.40		68.09
Renal Function					
Creatinine			1.28		1.65
Renal Dysfunction		12.24% (n=49)		15.38% (n=13)	
On Dialysis ?		0% (n=11)		0% (n=2)	
Pulmonary Function					
Mech. Vent?		11.36% (n=44)		25% (n=12)	
ECMO support?		8.33% (n=12)		0% (n=3)	
Pulmonary disease		12.24% (n=49)		23.08% (n=13)	
Coagulopathy					
PTT			49.66		53.33
INR			1.29		1.27
Platelet count			212.21		204.45
Hematocrit			33.01		34.10
Hemodynamics					
NYHA class			3.29		3.44
# of inotropes			1.19		0.82
PCW			24.11		23.84
PA sat			51.62		48.66
CI			2.31		2.19
IABP support?		62.5% (n=72)		57.9% (n=19)	
ECMO support?		6.67% (n=15)		0% (n=3)	
Infection					
WBC count			10.42		12.78
Co-morbidities					
PVD		6.45% (n=62)		11.11% (n=18)	
Diabetes		17.74% (n=62)		5.56% (n=18)	
Previous sternotomy		22.81% (n=57)		26.67% (n=15)	
Pulmonary disease		14.29% (n=49)		23.08% (n=13)	
Smoker		59.26% (n=54)		76.92% (n=13)	
Albumin < 3		23.53% (n=34)		28.57% (n=7)	
Renal Dysfunction		10.42% (n=48)		15.38% (n=13)	
Pulmonary Hypertension					
PA - systolic			48.48		54.00
PA - mean			32.82		36.37
TPG			9.30		11.47
PVR (woods units)			2.74		2.82
RV Function					
RAP			10.92		13.83
RV systolic			50.60		52.56
TR (>=mod-sev)		53.33% (n=15)		100% (n=1)	
Operative Assessment					
RAP			10.92		13.83
mean PAP			32.82		36.37
CI			2.31		2.19
CPB time (mins)			80.46		100.6
Estimated Waiting Time					
blood type: A		43.84%		36.84%	
blood type: B		6.85%		15.79%	
blood type: AB		5.48%		5.26%	
blood type: O		43.84%		42.11%	
weight (kg)			78.67		81.24
Etiology					
Ischemic acute		1.37%		5.26%	
Ischemic non-acute		45.21%		47.37%	
Non-ischemic acute		1.37%		0.00%	
Non-ischemic non-acute		52.05%		47.37%	

APPENDIX D

RESULTS

D.1 RESULTS USING WEIGHTS FROM PHYSICIAN #1

Table 39: Comparison of data from all BiVAD and LVAD patients based on weights from Physician #1 (If $p<0.05$ is not listed then difference in averages are not statistically different)

		All BiVADs	All LVADs
	ttest	Average	Average
Overall Risk of Surgery			
Etiology		0.46	0.48
Hemodynamics	p<0.05	0.14	0.25
Hepatic Function		0.75	0.84
Renal Function		0.70	0.77
Pulmonary Function		0.81	0.78
Hemostasis		0.54	0.65
Infection		0.52	0.60
Co-morbidities	p<0.05	0.71	0.86
Result	p<0.05	0.57	0.66
Overall Risk of RV Failure			
RV function (pre-op)	p<0.05	0.12	0.28
Other Assessment	p<0.05	0.35	0.52
Pulmonary Hypertension		0.33	0.28
Result	p<0.05	0.31	0.43
Final Result			
RV failure/surgery	p<0.05	0.12	0.50
Waiting		0.35	0.61
Timing	p<0.05	0.33	0.02
Result	p<0.05	0.31	0.52

Table 40: Comparison of data from all BiVAD and LVAD patients without RV Failure based on weights from Physician #1 (If $p<0.05$ is not listed then difference in averages are not statistically different)

		All BiVADs	LVAD 100%
	ttest	Average	Average
Overall Risk of Surgery			
Etiology		0.46	0.50
Hemodynamics	p<0.05	0.14	0.28
Hepatic Function		0.75	0.84
Renal Function	p<0.05	0.70	0.83
Pulmonary Function		0.81	0.80
Hemostasis		0.54	0.67
Infection		0.52	0.56
Co-morbidities	p<0.05	0.71	0.90
Result	p<0.05	0.57	0.68
Overall Risk of RV Failure			
RV function (pre-op)	p<0.05	0.12	0.35
Other Assessment	p<0.05	0.35	0.54
Pulmonary Hypertension		0.33	0.34
Result	p<0.05	0.31	0.47
Final Result			
RV failure/surgery	p<0.05	0.12	0.57
Waiting		0.35	0.60
Timing	p<0.05	0.33	0.01
Result	p<0.05	0.31	0.57

Table 41: Comparison of data from LVAD patients without RV Failure and with RVAD post-implant based on weights from Physician #1 (none of the averages are significantly different)

		LVAD 100%	LVAD 0%
	ttest	Average	Average
Overall Risk of Surgery			
Etiology		0.50	0.45
Hemodynamics		0.28	0.25
Hepatic Function		0.84	0.80
Renal Function		0.83	0.74
Pulmonary Function		0.80	0.66
Hemostasis		0.67	0.64
Infection		0.56	0.47
Co-morbidities		0.90	0.91
Result		0.68	0.64
Overall Risk of RV Failure			
RV function (pre-op)		0.35	0.20
Other Assessment		0.54	0.46
Pulmonary Hypertension		0.34	0.21
Result		0.47	0.36
Final Result			
RV failure/surgery		0.57	0.40
Waiting		0.60	0.59
Timing		0.01	0.03
Result		0.57	0.46

D.2 RESULTS USING WEIGHTS FROM PHYSICIAN #2

Table 42: Comparison of data from all BiVAD and LVAD patients based on weights from Physician #2 (If $p<0.05$ is not listed then difference in averages are not statistically different)

		All BiVADs	All LVADs
	ttest	Average	Average
Overall Risk of Surgery			
Etiology		0.46	0.47
Hemodynamics	p<0.05	0.43	0.58
Hepatic Function		0.75	0.84
Renal Function		0.70	0.76
Pulmonary Function		0.81	0.78
Hemostasis		0.95	0.98
Infection		0.80	0.85
Co-morbidities	p<0.05	0.54	0.74
Result	p<0.05	0.64	0.77
Overall Risk of RV Failure			
RV function (pre-op)	p<0.05	0.26	0.51
Other Assessment	p<0.05	0.32	0.54
Pulmonary Hypertension		0.33	0.28
Result	p<0.05	0.32	0.48
Final Result			
RV failure/surgery	p<0.05	0.26	0.60
Waiting		0.32	0.61
Timing	p<0.05	0.33	0.02
Result	p<0.05	0.32	0.59

Table 43: Comparison of data from all BiVAD and LVAD patients without RV Failure based on weights from Physician #2 (If $p<0.05$ is not listed then difference in averages are not statistically different)

		All BiVADs	LVAD 100%
	ttest	Average	Average
Overall Risk of Surgery			
Etiology		0.46	0.50
Hemodynamics	p<0.05	0.43	0.58
Hepatic Function		0.75	0.84
Renal Function		0.70	0.83
Pulmonary Function		0.81	0.80
Hemostasis		0.95	0.98
Infection		0.80	0.83
Co-morbidities	p<0.05	0.54	0.82
Result	p<0.05	0.64	0.80
Overall Risk of RV Failure			
RV function (pre-op)	p<0.05	0.26	0.61
Other Assessment	p<0.05	0.32	0.56
Pulmonary Hypertension		0.33	0.34
Result	p<0.05	0.32	0.51
Final Result			
RV failure/surgery	p<0.05	0.26	0.62
Waiting		0.32	0.60
Timing	p<0.05	0.33	0.01
Result	p<0.05	0.32	0.60

Table 44: Comparison of data from LVAD patients without RV Failure and with RVAD post-implant based on weights from Physician #2 (none of the averages are significantly different)

		LVAD 100%	LVAD 0%
	ttest	Average	Average
Overall Risk of Surgery			
Etiology		0.50	0.45
Hemodynamics		0.58	0.69
Hepatic Function		0.84	0.80
Renal Function		0.83	0.73
Pulmonary Function		0.80	0.65
Hemostasis		0.98	0.98
Infection		0.83	0.83
Co-morbidities		0.82	0.78
Result		0.80	0.76
Overall Risk of RV Failure			
RV function (pre-op)		0.61	0.44
Other Assessment		0.56	0.49
Pulmonary Hypertension		0.34	0.21
Result		0.51	0.45
Final Result			
RV failure/surgery		0.62	0.56
Waiting		0.60	0.59
Timing		0.01	0.03
Result		0.60	0.57

D.3 RESULTS USING WEIGHT FROM THE OPTIMIZATION

Table 45: Comparison of data from all BiVAD and LVAD patients based on weights from optimization (If $p<0.05$ is not listed then difference in averages are not statistically different)

		All BiVADs	All LVADs
	ttest	Average	Average
Overall Risk of Surgery			
Etiology		0.46	0.48
Hemodynamics	p<0.05	0.15	0.27
Hepatic Function		0.79	0.86
Renal Function		0.70	0.77
Pulmonary Function		0.81	0.78
Hemostasis		0.90	0.94
Infection		0.52	0.60
Co-morbidities		0.76	0.86
Result	p<0.05	0.63	0.71
Overall Risk of RV Failure			
RV function (pre-op)	p<0.05	0.10	0.28
Other Assessment	p<0.05	0.29	0.43
Pulmonary Hypertension	p<0.05	0.48	0.33
Result		0.34	0.36
Final Result			
RV failure/surgery		0.10	0.51
Waiting		0.29	0.61
Timing	p<0.05	0.48	0.01
Result		0.34	0.51

Table 46: Comparison of data from all BiVAD and LVAD patients without RV Failure based on weights from optimization (If $p<0.05$ is not listed then difference in averages are not statistically different)

		All BiVADs	LVAD 100%
	ttest	Average	Average
Overall Risk of Surgery			
Etiology		0.46	0.50
Hemodynamics	p<0.05	0.15	0.29
Hepatic Function		0.79	0.86
Renal Function	p<0.05	0.70	0.83
Pulmonary Function		0.81	0.80
Hemostasis		0.90	0.95
Infection		0.52	0.56
Co-morbidities	p<0.05	0.76	0.90
Result	p<0.05	0.63	0.74
Overall Risk of RV Failure			
RV function (pre-op)	p<0.05	0.10	0.38
Other Assessment	p<0.05	0.29	0.45
Pulmonary Hypertension		0.48	0.38
Result		0.34	0.40
Final Result			
RV failure/surgery	p<0.05	0.10	0.62
Waiting		0.29	0.60
Timing	p<0.05	0.48	0.01
Result	p<0.05	0.34	0.62

Table 47: Comparison of data from LVAD patients without RV Failure and with RVAD post-implant based on weights from optimization (note: Final Result is statistically different)

		LVAD 100%	LVAD 0%
	ttest	Average	Average
Overall Risk of Surgery			
Etiology		0.50	0.46
Hemodynamics		0.29	0.24
Hepatic Function		0.86	0.81
Renal Function		0.83	0.74
Pulmonary Function		0.80	0.66
Hemostasis		0.95	0.92
Infection		0.56	0.47
Co-morbidities		0.90	0.91
Result	p<0.05	0.74	0.68
Overall Risk of RV Failure			
RV function (pre-op)		0.38	0.18
Other Assessment		0.45	0.40
Pulmonary Hypertension		0.38	0.24
Result		0.40	0.29
Final Result			
RV failure/surgery	p<0.05	0.62	0.33
Waiting		0.60	0.59
Timing		0.01	0.01
Result	p<0.05	0.62	0.33

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