CLINICAL DECISION SUPPORT SYSTEM FOR OPTIMAL VAD WEANING

by

Linda Caroline Santelices

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This thesis was presented

by

Linda Caroline Santelices

It was defended on

July 6, 2005

and approved by

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

Marek J. Druzdzel, Ph.D., Associate Professor, School of Information Sciences

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

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Linda Caroline Santelices, MS

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Ventricular Assist Devices (VADs) have demonstrated their therapeutic role in cardiac rehabilitation. However, due to the complexities of caring for these patients and the relatively limited clinical experience, identifying candidates for weaning remains challenging. This study proposes the use of a Clinical Decision Support System (CDSS) to both aid in the identification of VAD weaning candidates, and as a tool for predicting patient outcome.

Based upon the UPMC VAD weaning experience, three CDSS models were developed: an expert model, a data model, and an expert/data hybrid model. The decision structures of the expert model were elicited from an 11 member, multi-disciplinary panel through a series of structured interviews and polls. Pattern recognition through Artificial Neural Networks and Natural Language Processing was used to analyze patient data and acquire the decision structures for the data model; all patients receiving a Thoratec VAD which were considered for weaning between 1996 and 2004 (n=19), regardless of outcome, were included in this study. Decision structures were modeled using Bayesian Belief Networks and their predictive values were assessed. A user interface, based on a pocket-PC, was developed to anticipate the translation of this system to clinical practice.

The hybrid model, consisting of a 21-parameter health screening and a 3-tier evaluation of cardiac recovery, was the best predictor of outcome, predicting 90% true weans, 100% true transplants, 0% false weans and 10% false transplants. By objectively combing knowledge from experts and data, this study illustrates how a CDSS can facilitate the decision making processes for identifying VAD weaning candidates and promote responsible and widespread use of VADs for cardiac rehabilitation.

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-Sir Isaac Newton, 1675

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1.0 INTRODUCTION

There is mounting evidence to suggest that the use of Ventricular Assist Devices (VADs) for the treatment of end-stage congestive heart failure can lead to myocardial recovery. In addition to providing circulatory support, studies report that by unloading the native ventricle with a VAD, the myocardium "reverse remodels" and indices of cardiac function improve [1-11]. Furthermore, several medical centers have reported the experience of recovery in patients who were supported while awaiting heart transplants [12-25]. In these cases, patients were weaned from VAD support and the devices were explanted, thus allowing the patients to forego a transplant altogether.

Despite the promising evidence for the use of VADs as a mechanism for recovery, the incidence of VAD weaning remains low [26, 27]. Due to the complexities of caring for these patients and the relatively limited clinical experience, identification of VAD weaning candidates presents a significant challenge.

Identifying these candidates requires that the clinicians, who make a decision regarding the patient's condition, do so under a large degree of uncertainty. Moreover, they must speculate as to the patients' benefit from weaning (versus a transplant) and find a way to combine the opinions of the entire clinical team. The manner in which clinicians face these challenges requires objectivity and time to assess all alternatives— a major difficulty in an atmosphere where decisions must be made quickly.

This study proposes the use of a Clinical Decision Support System as an aid in overcoming these challenges. By integrating expert- and data-derived knowledge into a portable, computer-based decision model, this study illustrates how such a system may aid in the identification and evaluation of VAD weaning candidates.

2.0 BACKGROUND

2.1 HEART FAILURE

The American Heart Association reports that in the United States alone, heart failure affects 4,900,000 people and associated costs amount to $27.9 billion each year. With 550,000 new cases diagnosed annually, congestive heart failure (CHF) has become a national epidemic, causing and contributing to approximately 300,000 deaths per year [28].

CHF can be defined as the inability of the heart to pump enough blood to sustain normal bodily functions. Risk factors include smoking, high cholesterol, diabetes, drug and alcohol abuse, and obesity. Causes include coronary artery disease, hypertension, metabolic disorder, infection, toxin exposure, valvular heart disease, and severe anemia [29, 30].

Signs and symptoms of heart failure include a decrease in cardiac output, an increase in ventricular filling pressures, and exercise intolerance. In response to these conditions, the body attempts to maintain homeostasis by augmenting blood volume via salt and water retention, maintaining pressure for perfusion of the vital organs via vasoconstriction, and increasing heart rate and ejection via sympathetic stimulation. In the long-term, this physiological response only exacerbates the condition. By retaining salt and water, the kidneys are adversely affected and the pulmonary and systemic venous systems become congested. Vasoconstriction and sympathetic

stimulation increase the energy expenditure of the heart which can lead to a dilated heart with impaired contractility. The pathogenesis of heart failure is detailed in Figure 1 below [31].

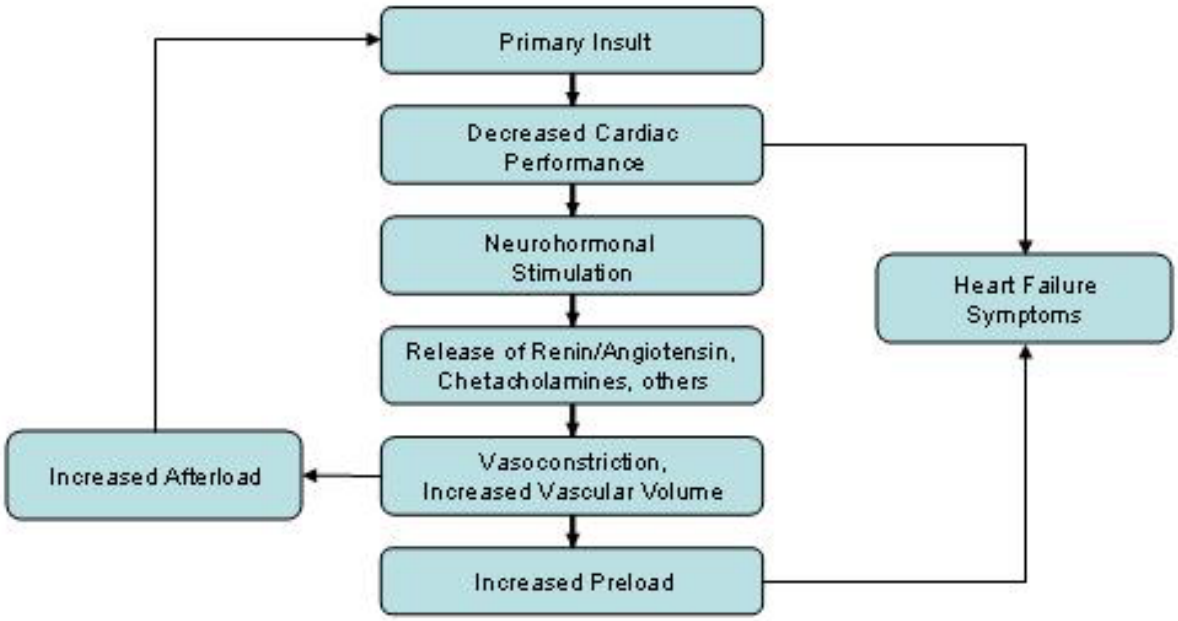

Figure 1: Pathogenesis of Congestive Heart Failure

2.1.1 Treatment Options

Treatment of CHF depends upon the severity of the condition. As shown in Figure 2, treatment modalities include lifestyle changes, pharmacotherapy, surgical intervention and mechanical circulatory assist.

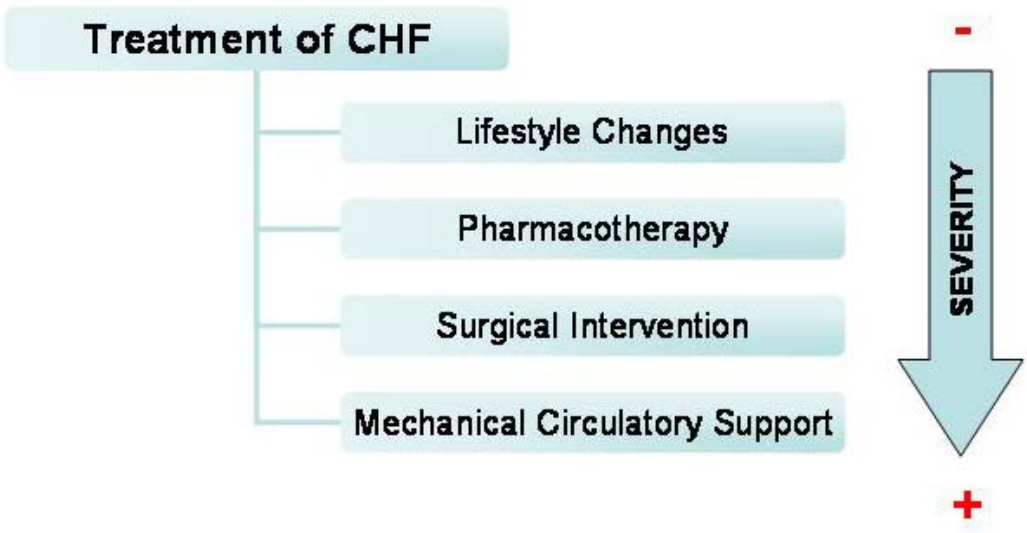

Figure 2: Treatment options for Congestive Heart Failure

Lifestyle changes are non-surgical, non-pharmacological treatments that are useful in less severe cases of heart failure. In this type of treatment, the clinician may advise the patient to exercise and eliminate certain foods from their diet. In addition, the patient should be educated regarding their disease and psychological intervention may be suggested. If the patient does not respond to these changes, pharmacotherapy may be added to their treatment.

There are several types of pharmacotherapy used to treat CHF: Diuretics, ACE Inhibitors, Beta Blockers, Inotropes, and Antirrhythmics. Diuretics assist in decreasing blood volume, or preload, by increasing the secretion of salt and water. ACE (Angiotensin Converting Enzyme) Inhibitors regulate the vasoconstrictive, and salt retentive actions of angiotensin. Beta Blockers decrease afterload, heart rate and renin release. Inotropes increase contractility to improve cardiac output. Antirrhythmics reduce the frequency and/or severity of arrhythmias. If the patient does not respond to pharmacotherapy, more aggressive treatment is often warranted.

Some minimally invasive procedures exist, which include angioplasty, coronary stents, and implanted pacemakers or defibrillators. However, more invasive surgical treatment is usually needed for severe heart failure patients. This may include coronary artery bypass surgery, valve repair/replacement, and ventricular remodeling. Patients who do not respond to these surgical interventions will typically require a heart transplant.

Heart transplants have been performed since 1967 and for patients with end-stage heart failure, transplantation offers the chance to extend life or improve the quality of remaining life; 71% of heart transplant recipients survive five years after transplant and, on average, the transplant will extend the patient's life by 9 years [28, 32, 33]. However transplantation is not without its problems. For example, to prevent rejection of the heart, the patient must receive chronic immunosuppressive therapy [34]. This therapy not only compromises the patient to infection, it also severely affects their quality of life [35]. As the demand for donor organs far exceeds the supply, approximately 70% of these patients are placed on a form of life support, including mechanical circulatory assist devices, while waiting for a transplant [32].

2.2 VENTRICULAR ASSIST DEVICES

In the United States, the use of mechanical circulatory assist devices has been increasing to accommodate those for whom a transplant is unavailable in a timely fashion, and also for those who are ineligible for transplant [36-38].

One of the widely used mechanical circulatory assist devices is the Ventricular Assist Device (VAD). This device restores blood flow, unloads the native ventricle and can support either the systemic circulation through the left ventricle, the pulmonary circulation through the right ventricle, or both.

VADs restore flow through either an electromechanically, pneumatically, magnetically, or hydraulically driven pump. These pumps can be classified as displacement pumps, which produce pulsatile flow, or rotary pumps, which produce continuous flow. The VAD is placed either extra- or intra-corporeally and the pump is powered by an implanted or external power source. Blood enters the pump though a cannula connected to the ventricle and is ejected into the body's arterial system through an outflow cannula. The VAD is monitored by an electronic controller that can respond to the recipient’s changing heartbeat and circulatory demands. A collection of various VADs is shown in Figure 3.

Although VADs are most often used to support the circulation of patients awaiting a donor heart, they are also used as temporary support for patients whose native heart is recoverable, and as permanent support for patients ineligible for transplant.

Figure 3: Ventricular Assist Devices

2.2.1 Bridge to Transplant

In 1969, Cooley et al were the first to use a VAD for supporting a patient awaiting transplantation [39]. This strategy of VAD therapy has since been termed “Bridge to Transplant” (BTT). In this case, there is no expectation for recovery of the heart, rather, the purpose of VAD support is to maintain blood flow and end organ function until a transplant becomes available.

In the United States, approximately 15% of transplant candidates require a VAD as a BTT [40]. The Food and Drug Administration (FDA) has approved the following four pulsatile VADs for use as a BTT: Thoratec, HeartMate 1000 IP, HeartMate VE, and Novacor.

When compared to patients managed by medical therapy alone, the use of VADs as a BTT has been shown to improve both clinical and quality of life outcomes and even lower expenses [20, 41-45]. This technology has made it possible for patients to be discharged from the hospital and await a donor heart from home. Furthermore, at least 67% of these patients survive to receive a donor heart and one-year post-transplant survival is 80%-- these results equal or exceed the survival rate in patients who undergo transplant alone [46, 47].

2.2.2 Destination Therapy

In cases where CHF patients are ineligible for transplant, VADs can be used to provide permanent circulatory support. This strategy of VAD therapy has been termed “Destination Therapy” (DT). As a result of the landmark REMATCH (Randomized Evaluation of Mechanical Assistance Therapy as an Alternative in Congestive Heart Failure) study, the FDA recently approved the HeartMate LVAD for DT. In the REMATCH study, it was concluded that even if no chance of transplant exists, long-term use of an LVAD can significantly improve survival rates and quality of life [48]. Although promising, DT is associated with only modest long-term device reliability and high costs.

2.2.3 Bridge to Recovery

"The heart, like any other diseased organ, improves with rest."

-George Burch, 1966 [49]

In some cases, VADs are used to temporarily support patients while the native heart recovers. After the heart has recovered its function, patients can be weaned from support and the device can be removed. This strategy of VAD therapy has been termed "Bridge to Recovery" (BTR). Currently, the FDA has only approved BTR for post-cardiotomy cardiogenic shock patients—patients who cannot be weaned from a cardiopulmonary bypass machine following open heart surgery. However, several medical centers have reported instances in which BTT patients have recovered function of their heart while waiting for a transplant; many of these patients were able to be weaned from VAD support and remain device/transplant free [12-25]. Recovery in BTT patients is a promising option; the patient is able to forego a transplant altogether, thereby avoiding the long-term complications associated with transplantation and opening up the availability of the organ for another patient on the waiting list.

Due to the large number of patients who could potentially benefit from BTR, in recent years, research efforts have been geared towards understanding the mechanisms behind VAD-induced myocardial recovery and learning from the collected clinical experience with weaning.

2.2.3.1 Myocardial Recovery. Improvement in indices of cardiac function as well as biological and histological remodeling of the myocardium of VAD recipients has been reported in numerous studies. The reversibility of CHF at the functional, structural, cellular, and molecular levels has been termed "reverse remodeling" [11].

A Columbia Presbyterian case study published in 1996 reported that at the time of intended transplantation, a VAD patient's native heart had returned to a normal geometry, had a normal ejection fraction, and was able to maintain normal pressures and flows [1]. Similarly, several other centers have reported an improvement in ejection fraction, increased exercise capacity and normalization of heart geometry [2-5].

Biological and histological evidence for cardiac recovery has been demonstrated through a comparative analysis of paired myocardial samples harvested at the time of VAD implantation and explantation. The Texas Heart Institute conducted a retrospective study comparing selected anatomic, physiologic, hemodynamic, histological, and biochemical parameters of the left ventricle before and after VAD support. Based on these parameters, they found that ventricular function did improve in patients after being supported by a VAD [19]. Several studies have also shown that unloading is associated with better myocyte function and the reversal of abnormal gene expressions; improved myocyte contractile properties and normalization of genes that regulate brain natriuretic peptide, calcium handling, tumor necrosis factor alpha and cytoskeleton proteins has been demonstrated [6-10].

2.2.3.2 Clinical Experience with VAD Weaning. In 1995, Nakatani et al were among the first to report on the recovery of the native ventricle in 4 BTT patients [21]. They were able to successfully wean 2 patients and since then, a limited number of other medical centers have reported experience with weaning BTT patients.

In 1999, the Texas Heart Institute reported weaning in 5 BTT patients [18]. Of these, one patient died of noncardiac-related causes and, at the time of publication, the remaining 4 patients were alive and well 2, 14, 33, and 35 months after VAD removal. They studied routine

echocardiographic and right heart catheterization measurements as indicators of recovery; a significant increase in cardiac output and ventricular ejection fraction were noted in the weaned patients.

In 2001, the Berlin Heart Center reported VAD weaning of 28 BTT patients [13]. Of those, 4 died, 8 eventually underwent transplant, and 16 showed stable recovery with follow-up times ranging from 1 month to 5.5 years. They used echocardiographic measures of ventricular ejection fraction and end-diastolic diameter made with the VAD turned off for 4 minutes as a guide to functional recovery.

Columbia Presbyterian has reported VAD weaning in 3 BTT patients [24, 25]. They studied a combination of echocardiography, right heart catheterization, exercise testing and serial endomyocardial biopsies for recovery of myocardial function. These studies introduced the value of exercise hemodynamics and metabolic studies in identifying patients with functional recovery.

In 2004, Toronto General Hospital published a case study of a BTT patient who was successfully weaned [12]. To assess recovery, they studied both echocardiographic measures and exercise performance. Echocardiographic measures, with simultaneous right heart catheterization, were performed every 10 minutes at VAD rates of 40, 30, and 20 cycles/min, and finally with the device off. Exercise testing was performed to exhaustion while respiratory gases and heart rate were monitored continuously.

The University of Pittsburgh Medical Center (UPMC), who currently holds the largest single-center experience with VAD weaning in the United States, has reported successful weaning in 10 BTT patients [14-16]. Of these, all survived to hospital discharge, 2 eventually underwent cardiac transplant, and 8 remain alive and well with follow-up times ranging from 1.5 to 5 years. Non-invasive echocardiographic and exercise study measurements were used to

assess recovery. Gorcsan et al have shown that these measurements can clearly define the population of patients that can be removed from VADs from those who will remain VAD dependent [14]. In a study of 19 BTT patients who were studied for possible recovery, Gorcsan was able to show that the patients who were eventually weaned demonstrated greater measures of cardiac function, such as ventricular power and peak oxygen consumption, as shown in Figure 4.

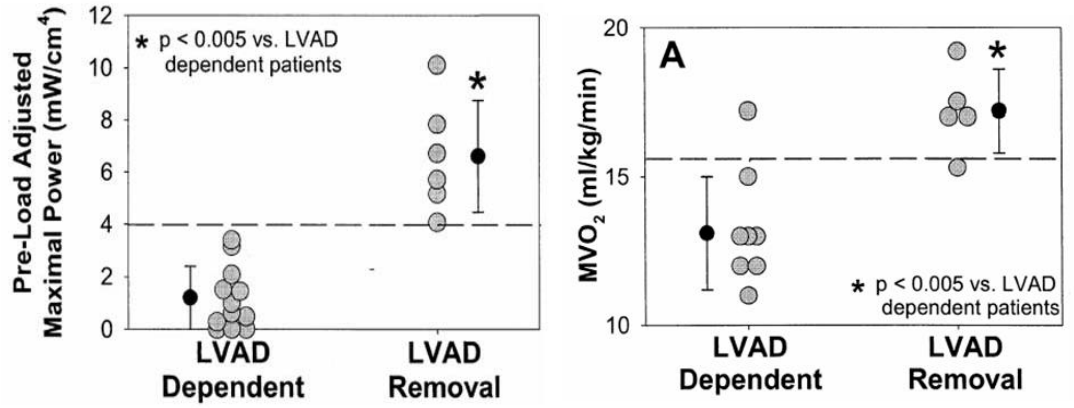

Figure 4: Echocardiographic and exercise data from recovery studies performed at UPMC

Listed in Table 1 are the cardiac recovery protocols used by the medical centers mentioned above. In summary, the protocols vary, but all include an echocardiographic assessment of the heart and may include additional assessments such as exercise and right heart catheterization tests.

Table 1: Protocols for assessing cardiac recovery

	Echocardiogram						Exercise		RH Catheterization		
Medical Center	EF	SA	ESD	EDD	FS	PWR	RER	MVO2	PCWP	CO	HR
Berlin Heart Center	✓			✓							
Columbia Presbyterian	✓			✓			✓	✓	✓	✓	
Texas Heart Institute	✓			✓						✓	
Toronto General			✓	✓	✓			✓			✓
University of Pittsburgh	✓	✓				✓	✓	✓	✓	✓	✓

EF= Ejection Fraction, SA= Stroke Area, ESD/EDD= End Systolic/Diastolic Diameter, FS= Fractional Shortening, PWR= Ventricular Power, RER= Respiratory Exchange Ratio, MVO2= Maximal Oxygen Uptake, PCWP= Pulmonary Capillary Wedge Pressure, CO= Cardiac Output, HR= Heart Rate

2.2.3.3 Challenges facing VAD weaning. Despite the mounting evidence to suggest that VAD patients can experience direct cardiac benefits from mechanical unloading of the ventricle, the incidence of VAD weaning remains relatively low [26, 27]. Although studies of myocardial function in VAD patients suggest that the native heart can mend itself after CHF and that VAD support appears to play a large role in the recovery process, the clinical significance of these findings must be better understood; it remains unclear why some patients exhibit recovery while others do not and if myocardial recovery can be sustained in the long-term. Furthermore, from the limited clinical experience with VAD weaning, it is evident that few centers regularly screen for recovery and protocols for assessing recovery vary across the board—indicating a lack of consensus regarding markers (or predictors) of recovery [13]. Although some centers claim to have found reliable markers of recovery, it is important to realize that, due to selection bias, these markers may not be applicable at other centers. Most reports of VAD weaning note that only a certain subset of patients were evaluated for recovery. While the subsets were most likely

not chosen randomly, the methods for choosing these groups were not published in any of the studies cited. Therefore, in order to fully understand the trends that govern the recovery of the patients at each center, the subset selection process must also be studied.

Methods for identifying potential candidates for recovery and development of weaning protocol are clearly in their infancy. While the limited clinical experience can be in part attributed to the lack of FDA approval for VAD use as a BTR (in non post-cardiotomy patients), the disparity between the number of patients that have been successfully weaned versus the number of patients evidencing myocardial recovery implies the need for a more systematic, quantitative approach. This study proposes the use of a Decision Support System for identifying and assessing VAD weaning candidates; the rationale for using this system is detailed in the Study Design section of this thesis.

2.3 DECISION SUPPORT SYSTEMS

Decision Support Systems (DSS) apply the principles of decision theory, probability theory, and decision analysis in an interactive computer-based tool to help decision makers answer questions, solve problems, and support or refute conclusions [50-53]. In *Making Hard Decisions*, Clemen and Reilly write that DSS provide the structure and guidance needed for thinking about hard decisions, which in turn allows people to make more effective decisions on a more consistent basis [54]. The main advantages of using these systems lie in their ability to integrate knowledge from multiple sources and minimize the biases of decision makers. When used properly, DSS have been shown to increase objectivity, productivity, efficiency and effectiveness

in decision making, in essence, enhancing human judgment— especially in complex and/or high-stress situations [51].

It should be emphasized that DSS, unlike so-called “Expert Systems,” are designed to aid the decision maker, not replace him or her. In response to criticism regarding the role of DSS, Derek Bunn writes, “The basic presumption of decision analysis is not at all to replace the decision maker’s intuition, relieve him or her of the obligations in facing the problem or to be, worst of all, a competitor to the decision maker’s personal style of analysis but to complement, augment and generally work alongside the decision maker [55].”

DSS are built upon a knowledge base derived from human experts and/or data. The system is designed such that when the user requests assistance with a decision, the knowledge base can be tapped using an inference engine and an analysis of the decision can be made based directly upon the expert- and/or data- derived knowledge. Since the methods used for this analysis are highly reliable and can be performed relatively quickly, DSS have continued to gain popularity in fast-paced, high-stakes domains such as the military, and in the fields of business, engineering, and medicine.

2.3.1 Clinical Decision Support Systems

Since the late 1950’s, there has been a growing interest in the use of computers as an aid in medical decision making [52]. Cooper writes “A major driving force [behind this interest was] the realization that the quantity of clinically relevant medical knowledge [was becoming] too great for one person to remember. [56]” Given the exponential growth of scientific literature and

specialty conferences, keeping current with the latest medical knowledge has become an even greater challenge, making the aid of computers more relevant than ever before.

Several Clinical Decision Support Systems (CDSS) have emerged as a result of this interest. A collection of current CDSS are shown in Table 2. These systems have been designed for use in various specialties of medicine including oncology, anesthesiology, cardiology, gynecology, and gastroenterology; from aiding clinicians in the decisions associated with anemia to those associated with ventilator control, applications are widespread [57-72]. Although a majority of CDSS are used for patient diagnosis, a number are also used in planning medication and therapy, and in routine patient evaluation [73].

Table 2: Clinical Decision Support Systems

	Patient Diagnosis	Medication and Therapy Planning	Patient Evaluation
Anemia	✓		
Anesthesia Delivery		✓	
Cardiovascular Disorders	✓	✓	✓
Circulatory Support Devices			✓
Diabetes	✓		
ER	✓		✓
Exercise Capacity			✓
Gastrointestinal Disorders	✓		
Hypercalcemic Disorders	✓		
Hypertension		✓	
ICU/NICU	✓	✓	✓
Liver Disorders	✓		
Pain	✓	✓	✓
Pap Smear Analysis	✓		
Pediatric Oncology		✓	
Ventilator Control	✓		

Many CDSS are used in critical care patient areas, such as the emergency room and intensive care unit, where decisions must be made quickly [62-65]. These systems are also quite useful in situations where physician expertise is constantly needed for optimal patient care, as in pain management [59].

2.3.1.1 Applications in Cardiology. In recent years, a large number of CDSS have been designed specifically for use in cardiac diagnosis, management, and evaluation; the increasing number indicates a distinct struggle over decision making in this medical specialty [66-69, 71, 72, 74-80].

Antonnson et al reported the development of a CDSS for supporting the decisions of surgeons before, during, and after implantation of certain circulatory support devices, including the intra-aortic balloon pump [66]. Their system uses a combination of rule- and case-based reasoning to provide predictions to the surgeon regarding the type of device that the patient ought to receive and the associated surgical procedures that should be used.

A team of computer scientists and clinicians at the Massachusetts Institute of Technology have been continuously developing a CDSS over the last decade for assisting in the differential diagnosis of cardiovascular disorders [69, 79, 80]. Comparing diagnoses made by the system to those made by physicians in a retrospective analysis of 600 patients cases, the system has a higher sensitivity (53.0% vs. 34.8%) and significantly higher comprehensiveness (57.2% vs. 39.5%).

A group at the Mayo Clinic has successfully used a CDSS to manage patients with resistant hypertension [68]. The system used serial hemodynamic measurements and a predefined treatment algorithm to select medication. A group of physicians were then asked to consult the

CDSS when managing their patients. In a 3-month clinical trial, the patients managed by the system demonstrated superior control over blood pressure than those managed by clinical judgment alone.

Several commercial CDSS are available for cardiac diagnosis and monitoring and are currently used at medical centers across the nation [72]. The Agilent Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (Agilent Technologies; Andover, MA) provides real-time guidance in the diagnosis of acute cardiac ischemia and improves the accuracy of triage decisions. CardioSys Exercise Testing System (GE Marquette) monitors and analyzes data from a patient undergoing exercise testing procedures. DynaPulse by Pulse Metric (San Diego) and Omron by Omron Healthcare Inc. (Vernon Hills, IL) are ambulatory blood-pressure monitors that use pattern recognition and fuzzy-logic algorithms to increase measurement accuracy.

3.0 STUDY DESIGN

3.1 RATIONALE

A challenging decision problem can be defined as one which is significantly complex enough to strain the limits of intuitive judgment [81]. As defined by Clemen and Reilly, a challenging decision involves at least two of the following four sources of difficulty [54]:

1. Complexity
    a. Keeping all issues in mind at one time is nearly impossible
2. Uncertainty
    a. Unknown values for variables involved in the decision
3. Multiple Objectives
    a. Progress in one direction may impede the progress in others
4. Different Perspectives
    a. Different individuals may disagree on the uncertainty of various outcomes

In the particular case of identifying and assessing VAD weaning candidates, the clinicians who make a decision regarding the patient's status must do so under a large amount of uncertainty, with multiple objectives in mind, while factoring in a number of different perspectives-- a challenging decision problem indeed.

While the care of VAD patients is complex by nature, the decision to wean the patient demonstrates an even greater degree of complexity. The limited clinical experience with VAD weaning, coupled with the lack of consensus regarding markers of recovery contribute to the large amount of uncertainty faced by clinicians. Furthermore, the clinicians are forced to speculate as to the patient's benefit from weaning versus a transplant, a risky assessment in light of the limited data; while it is well known that transplants can extend the life of CHF patients by, on average, 9 years, the longest follow-up data reported for a weaned patient is 5.5 years. Although the objective in all cases is to optimize the patient's quality of life and survival, a course of treatment directed towards optimal transplantation has different characteristics than one that is directed towards recovery. Finally, combining different perspectives not only involves combining input from the multiple disciplines involved in the patient's care, it also involves learning from past cases, and keeping current with the exploding amount of scientific literature related to VAD therapy.

In practice, clinicians find ways to cope with the uncertainty, the outcomes that extend over several time periods, the opinions from multiple individuals, and the often conflicting objectives. However, these coping mechanisms are often inefficient, highly subjective, and narrowly focused-- leading to non-optimal decision making which ultimately impedes progress.

In order to successfully address these difficulties, the decision maker requires a thorough understanding of the problem and careful thought regarding the important issues [54]. This requires time—a scarce resource in an environment where decisions need to be made quickly.

A DSS is an ideal solution for overcoming these difficulties. Through decision analysis, it is possible to organize complex problems into structures that can be more easily understood and analyzed, identify sources of uncertainty and represent that uncertainty in a systematic and useful manner, and address multiple objectives and different perspectives in an impartial, evidence-based manner [54].

3.2 OBJECTIVE AND SPECIFIC AIMS

This study proposes the use of a Clinical Decision Support System (CDSS) for both aiding in the identification of VAD weaning candidates and as a tool for predicting patient outcome. The objective of this study was to develop a CDSS that could mimic the decision-making processes used at UPMC when identifying VAD weaning candidates.

Toward this objective, knowledge was elicited from both experts and patient data. Three different decision models were developed and each was assessed for its predictive value.

Specifically, the aims of this study were to:

1. Develop and evaluate a decision model for predicting patient outcome based upon expert-derived knowledge.
2. Develop and evaluate a decision model for predicting patient outcome based upon data-derived knowledge.
3. Construct and evaluate a hybrid expert/data decision model for predicting patient outcome.
4. Design a graphical user interface for clinical implementation of the models.

It was hypothesized that the third model, which combined both expert- and data- derived knowledge, would predict patient outcome with greater accuracy than by using each source of knowledge separately.

3.3 EXPERT PANEL

The Artificial Heart Program (AHP) at UPMC is one of the top clinical programs of its kind in the world. Since 1985, UPMC researchers have been at the forefront of advances in VAD therapy, supporting nearly 300 patients for a period of time that amounts to more than 70 years [82]. Members of the AHP clinical team have received national recognition for their services, including prestigious awards, and are globally regarded as experts in this field [83-85].

11 members of the AHP clinical team were asked to participate on the expert panel for this study. As shown in Figure 5, and detailed in Appendix A, the panel was composed of a diverse, multi-disciplinary group representing many aspects of the patient's care including surgery, clinical bioengineering, nursing and psychiatry among others.

Figure 5: Disciplines represented in the expert panel

3.4 PATIENT DATA

In accordance with HIPAA (Health Insurance Portability and Accountability Act of 1996), de-identified patient data was obtained from the UPMC VAD registry via an honest broker. Patient cases considered for this study included patients on LVAD or BiVAD Thoratec devices who were BTT patients but considered for recovery at UPMC between 1996 and 2004. All patients had been assessed for recovery by the same clinical team and participated in echocardiographic and/or exercise weaning studies. Patient cases were included regardless of outcome or post-explant status.

Although a total of 161 VAD implants were performed between 1996 and 2004, the inclusion criteria described above resulted in a population of 19 patients (12%), of whom 10 were weaned, and 9 were transplanted. It should be noted that these were the same subjects considered in the Gorscan et al and Simon et al studies [14, 16].

Overall, patients in this group received VAD support for at least 42 days and at most 282 days, the mean age was 35 years old, 63% were female and 84% were Caucasian. Of the 9 transplanted patients, 2 received an LVAD, 7 received a BiVAD, and 6 remain alive. Of the 10 weaned patients, 5 received an LVAD, 5 received a BiVAD, and 8 remain alive and device/transplant free; the weaned group was composed of primarily female, non-ischemic patients (3 myocarditis, 4 post-partum cardiomyopathy, and 1 idiopathic cardiomyopathy). Outcome, device configuration, and post-explant status for each patient is shown in Table 3.

Table 3: Patient outcome, device configuration and post-explant status

Patient ID	Outcome	Device Configuration	Post-Explant Follow-Up
1560	Transplanted	Bi-VAD	Alive
4075	Transplanted	Bi-VAD	Alive
7869	Transplanted	Bi-VAD	Alive
8411	Transplanted	Bi-VAD	Alive
8883	Transplanted	Bi-VAD	Alive
8118	Transplanted	Bi-VAD	*Died*
9284	Transplanted	Bi-VAD	*Died*
8682	Transplanted	LVAD	Alive
8794	Transplanted	LVAD	*Died*
2297	Weaned	Bi-VAD	Transplant Free, Alive
8854	Weaned	Bi-VAD	Transplant Free, Alive
9061	Weaned	Bi-VAD	Transplant Free, Alive
9714	Weaned	Bi-VAD	Transplant Free, Alive
1838	Weaned	Bi-VAD	*Transplanted, Alive*
3496	Weaned	LVAD	Transplant Free, Alive
7747	Weaned	LVAD	Transplant Free, Alive
7822	Weaned	LVAD	Transplant Free, Alive
9264	Weaned	LVAD	Transplant Free, Alive
4823	Weaned	LVAD	*Transplanted, Died*

The seven data categories available for these patients included: demographics, complications, laboratory results, right heart catheterization results, exercise test results, echocardiography test results, and shift notes. While only 32% of the patients had complete data sets, 53% were missing only one category, and all remaining patients were missing at most two categories. Table 4 details the data categories available for each patient. The variables in each of numerical data categories (a total of 250) are detailed in Appendix B and an excerpt from a shift notes file is included in Appendix C.

Table 4: Patient data categories and data completeness

Patient ID	Demographics	Complications	Labs	RH Cath	Echo	Exercise	Shift Notes
1838	X	X	X	X	X		
2297	X	X	X	X	X		
3496	X	X	X	X	X	X	
4823	X	X	X	X	X	X	
7747	X	X	X	X	X	X	X
7822	X	X	X	X	X	X	X
8854	X	X	X		X	X	X
9061	X	X	X	X	X		X
9264	X	X	X	X	X	X	X
9714	X	X	X	X	X	X	X
1560	X	X	X	X	X	X	
4075	X	X	X	X	X	X	
7869	X	X	X	X	X		X
8118	X	X	X	X	X		X
8411	X	X	X	X	X		X
8682	X	X	X	X	X	X	X
8794	X	X	X		X		X
8883	X	X	X		X		X
9284	X	X	X	X	X	X	X

4.0 METHODS

First, knowledge was acquired from experts and patient data. Next, the structure and numerical parameters associated with this knowledge were used to build the decision models. Finally, a graphical user interface was designed for clinical implementation of the model.

4.1 KNOWLEDGE ACQUISITION

Knowledge was elicited directly from experts and patient data. In the case of experts, this was accomplished through interviews and questionnaires. In the case of patient data, knowledge was acquired through two data mining techniques: Artificial Neural Networks and Natural Language Processing.

4.1.1 Expert-derived Knowledge

Through a series of structured interviews and questionnaires, retrospective experience with weaning was acquired from the expert panel.

4.1.1.1 Interviews. Interviewing is considered the classic method for acquiring knowledge from experts [67, 86, 87]. However, if performed in the traditional free form, interviews can be inefficient; as experts are normally busy individuals, maintaining efficiency in the knowledge acquisition process is a must for both parties. Therefore, “structured interviews,” or interviews in which a prop is used to guide the expert in divulging information are often employed when designing DSS [86]. The prop assists in maintaining focus of the interview; it can be anything from a patient chart to a film clip.

In this study, experts were interviewed individually and in small groups 3 times over the course of 2 years. These interviews were informal and were conducted both in person and electronically. The goal of the interviews was to capture procedural knowledge related to VAD weaning.

During the first interview, the expert was asked to describe the protocol he or she would use to determine if a patient could be weaned. After the interview, the resulting protocol was transformed into a binary decision flowchart and presented to the expert during a second interview. At that time, the expert was asked to review and revise the flowchart. Upon receiving an approved or revised flowchart from each expert, flowcharts from all experts were combined into one. In a third interview, the combined flowchart was presented to each expert and they were asked to review and revise the flowchart. Upon receiving the approved or revised flowcharts from each expert, the commonalities from all flowcharts were combined into one final decision flowchart.

4.1.1.2 Questionnaires.

After the final decision flowchart was constructed, experts were asked to take part in a questionnaire. The goal of the questionnaires was to add a probabilistic dimension to the decision flowchart and capture expert treatment preferences and risk attitudes. Two 12-item questionnaires were completed in 2 sessions, and questions were asked in an informal, interview-style.

Due to the binary nature of the final decision flowchart, weaning was only recommended if all variables were in their positive form. Therefore, experts were asked to consider less than ideal situations (a combination of variables in their positive and negative states) and estimate the percentage of patients who could be successfully weaned based upon those characteristics. To ensure consistency in the responses, questions were repeated in their reverse form. For example, if for 4/5 variables they answered 90%, then 1/5 variables should be 10%. If the probabilities did not directly complement each other, the experts were asked to reevaluate their estimates. A final 8x6 matrix of probabilities was derived from averaging the probabilities elicited from all experts.

4.1.2 Data-derived Knowledge

According to Witten and Frank, data mining can be defined as the act of exploring and analyzing large amounts of data in order to detect meaningful rules, trends, insights and relationships [88]. Often referred to as pattern recognition, data mining is performed semi-automatically through the use of specialized software. Through data mining, it is possible for the computer to produce models of historical data that can be used later for predictions of new cases; the technique for building these models is called machine learning [89].

In this study, two data mining techniques were used to acquire knowledge and "learn" from the patient data: Artificial Neural Networks (ANN) and Natural Language Processing (NLP). ANN were used to analyze numerical data from the demographics, complications, labs, rh cath, echo, and exercise data. NLP was used to analyze the textual data found in the shift notes. The goal in using these data mining techniques was two-fold: to identify new patterns within the data and to confirm suspected relationships between variables.

4.1.2.1 Artificial Neural Networks.

ANN are designed to function like the human nervous system and, similarly, their basic units are called neurons [67, 86]. As shown in Figure 6, the neurons are organized into three layers: input layer (stimulus), hidden layer (processing of stimulus), and output layer (final response to stimulus). The neurons in each layer are linked in parallel through connections called synapses. The first layer, the input layer, is where the input data is presented for analysis. Values from the input layer are propagated from each neuron to every neuron in the next layer, the hidden layer, and the values are modified during transmission by randomly assigned weights. Using "error back propagation," each input is multiplied by the assigned weight and propagated forward through the network to generate a prediction. The error in prediction is fed backwards through the network, modifying the weights by small amounts. This process is repeated for all inputs, many times, until the network has the lowest error in prediction. Eventually, a result is delivered in the third layer, the output layer. The result is a list of the inputs, ranked in order of importance, that best model the data that was presented in the first layer.

Since the layer in which the complex processing takes place is hidden from the user, a common criticism of ANN is that it is difficult to understand the exact reasoning that goes into

the results; for this reason, ANN are sometimes referred to as “black boxes” [89]. However, the prediction accuracy of ANN is generally high and as such, they have gained widespread acceptance as a powerful data mining technique [67, 90, 91].

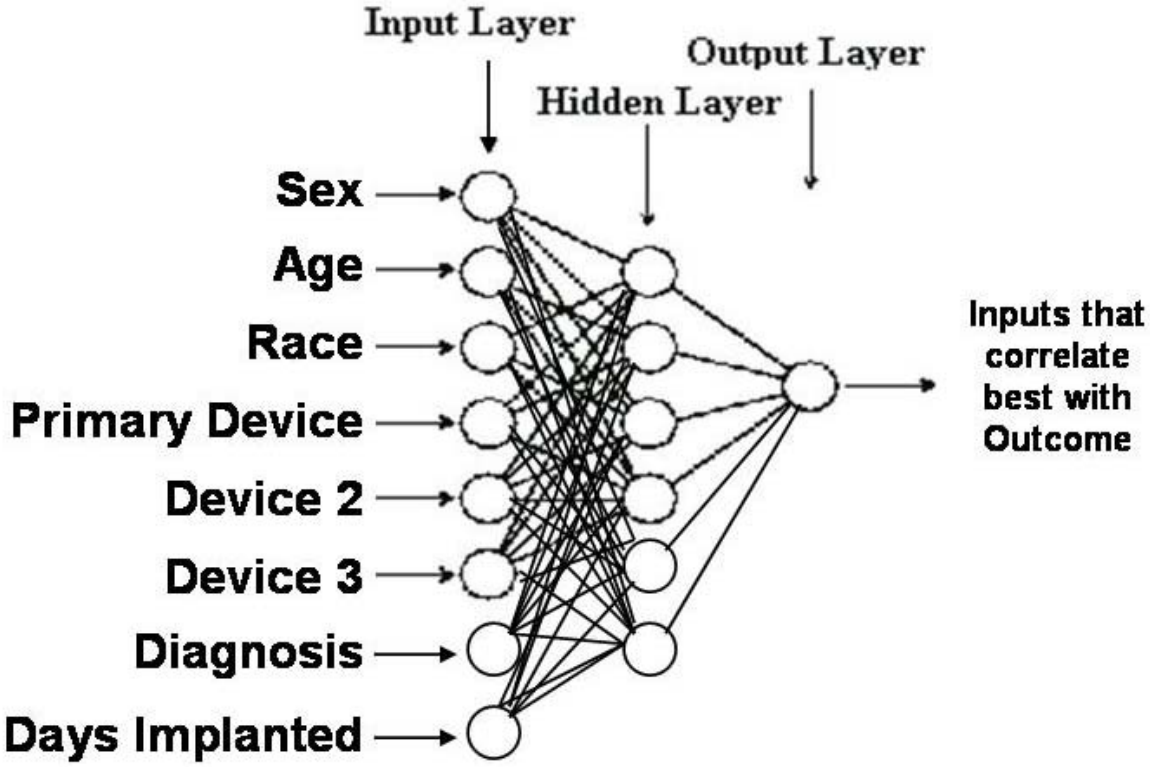

Figure 6: Artificial Neural Network

In this study, ANN analysis was performed using SPSS Clementine 7.0 [92]. The goal was to narrow down the sets of variables that best correlated with weaning among the 250 variables available. As shown in Figures 7-9, a data mining scheme was first defined (Figure 7); the input data was presented and the target, in this case Patient Outcome, was identified (Figure 8), then, the settings for running the ANN were assigned (Figure 9). The ANN was set to run in "Prune" mode with overtraining prevented by using only 50% of the data set at a time. Prune mode allowed the network to remove surplus inputs when training and yield a minimized data set; although time consuming, this setting has been known to yield the best results [89, 93].

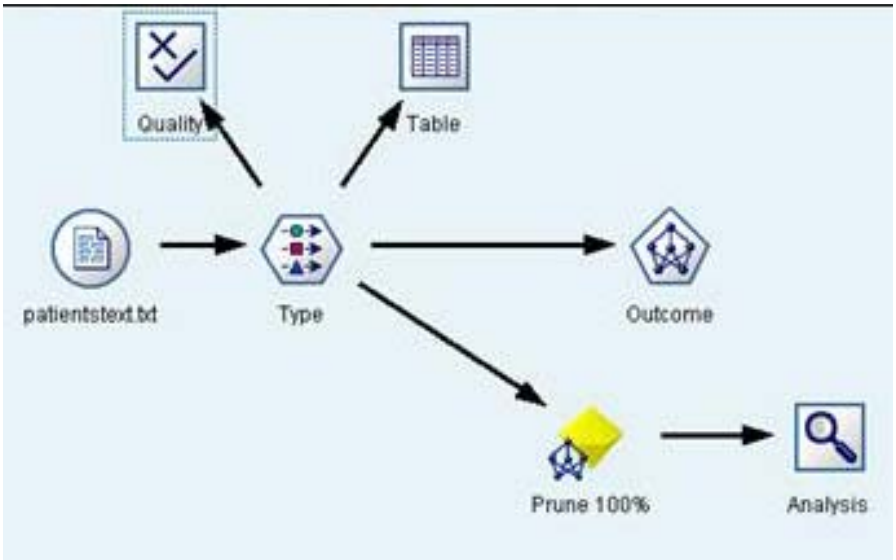

Figure 7: Clementine data mining scheme

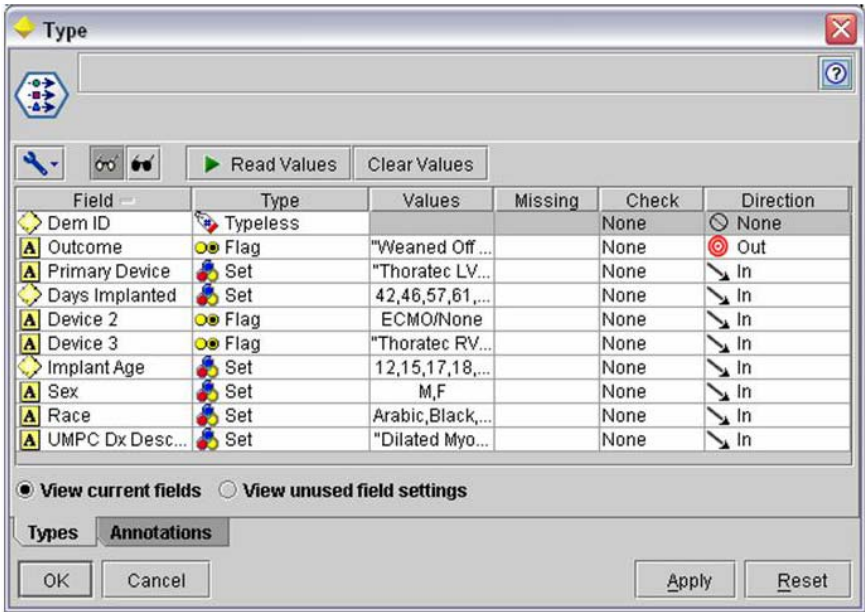

Figure 8: Defining inputs and target in Clementine

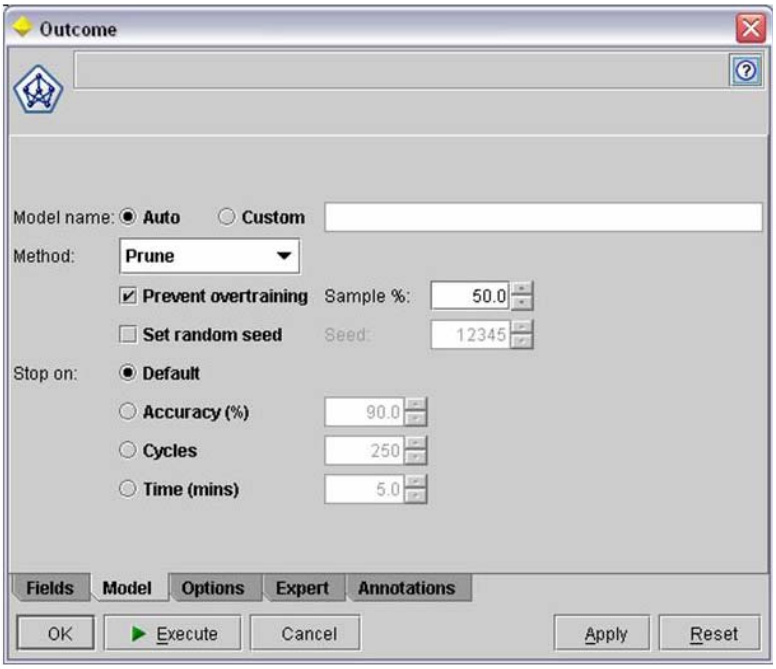

Figure 9: Artificial Neural Network settings

Upon running the ANN, a graph, as shown in Figure 10, was displayed in which the error back propagation could be visualized. Since training data sets often takes long durations of time (usually over the course of a night), the graph was useful in tracking training progress.

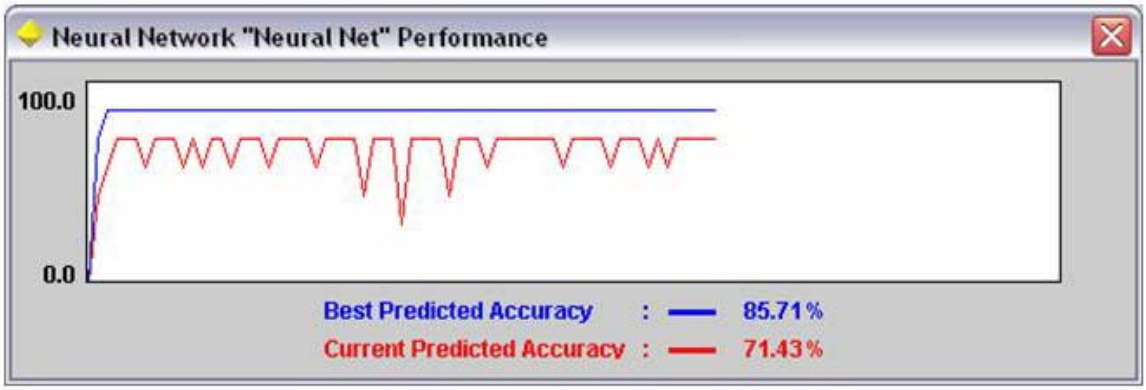

Figure 10: Artificial Neural Network real-time analysis

Eventually, the minimized data set, with inputs ranked in order of importance to the target, was given as output, which is shown in Figure 11. As a final step, known outcomes were compared to those given by the ANN, as shown in Figure 12. Each numerical data category was analyzed using this methodology.

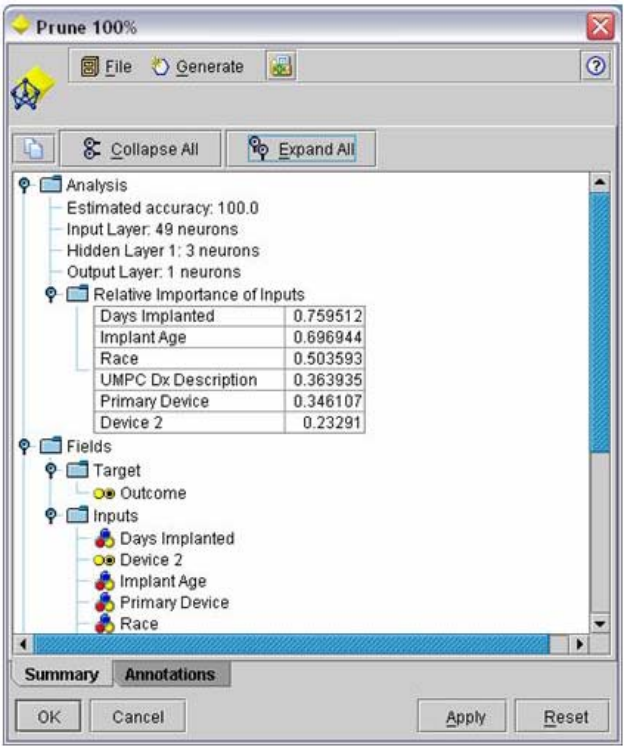

Figure 11: Artificial Neural Network output

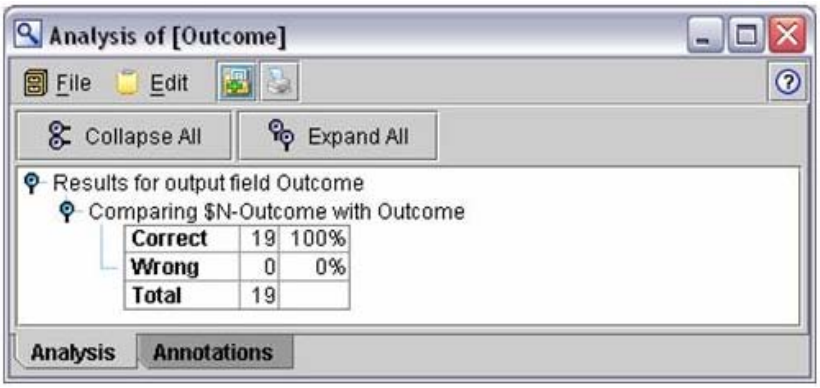

Figure 12: Artificial Neural Network output analysis

4.1.2.2 Natural Language Processing.

NLP, also known as text mining, is a subfield of Artificial Intelligence and Linguistics. It studies the problems inherent in the processing and manipulation of natural language, and, is devoted to making computers "understand" free text using predetermined rules and patterns of language [86].

In this study, the main software used for NLP was Concordance 3.2 [94]. This software is able to take a text of any size and organize words by frequency and context [95]. The goal in processing the text was to detect speech patterns that may be associated with weaned patients. In preparation for NLP, the shift notes were filtered for common words and checked for spelling errors using a word processor. The texts were then analyzed with Concordance one at a time; the output consisted of the words listed in order of frequency and context, as shown in Figure 13. Based upon the types of words in these documents, contextual categories were created. The word frequency lists were exported into Excel and words were manually assigned to their respective category; words that did not fall into a category were omitted. Finally, the total frequencies of words in each category were compared between the weaned and transplanted patients.

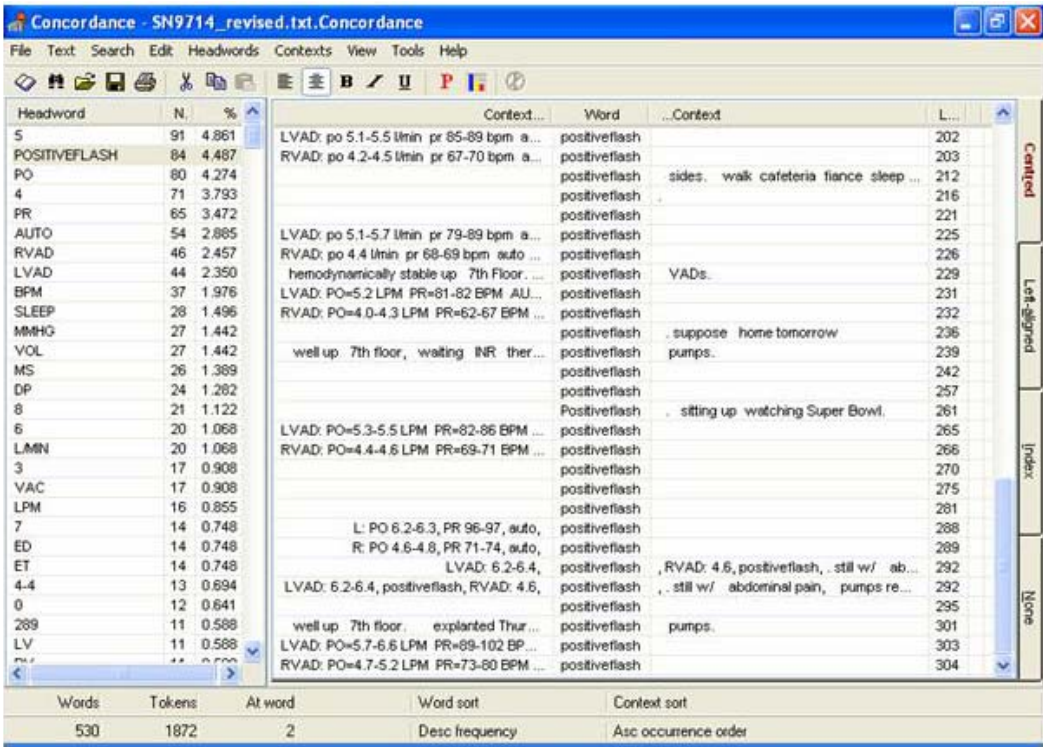

Figure 13: Concordance output showing words organized by frequency and context

4.2 DECISION MODELING

Decision structures were formed using the knowledge acquired from experts and/or learned from the patient data were modeled using Bayesian Belief Networks (BBN).

4.2.1 Bayesian Belief Networks

Bayesian Belief Networks (BBN) apply Bayes' Theorem to develop powerful, readily understood decision models. Some of the earliest clinical decision support systems were built

using BBN; recent examples include the application of BNN for providing diagnoses in liver and cardiovascular disease, in the evaluation of electroencephalograms in the intensive care unit, and in establishing prognosis for patients with head injuries [61, 67, 96].

BBN are acyclic directed graphs that paint both a quantitative and qualitative illustration of interactions among a set of variables [97]. In BBN, nodes (ovals) represent random variables and arcs (arrows) represent the direct probabilistic dependencies among the variables. When nodes are connected with arcs, the properties of the nodes become dependent upon each other, and a joint probability distribution is formed.

In this study, SMILE, an inference engine, and GeNIe 2.0, a development environment for building graphical decision-theoretic models, were used to create the BBN [98]. Both applications were developed at the Decision Systems Laboratory at the University of Pittsburgh by Marek Druzdzel and his colleagues.

In order to clearly demonstrate the structure and development of a BBN, a simple example illustrating the relationship between White Blood Cell (WBC) Count and Infection is shown in Figures 14-18 below. There are two nodes in this example: WBC Count and Infection. At least two states must exist for each node. In this case, WBC Count has three states: high, normal and low; and Infection has two: present and absent. The joint probability distribution is, as defined by the direction of the arc, the probability of each state according to the node upon which it is dependent. In this case, WBC Count is dependent upon Infection, meaning that the states for the WBC Count node must be defined for both states of the Infection node. The nodes and a hypothetical joint probability distribution are shown in Figure 14.

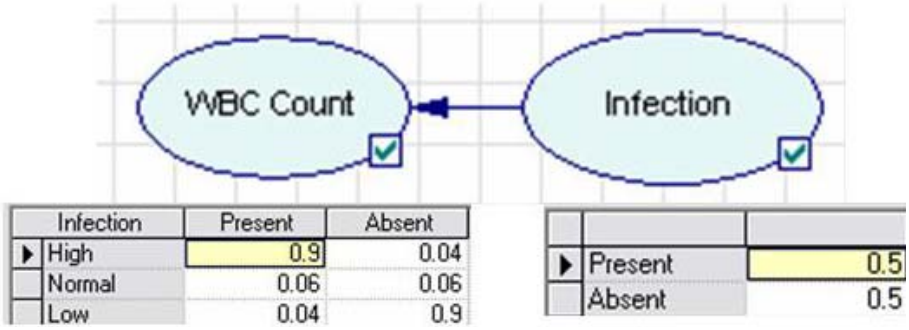

Figure 14: Bayesian Belief Network example- defining nodes, states and probabilities

By setting the evidence for WBC Count to high, infection can be predicted. As shown in Figures 15 and 16, if WBC Count is high, there is a 96% chance that Infection is present. The model can also be used in the reverse order, such that the presence of absence of Infection predicts the WBC count, as shown in Figures 17 and 18.

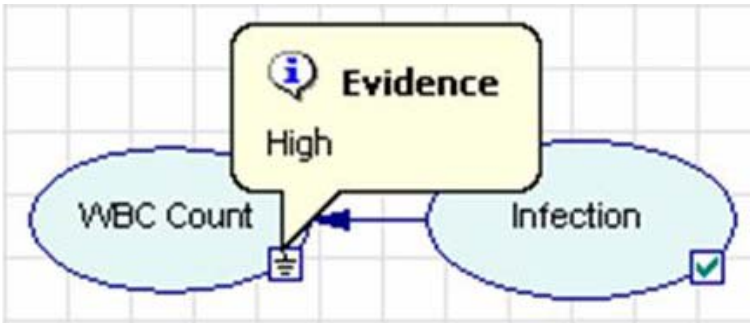

Figure 15: Bayesian Belief Network example- setting WBC Count evidence

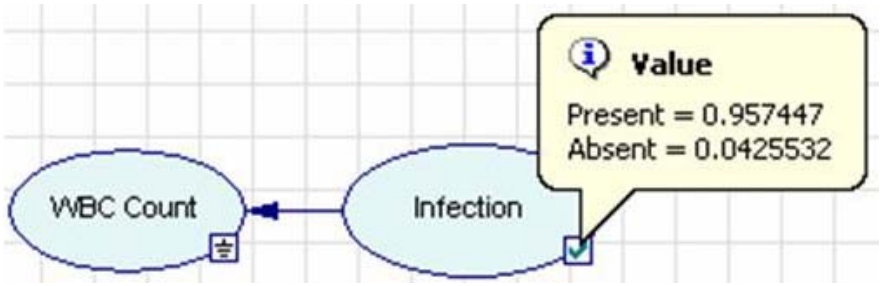

Figure 16: Bayesian Belief Network example- predicted Infection

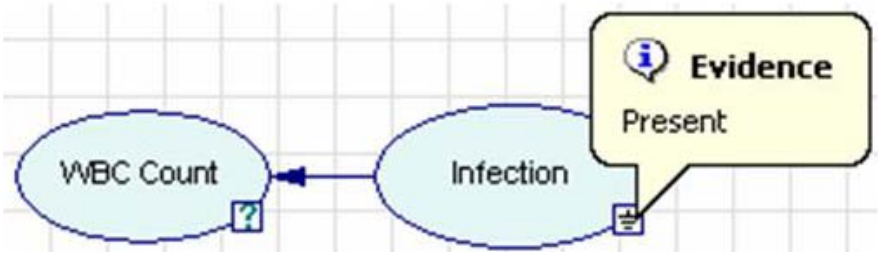

Figure 17: Bayesian Belief Network example- setting Infection evidence

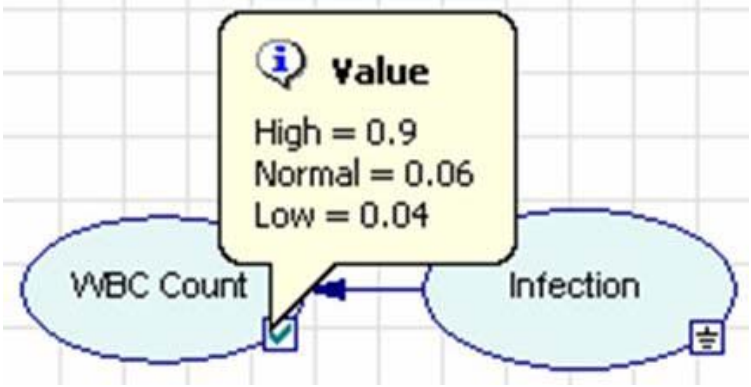

Figure 18: Bayesian Belief Network example- predicted WBC Count

In this study, the first step in creating the BBN was to define the nodes and their states. The nodes were those variables that were acquired through the expert interviews and data mining. For example, for the data category of patient demographics, the variables were primary device, days implanted, age, race, sex and diagnosis. Nodes were created to represent each of these variables and variable states were defined (e.g., for example, the states for sex were male and female). The second step was to define the direction of the arcs and the numerical parameters for filling in the joint probability distribution tables. All nodes were defined as having a direct relationship with patient outcome, and two states were defined for patient outcome: weaned and transplanted. Therefore, each variable state was defined for both weaned and transplanted patients, as shown in Table 5.

Table 5: Variable list with probabilities assigned for each state and outcome

		Wean	Transplant
Node Name	Primary Device		
State 0	Bivad	5	7
State 1	Lvad	5	2
Node Name	Days Implanted		
State 0	< 100	8	2
State 1	> 100	2	7
Node Name	Age		
State 0	<= 37	7	3
State 1	> 37	3	6
Node Name	Race		
State 0	Caucasian	9	7
State 1	Oriental	1	0
State 2	Black	0	1
State 3	Arabic	0	1
Node Name	Sex		
State 0	Female	7	5
State 1	Male	3	4
Node Name	Diagnosis		
State 0	DM Postpartum	4	2
State 1	DM Myocarditis	3	0
State 2	DM Idiopathic	1	3
State 3	DM Ischemic	1	1
State 4	Acute Ischemic HD	1	2
State 5	Valvular HD	0	1

4.3 MODEL INTERFACE DESIGN

Anticipating clinical translation, a user-friendly graphical interface to the decision model was designed for a Pocket PC. A prototype was developed using Visual C++ 4.0 programming and SMILE for the Pocket PC 2003.

4.3.1 Hardware

With the clinical user in mind, a graphical user interface (GUI) was designed for a portable, hand-held computer known as a Pocket PC. As clinicians are often “on the go,” Pocket PC applications can be useful and readily implemented in a clinical setting. Several commercial Pocket PC applications exist and are currently used by clinicians for various functions including medical record entry and quick reference [99, 100]. Since 2002, the cardiovascular surgery unit at Miami Children’s Hospital has successfully used a fleet of Pocket PCs to gather patient information and write prescriptions [101].

A rechargeable Toshiba Pocket-PC model e355 with 3.5” TFT color display, 64MB RAM, and 300 MHz Intel PXA255 processor was used. This Pocket-PC was synchronized to an IBM ThinkPad model T40 notebook computer via the USB port. Minimum computer system requirements for synchronization were a 233MHz processor, 128 MB memory, and 65MB available hard disk space.

4.3.2 Software

Both the Pocket-PC and notebook computer used in designing the GUI were running the most up-to-date Microsoft operating systems (Pocket PC 2003 and Windows XP SP2). The code for the GUI was written using eMbedded Visual C++ 4.0 and SMILE for the Pocket-PC 2003 [98, 102]. SMILE for the Pocket PC is a C++ library that performs decision analysis inference, it essentially allows the decision model that was created for the desktop computer to be fully implemented on the Pocket PC. To test the implementation, an emulated Pocket-PC, available as part of the Microsoft Software Development Kit for Pocket-PC 2003, was used [103].

5.0 RESULTS

As described in the methods section of this thesis, the structure and numerical parameters for the decision models were elicited from experts and/or learned from the patient data. Following the construction of Bayesian belief networks, each decision model was evaluated retrospectively. Models were evaluated based upon the accuracy with which they predicted the actual outcomes in the 19 patient cases considered for this study.

The following three sections describe the results from each of the models (expert model, data model and hybrid model). Results will be reported in terms of the model's ability to predict a True Wean (TW), a True Transplant (TT), a False Wean (FW) and a False Transplant (FT). A "true" scenario is one in which the model's prediction matches the actual patient outcome and a "false" scenario is one in which the model predicts a different outcome. To further clarify, a TW occurs when the model predicts a wean and the real patient outcome indicates that the patient was weaned, while a TT occurs when the system predicts a transplant and the real patient outcome indicates that the patient was transplanted. A FW occurs when the system predicts a wean however the real patient outcome indicates that the patient was transplanted, while a FT occurs when the system predicts a transplant however the real patient outcome indicates that the patient was weaned.

5.1 EXPERT MODEL

5.1.1 Decision Structure and Numerical Parameters

5.1.1.1 Interview Results. A decision flowchart describing the criteria used to identify VAD weaning candidates was compiled as a result of the expert interviews. The final decision flowchart is shown in Figure 19. The experts described a 5-tier health status screening followed by a 3-tier evaluation of cardiac recovery. They described an optimal weaning candidate as a non-ischemic patient who had been supported by the VAD greater than 4 weeks, had normal cardiac rhythm, positive nutritional status, and normal end organ function. Indices of cardiac recovery, as gathered through echocardiographic (ECHO) measurements, were considered optimal if the patient was able to maintain (with the VAD off) an ejection fraction (EF) of greater than 40%, ventricular power (PWR) greater than 4, and positive stroke area change (SA). Exercise study results were considered optimal if the patient was able to reach a peak oxygen consumption (MV02) of greater than 15 and maintain a respiratory exchange ratio (RER) greater than 1 when exercising with increased workload. Right heart catheterization (RH CATH) results were considered optimal if the patient demonstrated a pulmonary capillary wedge pressure (PCWP) of less than 20, a cardiac index (CI) of greater than 2.2, and a heart rate (HR) of less than 100. As an alternative, experts reported that cardiac recovery could also be considered sufficient if at least 3 out of the following 4 indices were in the optimal range: EF, PWR, SA, and MVO2.

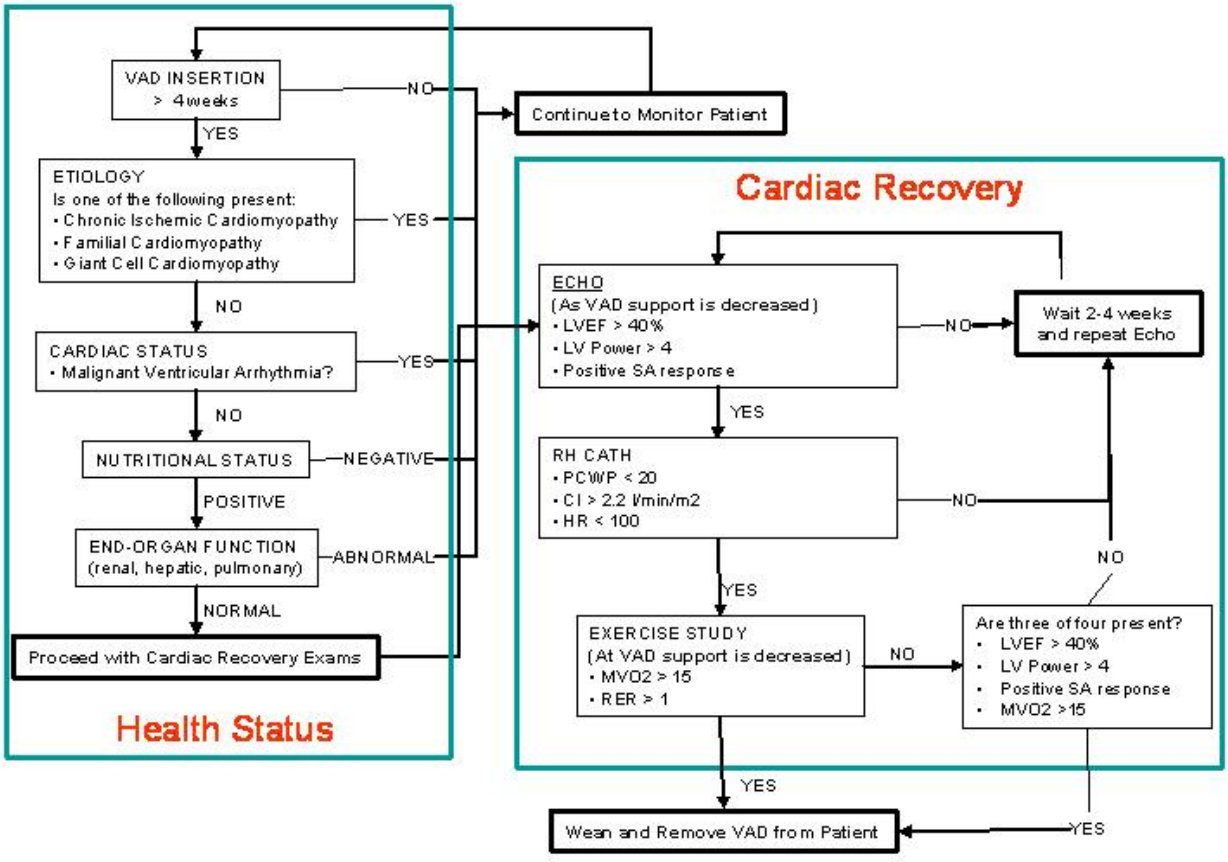

Figure 19: Final expert decision flowchart

5.1.1.2 Questionnaire Results. As a result of the expert questionnaires, an 8x6 matrix of probabilities describing expert risk attitudes and treatment preferences was compiled. Shown in Figure 20 is a sample question and a portion of the output matrix; the questionnaire in its entirety is included in Appendix D. In this example, the expert was asked if they would consider weaning a patient if the patient's health status was inadequate but cardiac recovery was adequate. In accordance with the decision flowchart, the expert said no. However, when asked to estimate the percentage of patients who could be successfully weaned if 1 out 5 health status parameters were adequate, the expert answered 10% and 2 out 5 health status parameters adequate, 40%. The matrix of probabilities was entered in the outcome node of the BBN, as described in the next section.

Would you wean if the patient's health status is inadequate but cardiac recovery is adequate?

Yes **No**

Percent of patients who would likely be successfully weaned if:

1 out of 5 health status parameters adequate

100 90 80 70 60 50 40 30 20 10 0

2 out of 5 health status parameters adequate

100 90 80 70 60 50 40 30 20 10 0

Cardiac Recov...	All_adequate					
Health Status	All_adequate	All_inadequ...	one_of_5_a...	two_of_5_a...	three_of_5_...	four_of_5_a...
Wean	1	0	0.1	0.4	0.8	0.9
Transplant	0	1	0.9	0.6	0.2	0.1

Figure 20: Sample question and probability matrix from expert questionnaire

5.1.2 Bayesian Belief Network Representation

The final expert decision model in BBN form is shown in Figure 21. This model is similar in structure to the decision flowchart in that two groups of nodes exist, those that describe the patient's health status and those that describe the patient's cardiac recovery (the states for each of the nodes are already shown in Figure 19, and as such will not be repeated here). The main difference between the BBN and the decision flowchart is the addition of the Outcome node, shown here in the center of the network. The outcome node contains the 8x6 matrix of probabilities given through the expert questionnaire. Specifically, this node contains a probability for the two states of Outcome (Wean, Transplant) for each of the 6 states of the Health Status node (all adequate, all inadequate, 1/5 adequate, 2/5 adequate, 3/5 adequate, 4/5 adequate) and each of the 8 states of the Cardiac Recovery node (all adequate, all inadequate, only echo adequate, only exercise adequate, only rh cath adequate, echo and exercise adequate, echo and rh cath adequate, and exercise and rh cath adequate).

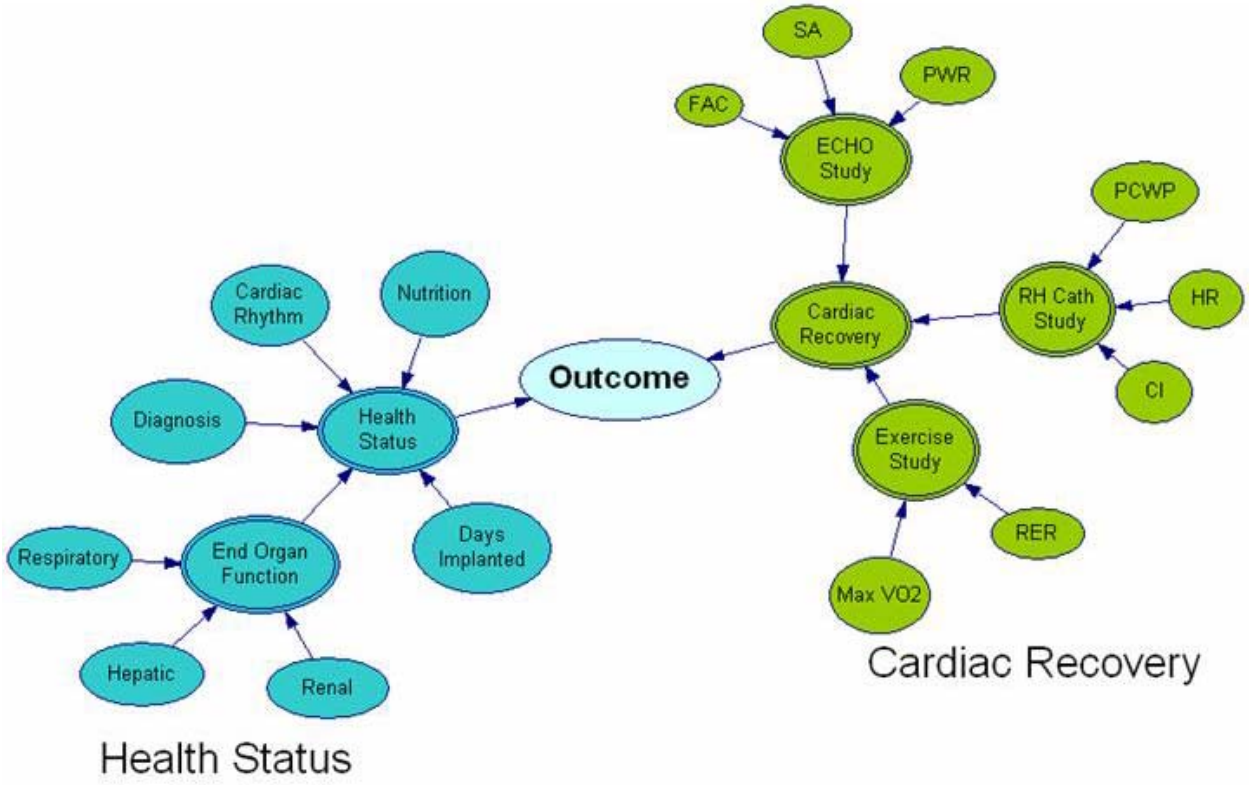

Figure 21: Final expert decision model

5.1.3 Evaluation

The predictive accuracy of the expert decision flowchart, shown in Figure 19, is given in Table 6. The predictive accuracy of the final expert decision model, shown in Figure 21, is shown in Table 7.

Table 6: Predictive value of expert decision flowchart

True Wean	True Transplant	False Wean	False Transplant
1	9	0	9

Table 7: Predictive value of expert decision model

True Wean	True Transplant	False Wean	False Transplant
6	9	0	4

5.2 DATA MODEL

5.2.1 Decision Structure and Numerical Parameters

In acquiring the knowledge from the data, 7 categories of data, 250 variables and 10 pages of text per patient were analyzed for each of the 19 patients, each with an average of 124 days worth of data.

5.2.1.1 Artificial Neural Network Results. The ANN were used to analyze the numerical data from the demographics, complications, labs, rh cath, echo, and exercise categories. The analysis resulted in an 89% reduction in the data set-- 28 of the 250 variables were found to correlate closely with outcome. These 28 variables are shown below, in Tables 8-13, organized by data category. The states for each of these variables, for each of the two patient outcomes are also shown.

In terms of Patient Demographics, the ANN analysis describes an ideal candidate for weaning as one who was supported by an LVAD rather than a BiVAD, implanted for less than 100 days, less than 38 years old, Caucasian, female, and non-ischemic (Table 8).

Table 8: Minimized set of Patient Demographics variables

		Wean	Transplant
Node Name	Primary Device		
State 0	Bivad	5	7
State 1	Lvad	5	2
Node Name	Days Implanted		
State 0	< 100	8	2
State 1	> 100	2	7
Node Name	Age		
State 0	<= 37	7	3
State 1	> 37	3	6
Node Name	Race		
State 0	Caucasian	9	7
State 1	Oriental	1	0
State 2	Black	0	1
State 3	Arabic	0	1
Node Name	Sex		
State 0	Female	7	5
State 1	Male	3	4
Node Name	Diagnosis		
State 0	DM Postpartum	4	2
State 1	DM Myocarditis	3	0
State 2	DM Idiopathic	1	3
State 3	DM Ischemic	1	1
State 4	Acute Ischemic HD	1	2
State 5	Valvular HD	0	1

As noted in the analysis of the Complications variables (Table 9), an ideal candidate for weaning is one with no history of renal complications or tamponade. In addition, the results indicate that candidates are more likely to be transplanted if they have a history of reoperation or complications associated with bleeding.

Table 9: Minimized set of Complications variables

		Wean	Transplant
Node Name	Bleeding		
State 0	No	6	2
State 1	Yes	4	7
Node Name	Reoperation		
State 0	No	4	2
State 1	Yes	6	7
Node Name	Tamponade		
State 0	No	9	7
State 1	Yes	1	2
Node Name	Renal		
State 0	No	10	7
State 1	Yes	0	2

In terms of Laboratory Tests (Table 10), the ANN analysis associated a greater chance of weaning with patients who had normal laboratory values for Aspartate Amino Transferase (AST), Urea Nitrogen (UREAN), Reticulocyte Count (RET), Lactic Dehydrogenase (LD), Magnesium (MG) and Creatinine Clearance (CREAT).

Table 10: Minimized set of Laboratory Test variables

		Wean	Transplant
Node Name	AST		
State 0	0-250	6	4
State 1	>250	4	5
Node Name	CREAT		
State 0	0-1.9	7	2
State 1	>1.9	3	6
Node Name	UREAN		
State 0	2.0-47.0	7	2
State 1	out of range	3	7
Node Name	RET		
State 0	3.2-10	5	3
State 1	out of range	2	5
Node Name	MG		
State 0	1-2.6	7	2
State 1	out of range	3	7
Node Name	LD		
State 0	167-1022	5	2
State 1	out of range	5	6

Indices of cardiac recovery, as described by the ANN analysis included measures derived from the exercise study, rh cath study and echo study. For the exercise test variables (Table 11), optimal candidates include those who are able to exercise for longer than 5 minutes, have greater than 45% of predicted peak exercise oxygen consumption (V02%), have metabolic equivalents greater than 4 (METS), and can perform at greater than 80% of maximum predicted heart rate

(HR% Target). Optimal RH Cath variables include (Table 12) a pulmonary capillary wedge pressure of less than 24 (PCWP), pulmonary vascular resistance of less than 1.1 (PVR), mean pulmonary artery pressure of less than 25 (mPap), and a transpulmonary gradient of less than 10 (TPG). Finally, the optimal echocardiographic measurements (with VAD off or at half support) include ventricular power of greater than 4 (PWR), a positive increase in stroke area (SA), stable systolic arterial pressure (ApSys), and stable fractional area change (FAC) (Table 13).

Table 11: Minimized set of Exercise Test variables

		Wean	Transplant
Node Name	Exercise Time		
State 0	>= 5 minutes	7	1
State 1	< 5 minutes	0	3
Node Name	VO2 %		
State 0	> 45	6	1
State 1	< 45	1	2
Node Name	Mets		
State 0	> 4	6	0
State 1	< 4	1	3
Node Name	HR % Target		
State 0	> 80	6	1
State 1	< 80	1	2

Table 12: Minimized set of RH Catheterization variables

		Wean	Transplant
Node Name	PCWP		
State 0	<24	7	3
State 1	>24	2	4
Node Name	PVR		
State 0	<1.1	5	1
State 1	>1.1	4	4
Node Name	mPap		
State 0	<25	7	3
State 1	>=25	2	4
Node Name	TPG		
State 0	<10	7	2
State 1	>=10	1	4

Table 13: Minimized set of Echocardiographic variables

		Wean	Transplant
Node Name	PWR		
State 0	> 4	7	1
State 1	< 4	1	7
Node Name	SA		
State 0	increased >0.2	5	0
State 1	maintained	2	1
State 2	decreased >0.2	2	6
Node Name	ApSys		
State 0	change <40	5	0
State 1	change >40	0	4
Node Name	FAC		
State 0	change <10	6	2
State 1	change >10	3	5

5.2.1.2 Natural Language Processing Results.

NLP was used to analyze the free text in the patient shift notes. Five contextual categories were formed as a result of the NLP: VAD malfunction, socialization, ambulation, positive descriptors, and nutrition. These categories, as well as an example of the words that fall underneath each, is detailed in an excerpt of raw data included in Appendix E. When compared to transplanted patients, weaned patients exhibit fewer reports of VAD malfunction, better nutritional status, greater activity level, can be described in more positive ways, and receive more visits from family and friends, as shown in Figure 22.

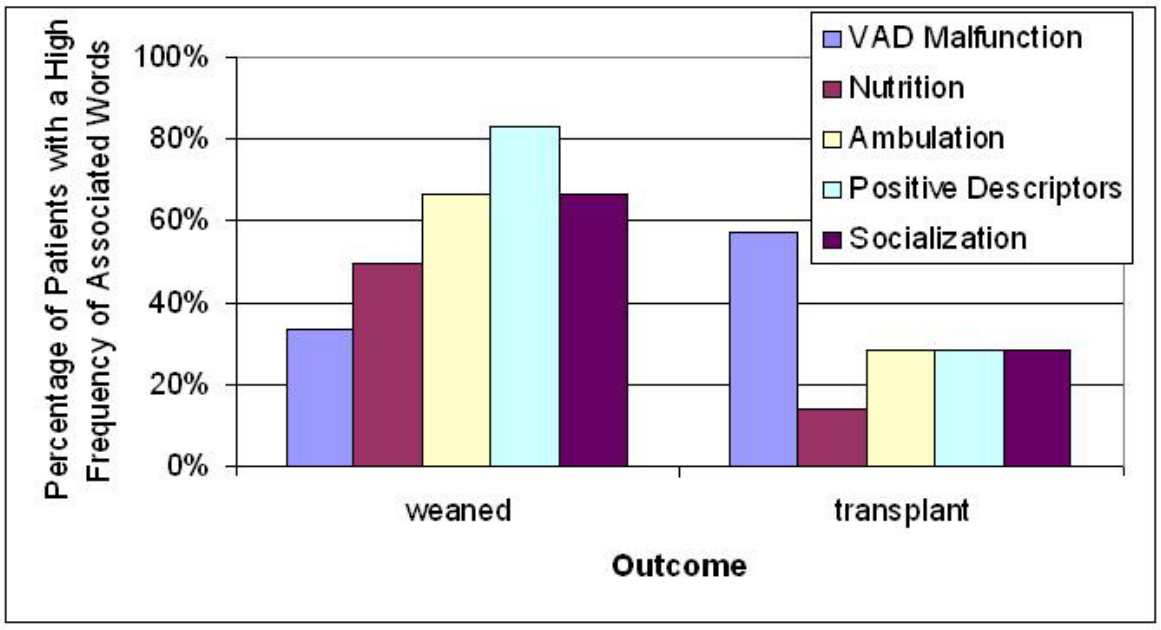

Figure 22: Natural language processing results for of shift notes

5.2.2 Bayesian Belief Network Representation

The final data decision model in BBN form is shown in Figure 23 below. For the sake of clarity, the 7 categories of data are color coded and variables belonging to each category are clustered together.

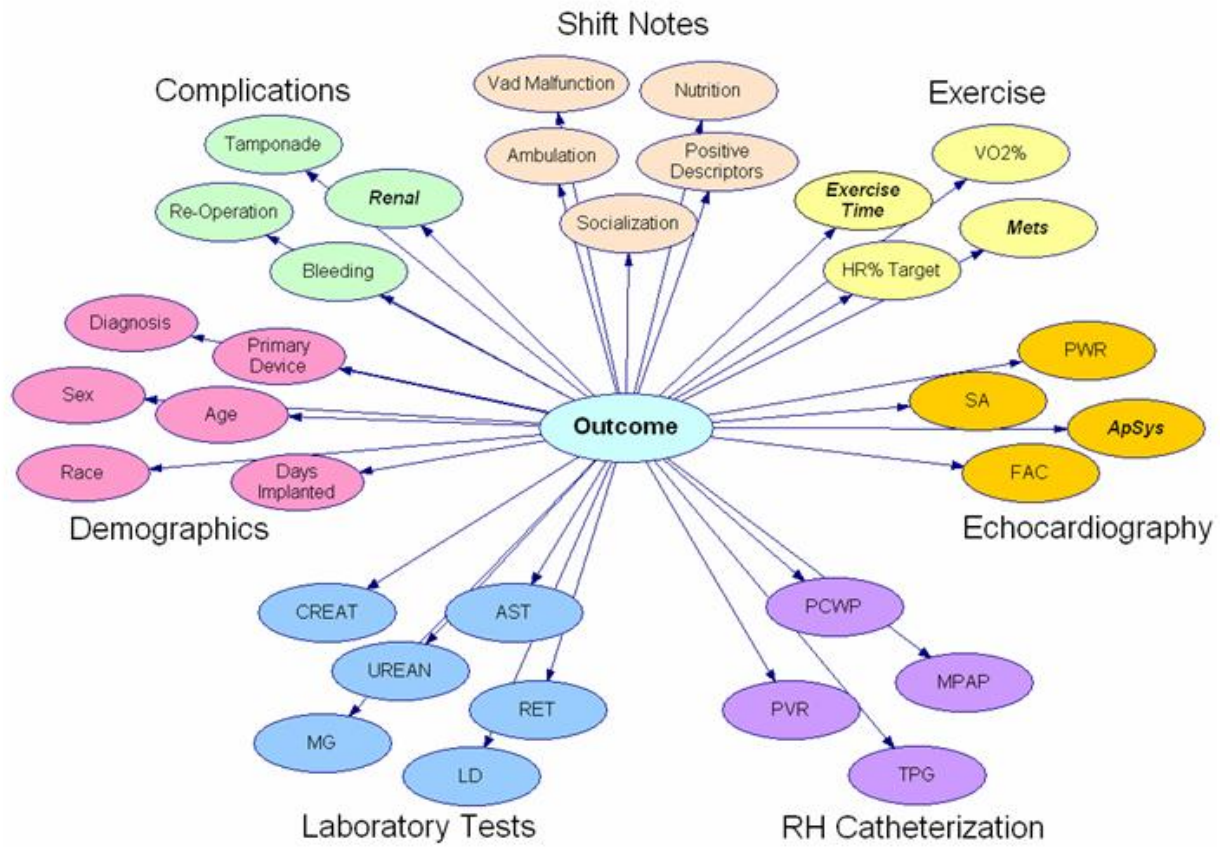

Figure 23: Final data decision model

5.2.3 Evaluation

The predictive accuracy of the final data decision model, shown in Figure 23, is shown in Table 14.

Table 14: Predictive value of data decision model

True Wean	True Transplant	False Wean	False Transplant
9	8	1	1

5.3 HYBRID MODEL

5.3.1 Decision Structure and Numerical Parameters

The structure and numerical parameters for the hybrid model were inherited directly from the expert and data models, shown in Figures 21 and 23.

5.3.2 Bayesian Belief Network Representation

The final hybrid decision model in BBN form is shown in Figure 24 below. This model was formed through a direct combination of the final expert and data models. As the variables and their states have been described in previous sections of this thesis, they will not be repeated here.

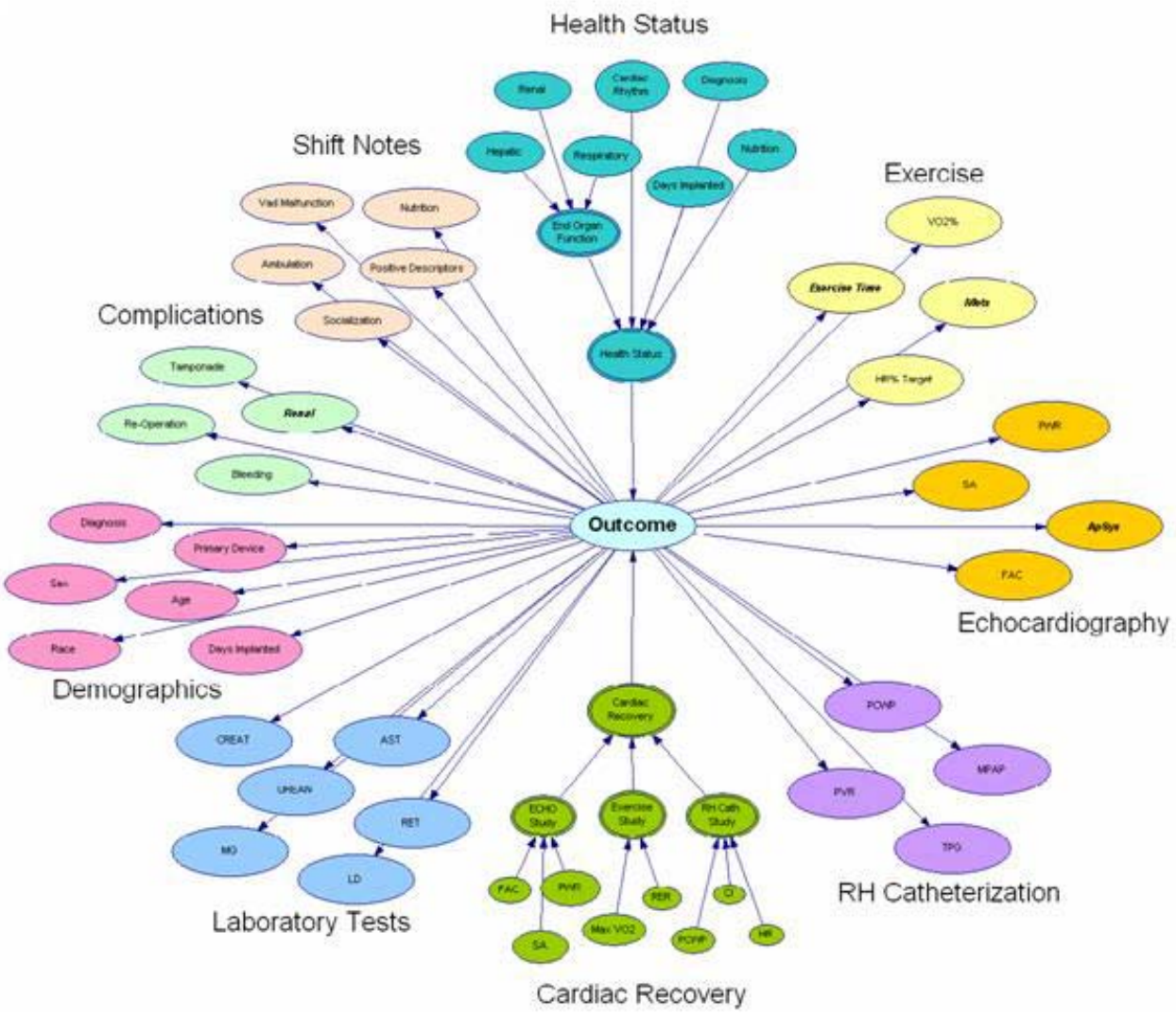

Figure 24: Final hybrid decision model

5.3.3 Evaluation

The predictive accuracy of the final hybrid decision model, shown in Figure 24, is shown in Table 15.

Table 15: Predictive value of hybrid decision model

True Wean	True Transplant	False Wean	False Transplant
9	9	0	1

5.4 MODEL INTERFACE

5.4.1 Expert model interface

5.4.1.1 Design Features. The Pocket PC model interface was designed to facilitate data entry and display the decision model results to the clinician in a user-friendly, uncomplicated format. When the program is started, a file management screen is presented to the user, as shown in Figure 25. This screen allows the user to choose whether they want to update, delete or add a patient file. The update and add functions allow access to the data entry and decision support levels of interface, shown in Figures 26 and 27. Due to the limited area to display information on the Pocket PC screen, the data entry level utilizes a series of tabbed panels. Also, in order to standardize the format in which data is entered, each data input field utilizes a pre-formatted drop down list. The user simply chooses a value for each field from this list and moves from tab to tab until all data is entered for the patient. Finally, on the decision support tab, the user is presented with a probability (percentage) that describes whether or not this patient can be successfully weaned, as well as a list of recommendations for improving their chances of recovery, as shown in Figure 27; these recommendations are simply a list of variables that are not in their optimal states for that particular patient.

5.4.1.2 Prototype Images

Figure 25: File management screen of user interface

Figure 26: Data entry tab of model user interface

Figure 27: Decision support tab of model user interface

6.0 DISCUSSION AND CONCLUSIONS

6.1 EXPERT MODEL

Of the 19 patients included in this study, the expert model was able to correctly predict 100% of the transplants and 60% of the weans. The expert model appears to be a rather conservative approach to identifying candidates for VAD weaning, given the number of false transplants it predicted.

The results of this model demonstrate that experts did not follow the rational approach that they defined in their interviews. The fact that this model, which was based solely on expert input, was not able to correctly predict the same cases that the experts themselves did can mean a number of things. It is possible that the knowledge acquisition techniques used to elicit information from the experts were not rigorous enough, leaving critical information out of the final decision flowchart. Furthermore, the interviews also have their limitations-- they do not reflect the disagreements and hierarchical conflicts that occur in group decisions. It is also possible that the experts themselves left out important input when they asked to edit the combined flowcharts. By comparing the predictive accuracy of the decision flowchart to the predictive accuracy of the BBN, it is clear that preferences and risk attitudes do play a large role in the decision making process for experts—for example, many clinicians will consider weaning

even if health status is technically inadequate. It is quite possible that clinicians are less conservative and algorithmic in real life than was described through these questionnaires.

6.2 DATA MODEL

The data model was able to correctly predict 90% of the transplants and 90% of the weans. However, this model also predicted a wean for a patient who was actually transplanted. As this is considered a dangerous scenario in clinical prediction, the data model can be considered a relatively aggressive approach to identifying candidates for VAD weaning.

The results of this model show that patterns in the patient data are significant and include variables that are not formally included in the experts' assessments of cardiac recovery. While none of the patterns in the data were particularly groundbreaking or surprising (and in fact correlated with many of the results in published studies), the idea of including these data in the decision making process addresses the problem of selector bias in clinical experience with VAD weaning. It is evident that clinicians choose to formally screen "healthier" patients who "exhibit signs of being recoverable;" however, a method for quantifying these signs is not yet in place. The data model gestures toward the importance of including these types of variables and toward a way of quantifying these signs. This would be the significant step in developing a standardized protocol for selecting patients to screen for recovery (so that clinical experience at one center can be compared to the clinical experience at another).

Although the results of this model are highly encouraging, there are two noteworthy limitations that must be considered before drawing large conclusions. The first limitation is associated with the sample size used in this study. When training data, typically, one takes only

half of the data to train with and uses the other half for evaluating the predictability of the model. While this would be an ideal course of action, because our data set was so small, the entire set had to be used; the subjects that were used to test the model were the same subjects that were used to train it. While SPSS Clementine uses a 50% method to minimize the risk of overtraining of the data, training and evaluating using the same data set is not ideal. The second limitation is the quality of the data. Although the data is being analyzed in an objective manner, the data itself is by no means objective. It needs to realized that there is a there is a layer of decision making that is already part of the data before it is ever entered into the decision model. To clarify through an example, all VAD patients suffer through bleeding problems. However, in some cases, the data indicates a complication due to bleeding and in other cases, the patient is not listed as having any such complications. The decision of whether bleeding is actually a complication is often interpreted differently by different clinicians and as such could be entered into the database already biased.

In addition to these limitations, there is a major assumption that was made when constructing this model: it was assumed that the clinician's final decision to wean or transplant the patient was correct. However, how can we ultimately know that clinician made the right choice for the patient? While we can look at the follow-up data to see if the weaned patients maintained their recovery, it is very important to realize that the model itself is based upon the fact that the decisions made by the clinicians were correct.

6.3 HYBRID MODEL

The hybrid model correctly predicted 100% of the transplants and 90% of the weans. Out of 19 cases, the model incorrectly predicted one patient case. In this case, the model predicted a transplant where the patient was actually weaned. Interestingly, it should be noted that follow-up data for the patient indicated that 1 year post-explant, ventricular failure occurred and the patient required a transplant. Due to the high predictive accuracy, in this study, the hybrid model is considered the best overall approach to identifying VAD weaning candidates.

This model has shown that if expert- and data-derived knowledge are combined into one model, it is possible to predict patient outcome with greater accuracy than by using each source of knowledge separately. This may be because the combined models appear to compensate for their limitations. For example, the data model may be adding information where the expert model lacked insight and the expert model may be adding some conservativism where the data model is too relaxed.

The predictive accuracy of this model indicates that a hybrid system has the potential to augment and support, as a decision support system should, the clinicians' decision making process when identifying VAD weaning candidates. Also, it represents a feasible method for sharing expert- and data-derived knowledge among other centers with varying degrees of experience.

6.4 MODEL INTERFACE

The model was able to be fully implemented on a Pocket PC. The interface is user-friendly and due to its portability, it is a convenient choice for clinicians. A pilot study would reveal areas for improvement and expansion, however, the infrastructure of the interface, as designed for this study, is flexible enough to incorporate these changes as they arise.

7.0 STUDY SIGNIFICANCE

This study has proven the feasibility of developing a DSS for identifying and evaluating VAD weaning candidates. While the study has its limitations, the results are encouraging and certainly warrant further investigation.

It is hoped that this study has made a step towards showing that the use of a DSS in this patient population has the potential to promote responsible and wide-spread use of VADs for cardiac rehabilitation, not only for the patients that are being treated with VADs as a BTT, but also for the thousands of heart failure patients who could potentially benefit from VAD therapy for the specific purpose of BTR.

Furthermore, this study represents the first efforts in applying a DSS in VAD patient care. As complex decisions surround many aspects of the care of VAD patients, this study can hopefully encourage and provide a framework for future development of DSS in this patient population.

8.0 FUTURE DIRECTIONS

Due to the promising results of this study, it is recommended that further development of this model continue. First, in order to strengthen the expert model, more knowledge should be acquired from the experts. However, a more rigorous technique should be employed; several computer-aided knowledge elicitation techniques exist and are available commercially for this purpose. Second, a local expansion of the data-derived knowledge base is recommended. This could include formal measures of quality of life, functional assessments, and temporal analysis of hemodynamic data. Thirdly, a prospective multi-center expansion of both the expert- and data-derived knowledge base is recommended. Not only would it be interesting to test the predictive accuracy of these models on a separate data set, but with this larger sample size, it would be possible to constructively respond to the main critique of this study—that the model was evaluated using the same data on which it was built. Fortunately, with the advent of the International Society of Heart and Lung Transplant VAD registry, a larger set of weaning data will soon be available for analysis. With a larger number of patient cases, the model can be built using half of the data set and tested on the other, thereby decreasing the chance of overtraining the Artificial Neural Networks and increasing the acceptance of the decision structures.

APPENDIX A

EXPERT PANEL AND AREAS OF EXPERTISE

Robert Kormos, MD: Cardiothoracic Surgeon, Director AHP, UMPC
Implant/weaning/explant of LVADs

Heart Transplant

LVAD patient treatment: from admission to discharge

Michael Mathier, MD: Cardiologist, UPMC

John Gorscan, MD: Cardiologist, UPMC

Echocardiography

Heart Failure

LVAD Patient Selection

Eileen Stanford, RN: Clinical Nurse Coordinator AHP, UPMC

Lisa Carozza, RN: Nurse Supervisor AHP, UPMC

Clinical interaction with patients

Nutrition

Exercise

Infection Management

Pharmacology

Patient Education/Consent

Margo Holm, PhD: Occupational Therapist, UPMC

Ketki Desai: Occupational Therapist, UPMC

Functional Assessment of LVAD patients

Cognitive Asessment

Physical Assessment

Mary Amanda Dew, PhD: Psychiatry, UPMC

Quality of Life of LVAD patients

Steve Winowich, PhD: Director of Clinical Engineering AHP, UPMC

Rick Schaub, PhD: Clinical Engineer AHP, UPMC

Don Severyn: Clinical Engineer AHP, UPMC

Echocardiography

Exercise Study

Clinical Application and Maintenance of LVADs

APPENDIX B

NUMERICAL DATA CATEGORIES AND VARIABLES

Table 16: Patient Demographics Variables

Outcome
Death Date
Primary Device
Primary Implant
Primary Explant
Implant days
Device 2
Implant 2
Explant 2
Device 3
Implant 3
Explant 3
Implant Age
Sex
Race
UPMC Diagnosis
Admit Date
Intention To Treat
Unos Death Cause
IABP inserted 1
IABP removed 1
IABP inserted 2
IABP removed 2

Table 17: Laboratory Test Variables

Lab Header Date		Median RET
Median ALB		Min RET
Min ALB		Max RET
Max ALB		Median CA
Median ALT		Min CA
Min ALT		Max CA
Max ALT		Median CL
Median AST		Min CL
Min AST		Max CL
Max AST		Median K
Median CREAT		Min K
Min CREAT		Max K
Max CREAT		Median MG
Median LD		Min Mg
Min LD		Max MG
Max LD		Median NA
Median TBILI		Min NA
Min TBILI		Max NA
Max TBILI		Median HCT
Median TPROT		Min HCT
Min TPROT		Max HCT
Max TPROT		Median HGB
Median UREAN		Min HGB
Min UREAN		Max HGB
Max UREAN		Median PLT
Median AWBC		Min PLT
Min AWBC		Max PLT
Max AWBC		

Table 18: Right Heart Catheterization Variables

Heart Cath Date		Heart Cath Pcwp Median
Heart Cath Cad Ynu		Heart Cath Pcwp Min
Heart Cath Rv Mean		Heart Cath Pcwp Max
Heart Cath Lvedp		Heart Cath Tpg Median
Heart Cath Lvef Low		Heart Cath Tpg Min
Heart Cath Lvef High		Heart Cath Tpg Max
Heart Cath Rvef		Heart Cath Pvr Median
Heart Cath Avo2		Heart Cath Pvr Min
Cath Type		Heart Cath Pvr Max
Heart Cath Findings		Heart Cath Psat Median
Heart Cath Comments		Heart Cath Psat Min
Heart Cath Pap Systolic Median		Heart Cath Psat Max
Heart Cath Pap Systolic Min		Cth Cardiac Output Median
Heart Cath Pap Systolic Max		Cth Cardiac Output Min
Heart Cath Pap Diastolic Median		Cth Cardiac Output Max
Heart Cath Pap Diastolic Min		Cth Cardiac Index Median
Heart Cath Pap Diastolic Max		Cth Cardiac Index Min
Heart Cath Pap Mean Median		Cth Cardiac Index Max
Heart Cath Pap Mean Min		Cth Right Atrium Median
Heart Cath Pap Mean Max		Cth Right Atrium Min
Heart Cath Rv Systolic Median		Cth Right Atrium Max
Heart Cath Rv Systolic Min		Heart Cath Heart Rate Median
Heart Cath Rv Systolic Max		Heart Cath Heart Rate Min
Heart Cath Rv Diastolic Median		Heart Cath Heart Rate Max
Heart Cath Rv Diastolic Min		
Heart Cath Rv Diastolic Max		

Table 19: Echocardiographic Variables

Echo Date		Off Vad EDA
Echo Type		Off Vad ESA
Echo Lvef Low		Off Vad Ap Systolic
Echo Lvef High		Off Vad SA
Echo Lv Dias Diam		Off Vad FAC
Echo Lv Systol Diam		Off Vad Max PWR
Echo Lv Septal		delta SA
Echo Post Wall		delta SA overall
Echo Aortic Root		delta ApSys
Echo Left Atrium		delta ApSys overall
Echo Mitral Regurg		delta FAC
Echo Tricuspid Regurg		delta FAC overall
Echo Ischemia		Echo Comments
Full Vad Flow		
Full Vad EDA		
Full Vad ESA		
Full Vad Ap Systolic		
Full Vad SA		
Full Vad FAC		
Half Vad Flow		
Half Vad EDA		
Half Vad ESA		
Half Vad Ap Systolic		
Half Vad SA		
Half Vad FAC		
Half Vad Max PWR		

Table 20: Exercise Test Variables

Name		Device
Implant Date		Rest LVAD rate
Transplant Date		Rest LVAD output
Weaning Date		Rest LVAD stroke
Still on Device as of		Rest LVAD res Vol
Ex Test date		Max LVAD rate
POD		Max LVAD output
B or T		Max LVAD stroke
Time		Max LVAD res Vol
VO2 MAX (mL/kg/min)		Rest RVAD rate
VO2%		Rest RVAD output
Mets		Max RVAD rate
Peak HR		Max RVAD output
HR (%)		Functional Capacity
Peak BPsys		Functional Class
Peak BPdia		Heart Rate Response
An Thres		Blood Pressure Response
Work - TM (Watts)		Ventilatory Response
RER		Exercise-induced Ischemia
Pred Max VO2 (mL/kg/min)		Exercise-induced Arrythmia
Pred Max Mets		ECG at rest
Pred Max Work Rate (Watts)		Comments
Pred Max HR		
Pred Max Sys Pres		
Diagnosis		
Reason for Test		

Table 21: Complications Variables

Bleeding
Infection
Re-Operation
Mechanical
RV Failure
CV Dysfunction
Hemolysis
Tamponade
Respiratory
Hepatic
Renal
GI
Neurologic
Complication Date
Resolved Date
Comments

APPENDIX C

EXCERPT FROM A SHIFT NOTES FILE

Patient ID: 9264

Outcome: Weaned

PO 3.5 initially but quickly poor flows -tried ECMO to Left Atrium but lots of air in ECMO circuit

Back on CPB Then LVAD only @1:09am PO 4.3.-4.7 VOL; ET = 300MS ;DP=200;VAC=-8;+FILL ;+EMPTY

Dr Kormos wants low vac allow Lv to do some work and not

PO:5.2-5.3; PR: 80-89, VOL, ET 290ms; DP: 202-204; Vac: -4 to -10 +flash

MAP 80-90, CVP 11-18. IVAD had a few vacuum alarms early in the shift, going to +4. Vac was dialed slightly more negative, as we were told to keep it under -10. No other alarms d

PO 4.5 through most of day. wking up in mid-morning. possibility to extubate this evening. IVAD flash functioning properly. vaccuum still kept low at Dr. Kormos' request.

LVAD: PO 5.0 PR 77 %sys 38,290 DP 202 V -10

MAP 86 PAP 27 HR 94 CVP 17

flash working properly.

PO 5.2-5.7 lpm in volume. Good flash on black box. Patient seeming to have difficluties in being responsive

Pt is still intubated in the ICU.. Flows were 5.0-6.1 Left with good ejection on the black box. CVP: 11-18..

PO:5.2-6.1, PR:80-95, %sys:39-46, Et 290, Prs:218-220, Vac:-12 -14

No events

PO:4.8-5.9, PR:76-93, ET 300ms, DP 224-228, Vac: -5 to -16 +flash

Patient was extubated this morning and seems to be coherent. Nurse got him out of bed and he sat in the chair from 4pm on. Flows dropped when he first sat up, but quickly rebounded. Ever

LVAD: PO 5.0-6.1 PR 80-84 %sys 40, 300 DP 226 V -6,-14

CVP 9; HR 94 MAP 85

PO 5.3-5.7, PR 82-87, ET 300ms, DP 224-225, Vac -10 to-14 +flash

Patient was sitting in the chair at beginning of the shift. He was complaining about abdominal discomfort and nurse thinks it may be pump related.

PO: 5.3-4.8 PR: 83-75 ED: 300 good flash stable BPs

LVAD: PO=5.3-5.5 LPM; PR=83-86 BPM; VOL; ET=300 ms; DP=223-225 mmHg; VP= -10 to -16 mmHg; + Flashes

No alarms. Patient was awake and sitting upright in a chair during the early evening before being laid down again and sleeping for the duration of the nig

5.1-5.3 Vol 79-82

+ flash

sleeping - sitting in chair this morning

MAP 64-65; CVP 6-8; HR 88-104 bpm

po 5.3-5.7 l/min; pr 82-87 bpm; 37-44%; 300 ms; + flash

In bed. Had visitors/asleep.

LVAD 5.0-5.4, DP ~ 225 mmHg, vac ~ -15 mmHg, MAP ~ 65 mmHg, consistent eject flash, was to go to 7F but no available beds, will go in am

MAP 61-86; CVP 13-16; HR 93-102 bpm

po 5.4-6.2 l/min; pr 84-96 bpm; 42-48%; 300 ms; + flash

In bed, asleep. Awake in morning watching tv.

LVAD: 5.2-6.2, good eject flash, MAP ~ 68-89 mmHg, pt. sat in chair from 11:30 am on. Pt. will stay in icu because of hypotension last night and becuase he was febrile.

5.5-6.1 Vol 86-95

+ flash

sleeping

getting swan this morning, hopefully moving upstairs today

MAP 66-79; HR 92-97 bpm

po 5.3-6.1 l/min; pr 82-95 bpm; 41-47%; 300 ms; + flash

In chair/in bed.

Hemodynamically stable. Outputs about 5.5 liters per min, and a consistent empty signal. Some concern over WBC and Temp.; Swaned late in afternoon - cardiac output > 11 lit/min causing some concern over possible sepsis. Also have a TTE scheduled for to

PO 5.7-5.9; PR 89-91; vol; %sys 44-45; ET 300ms; DP 223-224; Vac -15 to -14; +Empty Signal

In bed/sleeping all shift.

HR 91-96 bpm; MAP 62-79

po 5.9 l/min; pr 80-92 bpm; 41-46%; 300 ms; + flash

In chair.

5.6-5.9 vOL 87-92

+ FLASH

sleeping

nurse said pt going for wean test today

PO: 5.7-5.9 PR: 89-92 VOL (299msec) max:223 min:-15/-20

good flash

LVAD 5.6-.6.0 VOL + FLASH

moved up to 7F yesterday

worked with PT Stood -a lttle light headed and VERY nauseas sat down

after a little bit felt better stood walked 4 steps and back to bed

became orthostatic as flows dropped and had asynch alarm

prevouisl

LVAD: PO 5.3-6.1 PR 82-93 VOL ED 299 DP 221/226 V -13/-18

+ Flash...got paged because of sync alarms...pt was using the bathroom and flows were 4.2...nurses got patient into bed and flows returned to previous values...

APPENDIX D

EXPERT QUESTIONNAIRE

A. Would you wean if the patient's health status and cardiac recovery are adequate?

Yes No

Percent of patients who would likely be successfully weaned if:

100 90 80 70 60 50 40 30 20 10 0

Percent of patients who would likely be unsuccessful weaned if:

100 90 80 70 60 50 40 30 20 10 0

B. Would you wean if the patient's health status and cardiac recovery are inadequate?

Yes No

Percent of patients who would likely be successfully weaned if:

1 out of 5 health status parameters inadequate and

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

2 out of 5 health status parameters inadequate and

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

3 out of 5 health parameters inadequate and

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

4 out of 5 health parameters inadequate and

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

5 out of 5 health parameters inadequate and

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

Percent of patients who would likely be unsuccessful weaned if:

1 out of 5 health status parameters inadequate and

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

2 out of 5 health status parameters inadequate and

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

3 out of 5 health parameters inadequate and

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

4 out of 5 health parameters inadequate and

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

5 out of 5 health parameters inadequate and

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

C. Would you wean if the patient's health status is inadequate but cardiac recovery is adequate?

Yes No

Percent of patients who would likely be successfully weaned if:

1 out of 5 health status parameters inadequate

100 90 80 70 60 50 40 30 20 10 0

2 out of 5 health status parameters inadequate

100 90 80 70 60 50 40 30 20 10 0

3 out of 5 health status parameters inadequate

100 90 80 70 60 50 40 30 20 10 0

4 out of 5 health status parameters inadequate

100 90 80 70 60 50 40 30 20 10 0

5 out of 5 health status parameters inadequate

100 90 80 70 60 50 40 30 20 10 0

Percent of patients who would likely be unsuccessfully weaned if:

1 out of 5 health status parameters inadequate

100 90 80 70 60 50 40 30 20 10 0

2 out of 5 health status parameters inadequate

100 90 80 70 60 50 40 30 20 10 0

3 out of 5 health status parameters inadequate

100 90 80 70 60 50 40 30 20 10 0

4 out of 5 health status parameters inadequate

100 90 80 70 60 50 40 30 20 10 0

5 out of 5 health status parameters inadequate

100 90 80 70 60 50 40 30 20 10 0

D. Would you wean if the patient's health status is adequate but cardiac recovery is inadequate?

Yes No

Percent of patients who would likely be successfully weaned if:

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

Percent of patients who would likely be unsuccessfully weaned if:

2 out of 2 weaning trials adequate but RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath adequate

100 90 80 70 60 50 40 30 20 10 0

1 out of 2 weaning trials adequate and RH Cath inadequate

100 90 80 70 60 50 40 30 20 10 0

RH Cath adequate but no weaning trials adequate

100 90 80 70 60 50 40 30 20 10 0

APPENDIX E

EXCERPT OF NATURAL LANGUAGE PROCESSING DATA

Table 22: Natural Language Processing Frequency and Category Assignment

Word	Original Frequency	Vad Related Issues- OK	Vad Related Issues- Problems	Nutrition- OK	Activity Level- Active	Activity Level- Medium	Activity Level- Resting	Psychological Assessment- Positive	Psychological Assessment- Negative	Pain/Distress	General Descriptors- Positive	General Descriptors- Negative	Socialization
POSITIVEFLASH	81	81											
WALK	33				33								
SLEEP	29						29						
FLASH	22	17	5										
BED	14						22						
GOOD	12										12		
PHYSICALTHERA	12				12								
BIKE	11				11								
NOALARM	11	11											
SITTING	10					11							
CHAIR	8					11							
ALARM	7	4	3										
CONSISTENT	7										7		
STABLE	6										6		
TREADMILL	6				6								
VISITING	6												6
WELL	6										6		
UPRIGHT	5					5							
FAMILY	4												4
COMPLAIN	3									3			
STATIONARY	3				3								
TALKATIVE	3							3					

BIBLIOGRAPHY

1. Levin, H.R., et al., Transient normalization of systolic and diastolic function after support with a left ventricular assist device in a patient with dilated cardiomyopathy. J Heart Lung Transplant, 1996. **15**(8): p. 840-2.

2. Holman, W.L., R.C. Bourge, and J.K. Kirklin, Case report: circulatory support for seventy days with resolution of acute heart failure. J Thorac Cardiovasc Surg, 1991. **102**(6): p. 932-4.

3. Mueller, J., et al., Predictive factors for weaning from a cardiac assist device. An analysis of clinical, gene expression, and protein data. J Heart Lung Transplant, 2001. **20**(2): p. 202.

4. Termuhlen, D.F., et al., Hemodynamic predictors for weaning patients from ventricular assist devices (VADs). J Biomater Appl, 1990. **4**(4): p. 374-90.

5. Garg, S. and J. Narula, Pathogenetic basis of myocardial dysfunction and amenability to reversal. Cardiol Clin, 2003. **21**(1): p. 83-91.

6. Heerdt, P.M., et al., Chronic unloading by left ventricular assist device reverses contractile dysfunction and alters gene expression in end-stage heart failure. Circulation, 2000. **102**(22): p. 2713-9.

7. Torre-Amione, G., et al., Decreased expression of tumor necrosis factor-alpha in failing human myocardium after mechanical circulatory support : A potential mechanism for cardiac recovery. Circulation, 1999. **100**(11): p. 1189-93.

8. Wolff, M.R., et al., Myofibrillar calcium sensitivity of isometric tension is increased in human dilated cardiomyopathies: role of altered beta-adrenergically mediated protein phosphorylation. J Clin Invest, 1996. **98**(1): p. 167-76.

9. Sodian, R., et al., Decreased plasma concentration of brain natriuretic peptide as a potential indicator of cardiac recovery in patients supported by mechanical circulatory assist systems. J Am Coll Cardiol, 2001. **38**(7): p. 1942-9.

10. Dipla, K., et al., Myocyte recovery after mechanical circulatory support in humans with end-stage heart failure. Circulation, 1998. **97**(23): p. 2316-22.

11. Barbone, A., et al., Comparison of right and left ventricular responses to left ventricular assist device support in patients with severe heart failure: a primary role of mechanical unloading underlying reverse remodeling. Circulation, 2001. **104**(6): p. 670-5.

12. Delgado, D.H., et al., Explantation of a mechanical assist device: assessment of myocardial recovery. J Card Surg, 2004. **19**(1): p. 47-50.

13. Hetzer, R., et al., Bridging-to-recovery. Ann Thorac Surg, 2001. **71**(3 Suppl): p. S109-13; discussion S114-5.

14. Gorcsan, J., 3rd, et al., Non-invasive assessment of myocardial recovery on chronic left ventricular assist device: results associated with successful device removal. J Heart Lung Transplant, 2003. **22**(12): p. 1304-13.

15. MIRM, Artificial heart Program-Ventricular Support to recovery. 2005, McGowan Institute for Regenerative Medicine: Pittsburgh, PA.

16. Simon, M., et al., Myocardial Recovery Using Ventricular Assist Devices: Prevalence, Clinical Characteristics and Outcomes. Circulation, 2005. **In Press**.

17. Entwistle, J.W., 3rd, Long-term mechanical ventricular assistance toward myocardial recovery. Cardiol Clin, 2003. **21**(1): p. 75-82.

18. Frazier, O.H. and T.J. Myers, Left ventricular assist system as a bridge to myocardial recovery. Ann Thorac Surg, 1999. **68**(2): p. 734-41.

19. Frazier, O.H., et al., Improved left ventricular function after chronic left ventricular unloading. Ann Thorac Surg, 1996. **62**(3): p. 675-81; discussion 681-2.

20. McBride, L.R., et al., Clinical experience with 111 thoratec ventricular assist devices. Ann Thorac Surg, 1999. **67**(5): p. 1233-8; discussion 1238-9.

21. Nakatani, T., et al., Long-term circulatory support to promote recovery from profound heart failure. Asaio J, 1995. **41**(3): p. M526-30.

22. Muller, J., et al., Weaning from mechanical cardiac support in patients with idiopathic dilated cardiomyopathy. Circulation, 1997. **96**(2): p. 542-9.

23. Hetzer, R., et al., Cardiac recovery in dilated cardiomyopathy by unloading with a left ventricular assist device. Ann Thorac Surg, 1999. **68**(2): p. 742-9.

24. Maybaum, S., et al., Assessment of myocardial recovery in a patient with acute myocarditis supported with a left ventricular assist device: a case report. J Heart Lung Transplant, 2003. **22**(2): p. 202-9.

25. Mancini, D.M., et al., Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation, 1991. **83**(3): p. 778-86.

26. Mancini, D.M., et al., Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure. Circulation, 1998. **98**(22): p. 2383-9.

27. Richenbacher, W.E., Recovery of myocardial function with long-term ventricular assist device support. Asaio J, 2001. **47**(6): p. 586-7.

28. AHA, Heart Disease and Stroke Statistics. 2005, American Heart Association: Dallas, Texas.

29. A.D.A.M., MedLine Plus Medical Encyclopedia. 2005, United States National Library of Medicine and National Insitutes of Health.

30. Bales, A.C. and M.J. Sorrentino, Causes of congestive heart failure. Prompt diagnosis may affect prognosis. Postgrad Med, 1997. **101**(1): p. 44-9, 54-6.

31. Schaub, R., Heart Failure, in Cardio-Pulmonary and Vascular Organ Replacement. 2004, Cardio-Clinical Internship Lecture: University of Pittsburgh Department of Bioengineering.

32. UNOS, 2004 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1994-2003. , Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD; United Network for Organ Sharing, Richmond, VA; University Renal Research and Education Association, Ann Arbor, MI.

33. Barnard, C.N., The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. S Afr Med J, 1967. **41**(48): p. 1271-4.

34. Baran, D.A., I.D. Galin, and A.L. Gass, Current practices: immunosuppression induction, maintenance, and rejection regimens in contemporary post-heart transplant patient treatment. Curr Opin Cardiol, 2002. **17**(2): p. 165-70.

35. Aravot, D., et al., Functional status and quality of life of heart-lung transplant recipients. Transplant Proc, 2001. **33**(6): p. 2890-1.

36. Schocken, D.D., et al., Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol, 1992. **20**(2): p. 301-6.

37. Rose, E.A. and O.H. Frazier, Resurrection after mechanical circulatory support. Circulation, 1997. **96**(2): p. 393-5.

38. Murali, S., Mechanical circulatory support with the Novacor LVAS: world-wide clinical results. Thorac Cardiovasc Surg, 1999. **47 Suppl 2**: p. 321-5.

39. Cooley, D.A., et al., Human cardiac transplantation. Circulation, 1969. **39**(5 Suppl 1): p. I3-12.

40. Vandenberghe, S., Modeling the interaction between cardiac assist devices and the left ventricle. 2004, Ghent University: Ghent.

41. Kormos, R.L., et al., Chronic mechanical circulatory support: rehabilitation, low morbidity, and superior survival. Ann Thorac Surg, 1994. **57**(1): p. 51-7; discussion 57-8.

42. Levin, H.R., et al., Potential of left ventricular assist devices as outpatient therapy while awaiting transplantation. Ann Thorac Surg, 1994. **58**(5): p. 1515-20.

43. Dew, M.A., et al., Early post-transplant medical compliance and mental health predict physical morbidity and mortality one to three years after heart transplantation. J Heart Lung Transplant, 1999. **18**(6): p. 549-62.

44. Winowich, S., et al., Discharging patients who are undergoing mechanical circulatory support. Ann Thorac Surg, 1996. **61**(1): p. 478-9.

45. Morales, D.L., M. Argenziano, and M.C. Oz, Outpatient left ventricular assist device support: a safe and economical therapeutic option for heart failure. Prog Cardiovasc Dis, 2000. **43**(1): p. 55-66.

46. Frazier, O.H., et al., Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. Ann Surg, 1995. **222**(3): p. 327-36; discussion 336-8.

47. Pennington, D.G., et al., Eight years' experience with bridging to cardiac transplantation. J Thorac Cardiovasc Surg, 1994. **107**(2): p. 472-80; discussion 480-1.

48. Rose, E.A., et al., The REMATCH trial: rationale, design, and end points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. Ann Thorac Surg, 1999. **67**(3): p. 723-30.

49. Burch, G.E. and N.P. DePasquale, On resting the human heart. Am Heart J, 1966. **71**(3): p. 422.

50. Turban, E., Decision support and expert systems : management support systems. 4th ed. 1995, Englewood Cliffs, N.J.: Prentice Hall. xxv, 887, 36, 7 p.

51. Druzdzel, M. and R. Flynn, Decision Support Systems, in Encyclopedia of Library and Information Science, A. Kent, Editor. 2000, Marcel Drekker, Inc.: New York. p. 120-133.

52. Shortliffe, E.H., et al., Medical informatics : computer applications in health care. 1990, Reading, Mass.: Addison-Wesley Pub. Co. xx, 715 p.

53. Finlay, P.N., Introducing decision support systems. 1994, Oxford, UK Cambridge, Mass., USA: NCC Blackwell; Blackwell Publishers. 274 p.

54. Clemen, R.T., T. Reilly, and R.T. Clemen, Making hard decisions with DecisionTools. 2nd rev. ed. 2001, Pacific Grove, CA: Duxbury/Thomson Learning. xxv, 733 p.

55. Bunn, D.W., Applied decision analysis. McGraw-Hill series in quantitative methods for management. 1984, New York: McGraw-Hill. vii, 251 p.

56. Cooper, G.F., Nestor: A computer-based medical diagnostic aid that integrates causal and probabilistic knowledge, in Medical Information Sciences. 1985, Stanford University.

57. Tsiftsis, D.D., Objective Medical Decision-Making: Systems Approach in Disease. 1985, Crete, Greece: Springer-Verlag.

58. Pizzorno, J.E., A.K. Evans, and B. Levin, System and Method for Providing Health Care Advice by Diagnosing System Function, U.P. Office, Editor. 2003, Pizzorno, Joseph E. et al.: USA.

59. Brynjestad, U., Knowledge-Based Expert Interactive System for Pain, U.P. Office, Editor. 1999, Ulf Brynjestad: USA.

60. Illif, E., Disease Management System and Method, U.P. Office, Editor. 2001, First Opinion Corproation: USA.

61. Onisko, A., Probabalistic Causal Models in Medicine: Applications to Diagnosis of Liver Disorders, in Institute of Biocybernetics and Biomedical Engineering. 2002, Polish Academy of Science: Warsaw, Poland. p. 140.

62. Yang, D., Reinforcement Learning in Optimal Ventilator Control, in Computer Science. 2002, Peking University: Bejing, China. p. 62.

63. Frize, M. and R. Walker, Clinical decision-support systems for intensive care units using case-based reasoning. Med Eng Phys, 2000. **22**(9): p. 671-7.

64. Michalowski, W., et al., Design and development of a mobile system for supporting emergency triage. Methods Inf Med, 2005. **44**(1): p. 14-24.

65. Dojat, M. and L. Brochard, Knowledge-based systems for automatic ventilatory management. Respir Care Clin N Am, 2001. **7**(3): p. 379-96, viii.

66. Antonsson, J., et al. Design of a Clinical Decision Support System for Assist Support Devices in Thoracic Surgery. in American Medical Informatics Association. 2000. Los Angeles, CA.

67. Hudson, D.L., M.E. Cohen, and IEEE Engineering in Medicine and Biology Society., Neural networks and artificial intelligence for biomedical engineering. IEEE Press series in biomedical engineering. 2000, New York: IEEE Press. xxiii, 306 p.

68. Taler, S.J., S.C. Textor, and J.E. Augustine, Resistant hypertension: comparing hemodynamic management to specialist care. Hypertension, 2002. **39**(5): p. 982-8.

69. Long, W., Temporal reasoning for diagnosis in a causal probabilistic knowledge base. Artif Intell Med, 1996. **8**(3): p. 193-215.

70. Muller, R., et al., THEMPO: a knowledge-based system for therapy planning in pediatric oncology. Comput Biol Med, 1997. **27**(3): p. 177-200.

71. Cheng, C.H., et al., Design of a modular, extensible decision support system for arrhythmia therapy. Proc AMIA Symp, 1998: p. 693-7.

72. Begley, R., Adding Intelligence to Medical Devices, in Medical Device and Diagnostic Industry. March, 2000. p. 150.

73. Perreault L, M.J., A pragmatic framework for understanding clinical decision support. Journal of Healthcare Information Management, 1999. **13**(2): p. 5-21.

74. Brohet, C., et al. Medical Decision-Making applied to the Diagnosis of Coronary Artery Disease. in Objective Medical Decision-Making: Systems Approach in Disease. 1985. Crete, Greece: Springer-Verlag.

75. Morice, V., et al. Hypertension Management: Connection of an Expert System to the Artemis Patient Database. in Objective Medical Decision-Making: Systems Approach in Disease. 1985. Crete, Greece: Springer-Verlag.

76. Nakache, J. and P. Lorente. Prognostic Indicators for Patients with Acute Myocardial Infarction Complicated by Pump Failure Undergoing Intraaortic Counterpulsation. in Objective Medical Decision-Making: Systems Approach in Disease. 1985. Crete, Greece: Springer-Verlag.

77. Holper, K., et al. Improved Estimation of Operative Risk After Heart Valve Replacement: Medical Decision-Making based on Multivariate Logistic Regression Analysis. in Objective Medical Decision-Making: Systems Approach in Disease. 1985. Crete, Greece: Springer-Verlag.

78. de Dombal, F.T., B.J. Unwin, and S. Pearson. Practical Experience in Provision of Objective Decision Support for Acute Chest Pain in Primary Care. in Objective Medical Decision-Making: Systems Approach in Disease. 1985. Crete, Greece: Springer-Verlag.

79. Fraser, H.S., W.J. Long, and S. Naimi, Evaluation of a cardiac diagnostic program in a typical clinical setting. J Am Med Inform Assoc, 2003. **10**(4): p. 373-81.

80. Long, W.J., S. Naimi, and M.G. Criscitiello, Evaluation of a new method for cardiovascular reasoning. J Am Med Inform Assoc, 1994. **1**(2): p. 127-41.

81. Druzdzel, M.S., Decision Analysis and Decision Support Systems. 2004, Course Lecture: University of Pittsburgh Department of Information Sciences.

82. UPMC, Artificial Hearts Move Into Mainstream. 2005, UPMC Health Journal: Pittsburgh, PA.

83. Seven Receive Health Care Hero Awards, in Pittsburgh Business Times. 2003: Pittsburgh.

84. MIRM, Health Care Hero Awards Presented to Dr. Kormos and Dr. Herberman. 2005, McGowan Institute for Regenerative Medicine: Pittsburgh, PA.

85. Castle Connolly Medical Ltd., America's top doctors. A Castle Connolly guide. 2001, New York: Castle Connolly Medical Ltd. xiii, 1134 p.

86. Bronzino, J.D., The biomedical engineering handbook. 1995, Boca Raton: CRC Press : IEEE Press. xxxii, 2862 p.

87. Raeth, P.G., Expert systems : a software methodology for modern applications. IEEE Computer Society Press reprint collection. 1990, Los Alamitos, Calif.: IEEE Computer Society Press. xi, 460 p.

88. Witten, I.H. and E. Frank, Data mining : practical machine learning tools and techniques with Java implementations. 1999, San Francisco, Calif.: Morgan Kaufmann. xxv, 371 p.

89. Clementine, S., Understanding Data Mining, in User's Manual. 2002, Integral Solutions Ltd. : Chicago, IL. p. 39-54.

90. Collins, B.A. Driving Out Statistical Results with Neural Nets. in ANZMAC. 2000. Griffith University, Gold Coast, Australia.

91. Johansson, U., K.R. and, and L. Niklasson. The Truth is There - Rule Extraction from Opaque Models using Genetic Programming. in Preceedings of the 17th Florida Artificial Intelligence Research Society Conference. 2004. Miami, Florida: AAAI Press.

92. Clementine, S., Clementine 7.0. 2002, Integral Solutions Ltd.: Chicago, IL.

93. Gal-Or, M., J.H. May, and W.E. Spangler, Assessing the Predictive Accuracy of Diversity Measures with Domain-Dependent, Asymmetric Misclassification Costs. Information Fusion, 2005. **6**(1): p. 37-48.

94. Watt, R.J.C., Concordance 3.2. 2004, RJC Watt: Dundee, UK.

95. Watt, R.J.C., Concordance User's Manual. 2004, RJC Watt: Dundee, UK.

96. Hanson, C.W., 3rd and B.E. Marshall, Artificial intelligence applications in the intensive care unit. Crit Care Med, 2001. **29**(2): p. 427-35.

97. Druzdzel, M.S., Genie User's Manual. 2005, Decision Systems Laboratory University of Pittsburgh: Pittsburgh, PA.

98. Druzdzel, M.S., SMILE and Genie 2.0. 2005, Decision Systems Laboratory University of Pittsburgh: Pittsburgh, PA.

99. Boone, B., Medical Pocket PC Applications. 2005.

100. Taeed, O., Using Multimedia in Medicine, in Pocket PC Magazine. March, 2002.

101. Austen, I., For the Doctor's Touch, Help in the Hand. 2002, New York Times: New York.

102. Corporation, M., eMbedded Visual C++ 4.0. 2004, Microsoft Corporation: Redmond, WA.

103. Corporation, M., SDK for Windows Mobile2003-Based Pocket PCs. 2003, Microsoft Corporation: Redmond, WA.