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ABSTRACT

The human heart is one of the most vital organs in the body. It distributes blood throughout the body, providing the body with oxygen and nutrition, and contributes to metabolism. When the heart fails, blood flow is impaired, thereby limiting the exchange of oxygen within the cardiopulmonary system as well as diminishing oxygenation and nutrition to the other major organs and periphery. The only current proven treatment for advanced heart failure is cardiac transplant. Given the heart's importance and the scarcity of donated organs, modern medicine has experimented with the creation of an artificial heart. Because the heart is primarily a pump controlled via electrical impulses, it lends itself to artificial replication, and advancements in modern engineering and medicine have turned this theory into reality. Currently, there are mechanical devices which can act as a bridge to transplant and, in many cases, improve the quality of life of their recipients. Due to a scarcity of available donor hearts as well as the high cost and complications associated with conventional heart transplants, it is imperative to do an analysis as to whether left ventricle assist devices or the total artificial heart are viable alternatives to conventional cardiac transplants. If the artificial devices can be as productive as a transplanted heart without any overt risk, they greatly expand and improve the prognosis of patients in end stage of heart failure. This paper will weigh the benefits of artificial devices as viable alternatives for the conventional heart transplant within the different aspects of treatment for end stage heart failure.

INTRODUCTION

The body requires that all its organs and supporting systems work symbiotically to achieve its optimum level of health and wellness. Failure of any organ can have an effect on the entire system. When an organ such as the heart fails, all other bodily functions suffer. Given the role of the heart in oxygenation and nutrition, it is quite obvious why heart failure leads to decreased quality of life and eventual death. It is, thus, imperative that every effort be made to take care of this very necessary organ and to try to preserve its form and function for as long as possible.

Heart disease is rapidly becoming one of the top killers of American men and women. Poor dietary habits and lack of exercise tend to lead to high cholesterol and buildup of plaque in the arteries, paving the way toward heart disease. Statistics show that every 30 seconds, someone dies of heart failure (Debakey 2000). Such staggering numbers beg a question. Why can these patients not be saved? The answer is that those who are dying have generally entered advanced stage IV heart failure. Once this stage has been reached, there is little a doctor can do aside for transplanting a new living heart. It is for this reason that research into the creation of a feasible, functional artificial heart is so crucial.

Conventional heart transplantation is still considered the gold standard in treatment for end stage heart failure due to its associated successes and the overall improvement in the quality of life experienced by the recipients (Jovic 2011). Studies show that the survival rate for transplant recipients is 86% in the first year and 64% after 5 years (Jarvik 2011). Therefore, before analyzing the effectiveness of artificial devices as a replacement for conventional heart transplant, a complete understanding of the conventional transplantation procedure as well as its advantages and disadvantages must be gained.

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CONVENTIONAL HEART TRANSPLANTS

The conventional heart transplant involves surgically removing the damaged or diseased heart and replacing it with a healthy donor heart. Although simple in theory, this procedure is difficult to execute due to the scarcity of donor hearts as well as the high cost associated with it. In order for a heart to qualify for donation, it must meet extremely stringent requirements. The potential donor must be one who has been declared brain dead but still remains on life support and satisfies established criteria in regard to age, medical condition, cause of death, and psychosocial history (Massad 2004). Additionally, the donor heart must match the blood and tissue types of the recipient almost perfectly in order to prevent rejection. Furthermore, once the organ is removed from the donor, it is packed in ice in order to preserve it, leaving the surgeon with a maximum of four to six hours to implant it into the recipient. Thus, it is crucial that the recipient be ready for surgery at a moment's notice. The convergence of all these prerequisite conditions is quite rare to the extent that in 2008 there were 3,500 heart transplants performed worldwide, while 800,000 patients were in stage IV heart failure waiting for donors (Korfer 2007).

The procedure of replacing a failing heart with a donor heart is complicated and invasive. Time, technique, and skill are of the essence. Once the donor heart is identified and allocated to a recipient based on certain criteria, the timetable from removal to implantation is kept to a minimum. At the time of procurement, the healthy donor heart is arrested by injecting into it two liters of potassium and covered with ice before removal. Once it is excised from the mediastinum, the heart is inspected for any septal defects or abnormalities. After determining that no defects are present, the heart is then placed in a sterile bag with slush and saline and transported to the transplant center. Upon the heart's arrival at the transplant center, the recipient is placed on pulmonary bypass, and a cardioectomy is performed using the Lower and Shumway technique to remove the native heart and attach the new heart to the native left and right atrial cuffs (Massad 2004).

Even if all the details of the transplant surgery are executed successfully, the transplant of a living heart remains fraught with many dangers and difficulties. The threat of contracting graft versus host disease is constant. Therefore, the patient is placed on immunosuppressive drug therapy to suppress the production and activity of T-cells which would attack the foreign organ (Jovic 2011). Consequently, routine endomyocardial biopsies must be conducted in order to ensure that the medication is effective and rule out acute cellular rejection. While immunosuppressive medication diminishes the threat of graft resistance, long-term use of immunosuppressive drugs is associated with renal failure as well as thromboembolic disease (Atasever et al. 2006). Additional complications experienced in postoperative patients include cardiac failure, pulmonary and systemic hypertension, and opportunistic infections such as pneumonia (Jovic 2011). In a study of 34 post-transplant patients, conducted by the Ege School of Medicine, researchers found that nearly one third of heart transplant patients die of pulmonary complications. In this particular study, two patients died of cardiac failure in the early postoperative period, and another 10 patients developed severe pulmonary complications, most commonly in the form of pneumonia (Atasever et al. 2006).

ETHICAL ISSUES DUE TO SCARCITY OF DONOR HEARTS

Due to the stringency of the criteria that a donor heart must meet in order to be suitable for transplant, donor hearts remain a rare commodity. Due to issues of supply and demand, ethical questions arise as to whether age, physical illness, mental capacity, or value to society should be considered in evaluating a potential transplant recipient (Jarvik 2011). If any of these

factors are taken into account, there is an inherent selection bias that is present. Furthermore, it leads into other ethical quagmires, such as determining whose life is more valuable. Therefore, there are strict guidelines set by the National Health and Medical Research Council regarding the criteria and procedures that must be adhered to in this grey area. The Australian National Health and Medical Research Council put forth a set of guidelines by stating that "there should be no discrimination between potential recipients on the basis of… race, nationality, religious belief, gender, marital status, sexual orientation, social status, disability or age, except where conditions associated with the persons age directly determine the likelihood of a poorer outcome" (Macdonald 2008). Yet, many believe that these factors should be taken into consideration when screening potential recipients. They are, therefore, fighting to further narrow the spectrum of eligible recipients.

Although conventional heart transplants are the preferred cure for advanced heart failure, there are many disadvantages associated with it, mainly high cost, scarcity of donor organ, and postoperative complications. Therefore, research into an alternative artificial device is crucial.

ARTIFICIAL HEART IMPLANTATION

Mechanical circulatory devices have the potential to eliminate the problems that plague conventional heart transplants and are changing the face of heart failure therapy (Frazier et al. 2009). Because they can be mass-produced in a factory, the scarcity of donor hearts becomes a non-issue, and their cost is lower. To date, approximately 15,000 artificial devices have been implanted worldwide, and the numbers are projected to increase (Copeland 2011).

DEVELOPMENT OF ARTIFICIAL DEVICES

As early as 1960, researchers embarked on the road to find a permanent solution to the heart problem. They simultaneously pursued a technique for heart transplantation as well as a proposal for an implantable mechanical circulatory device that would replace the failing organ. Research into artificial devices focused on two types of pulsatile devices, one to replace and the other to aid the failing heart. One device was the total artificial heart (TAH), which would completely replace the failing heart, and the second device researched was the ventricular assist device (VAD), which would assist the failing heart in blood circulation. Both devices would be pulsatile and attached to an internal and external battery source to propel the motor. Additionally, they would have sensors to monitor and adjust the pressure at which the device pumps blood in order to allow for a natural beat (Morlacchi and Nelson 2011) (See Figure 1).

Figure 1: Cardiowest TAH.
Source: Platis and Larson 2009

PULSATILE TOTAL ARTIFICIAL HEART

The total artificial heart was designed to replace and mimic the natural heart, with one component pumping deoxygenated blood from the heart to the lungs via the pulmonary artery and a second component pumping the oxygenated blood from the lungs to the heart via the pulmonary vein. The mechanical valves provide unidirectional flow and work complementary to the diaphragm during the cardiac cycle to eject the blood of the right and left ventricles. An attached external drive console provides controllers that give the device the ability to adjust the heart rate, systolic pressure, and vacuum for the ventricle. Devices like these, such as the Cardiowest temporary Total Artificial Heart, could produce a cardiac blood output of more than nine liters per minute and allow normal metabolic functions to continue. However, the earliest versions of these devices did not function efficiently, causing many complications, such as clot formation, bleeding, hypertension, and death due to failure of mechanical parts (Platis and Larson 2009). Two major technical problems associated with these devices were the lack of appropriate materials that would not be rejected by the body and the large size of the device, making it poorly suited for long-term use. The device, with two components surgically implanted into the chest and another two into the stomach, was extremely large and heavy, requiring a lot of space to be implanted into the body (Morlacchi and Nelson 2011). Additionally, other components, such as the large external power console located exterior to the body, confined patients to the hospital and inhibited improvement in their quality of life. Therefore, this model was phased out of use.

LEFT VENTRICULAR ASSIST DEVICES

Due to the failures associated with the total artificial heart, researchers turned their focus to the smaller ventricular assist device in the 1980s. The device is most commonly referred to as left ventricular assist device (LVAD) because the majority of the pumping work of the heart is done by the left ventricle. The objective of this device was to act as an alternative to organ transplant and aid the heart in its pumping of the blood and regulation of the heartbeat. This was accomplished through implantation of the device near or within the heart, with a direct connection to the heart, causing a complete bypass of blood flow to the left ventricle. This technique allowed the blood to flow through the pump, eliminating the symptoms caused by ventricular failure, thereby providing complete support of the circulation of blood within the patient's body (Morlacchi and Nelson 2011).

Because the left ventricular assist device is less technically demanding, researches and developers have been able to achieve quick advancement in a relatively short amount of time. There have been major improvements in its size, durability, simplicity, and ease of implantation within the last 20 years. A very significant improvement in the device has been the implementation of self-contained mechanisms that have eliminated the need for an external driver (Morshuis et al. 2010). The small size of the device allows for the pumps as well as the additional components to be implanted into the body. Additionally, due to its small size, the implantation procedure does not require a complete opening of the chest, reducing the amount of recovery time following surgery (Morlacchi and Nelson 2011). Moreover, the introduction of batteries as a rechargeable external power source allowed patients to have a small external battery and controller attached to them, thereby promoting mobility and allowing patients to return home, improving their quality of life.

The design of the left ventricular assist device has evolved from the first-generation pulsatile volume displacement pump to the more commonly used second-generation continuous flow pump. The pulsatile volume displacement pump was designed to simulate the natural

heartbeat during the circulation of blood from systemic circulation to pulmonary circulation and vise versa. It mimicked the natural pulsing action of the heart with its own pulsatile action, sucking the blood from the left ventricle into the pump and then forcing it out into the aorta. It consisted of inflow and outflow valves as well as a diaphragm to exert pressure on the blood, causing a natural pulse. The typical stroke volume associated with these pumps was 50-70ml, with the afterload of the device depending on the amount of blood that filled the device during the preload period (Copeland 2011).

The more recent continuous flow device (see Figure 2) uses either an axial flow pump or a centrifugal pump to provide pulseless circulation of blood throughout the body. Both pumps use rapidly spinning rotors to enable continuous blood flow. The axial pump design includes a magnetically suspended motor which rotates the axial pump without any physical contact. In this design, the rotor is the sole moving part, and the additional components of the motor, the two stators, are "passively stable" and are "controlled according to the rotors position so as to levitate the rotor" (Okada et al. 2003). These motors can spin up to 8000-10000 rpm, thereby facilitating the blood in reaching all the necessary destinations in systemic circulation (Copeland 2011).

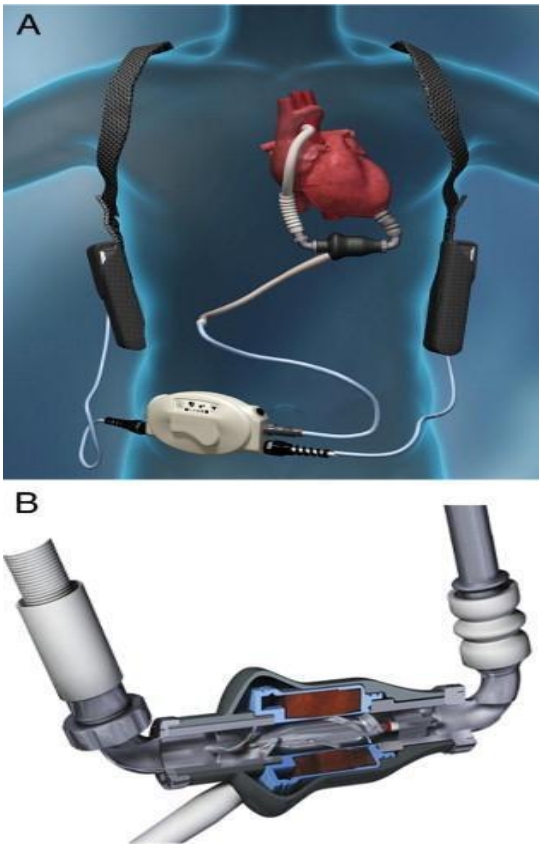

Figure 2: Components of the Continuous-Flow LVAD. Source: Pagani et al. 2009
(A) The inflow cannula is inserted into the apex of the left ventricle, and the outflow cannula is anastomosed to the ascending aorta. Blood exits through the left ventricular apex and into the left ventricular assist device (LVAD), which pumps throughout cardiac diastole and systole into the ascending aorta.
(B) The LVAD pump is placed within the abdominal wall or peritoneal cavity. A percutaneous lead carries the electrical cable to an electronic controller and battery packs, which are worn on a belt and shoulder holster, respectively.

The centrifugal pump design is very similar to the axial pump with exception to its size. It is somewhat larger than its axial pump counterpart, but is more energy efficient. It has a circular shape and uses a rotating impeller, which can have numerous blades, to create flow. The average speed of the motor is 2000 rpm, generating an output of eight liters per minute, and the hydraulic flow is from the left side while the inflow is from the right. A negative side effect associated with both of these models is the formation of clots around the bearings of the motor that are lubricated by the blood (Anderson et al. 2000).

Researchers used the success of the continuous flow left ventricular assist device as a blueprint for a model of a new artificial heart that would completely replace the native heart with the implantation of two continuous flow devices working in tandem. This device is an improvement of the original total artificial heart in size, reliability, function, and energy efficiency. The continuous flow total artificial heart (CFTAH) consists of two rotary pumps which control the systemic and pulmonary circulation. Instead of mimicking the natural heartbeat by pumping the blood, they allow for the continuous flow of blood through the body using the mechanisms discussed above. Since little is known about the physiological effects of pulseless circulation of blood, it is currently undergoing phase II animal trials (Frazier et al. 2009).

DISADVANTAGES AND ADVERSE SIDE EFFECTS

The disadvantages and complications associated with the artificial models are numerous and include the biomaterial used to make the device, mechanical failures, and blood clotting. The procurement of a suitable biomaterial with which to make the artificial device has proven difficult, because antibodies in the blood tend to react with almost all manmade substances, causing infection. Therefore, developers are currently coating the internal and external surfaces of the device with polyurethane, which has demonstrated compatibility, to reduce the potential for infection. Additionally, researchers at the Milwaukee Heart Institute are attempting a method of lining the device with the patient's own endothelial cells. This is done by removing cells from the inner lining of the stomach through a procedure similar to liposuction, culturing them in a lab, and subsequently growing them on the device (Cecchin and Pfeiffer 1993).

Researchers are addressing the side effect of thrombi formation around the movable parts of the motors resulting in thromboembolism (stroke). The clotting is a result of the minimal clearance space between the device and the myocardial tissue, which interferes with the blood flow patterns. In order to prevent this, there is a need to improve the model of the motor by providing additional clearance space or with a mechanism to prevent clotting (Anderson et al 2000). Currently, patients with implanted left ventricular assist devices are prescribed long-term antithrombotic therapy in order to prevent the formation of clots (Pagani et al 2009).

Additional risk associated with implantation of mechanical devices is death due to failure of mechanical parts. Although the device is small in size, there are many mechanisms involved in the delivery of energy to the motor which powers the pump. If any of the components fail, there is a narrow window of time during which the patient can survive without replacing the component. Therefore, patients are given additional battery packs to prevent death due to failure of an external component. Nevertheless, if there is a glitch in any of the internal components or in case of a power failure, there is little that can be done for the patient at that point. Therefore, these mechanisms need continuous improvement in their reliability and durability to prevent such failures from occurring.

EXPERIMENTATION AND STUDIES

There are various models for artificial devices to replace or aid a failing heart. Therefore, experimental testing is needed to determine which designs are effective and what improvements must be made to ensure minimal adverse side effects. Once the development phase of the device is complete, there are various stages in the rigorous experimental process. Experimentation begins with phase I testing (i.e. in vitro), during which the device is placed in a simulated human body environment with a mock circulatory system in place (Morlacchi and Nelson 2011). The device is then tested in regard to implantation techniques, size, mechanical operation of parts, motor efficiency, battery life, durability, reliability, and adaptation to various stimuli. According

to the successes or failures of the various aspects of the device, certain modifications are made in the model.

Once phase I is complete, barring any complications, the researchers move forward to phase II testing, in which they implant the device in an animal with a failing heart and monitor the various improvements as well as complications that arise in the operative and postoperative stages. If the device passes animal trial, it proceeds to clinical trials and is usually implanted in patients who are not eligible for cardiac transplant. The clinical trials are primarily for testing of surgical implantation technique, effectiveness and durability of the devices, as well as any complications that may arise due to the device.

Jack G. Copeland and colleagues conducted a clinical trial to provide comprehensive analysis as to the efficacy of the CardioWest temporary total artificial heart, a pulsatile total artificial heart. The patients in the protocol group were in acute heart failure and at high risk of imminent death. These patients did not meet criteria for left ventricular assist devices for different reasons, and their last resort was to receive the total artificial heart while waiting for a heart transplant. In this particular study, 79% of the protocol group survived to receive a heart transplant versus 49% of the control group. Furthermore, immediately after implantation, the protocol group's mean arterial pressure rose and their mean venous pressure dropped significantly, showing the effectiveness of the device. Although the results of the analysis look promising, there were many ensuing adverse effects associated with the implantation of the total artificial heart, including loss of blood, device malfunction, the large size of the device (limiting the population size which can receive the implant only to those with enough space in their mediastinum), and death (Copeland et al. 2004). These results indicate that the total artificial heart is not the ideal artificial device to be used as a replacement for a failing heart.

Clinical trials for the HeartMate continuous flow left ventricular assist device (see Figure 3) began in 2003. The trials consisted of 18 months of follow up data on 281 patients who, in urgent need of heart transplant, underwent the implantation of the HeartMate left ventricular assist devices. The trial results showed that patients exhibited greater survival rates, less frequent adverse events, and improved reliability with continuous flow left ventricular assist devices as compared to pulsatile flow devices. At 18 months, of the 281 patients in the trial, 157 had meanwhile received heart transplants, 58 were living mobile lives with left ventricular assist devices in their bodies, seven had their left ventricular assist devices removed due to recovery of their hearts, 56 had died, and three had been removed from the trial after exchanging their devices for another type of device. The results demonstrated that heart function had significantly improved after six months of LVAD support as compared to the pre-LVAD baseline. Although the results seem promising, there were many side effects associated with this device, including sepsis, stroke, multi-organ failure, bleeding, and device malfunction. Therefore, additional improvement is called for in order for this model to be considered for the vast majority of end stage heart failure patients (Pagani et al. 2009).

Figure3: HeartMate II Left Ventricular Assist System. Source: FDA 2009

Phase II trials conducted by the Texas Heart Institute tested the physiological effects of the continuous flow total artificial heart implanted in a calf. The findings were significant. On postoperative day one, the calf was standing for several hours at a time, and by day three the calf was eating a full diet and had been weaned off the ventilator. Throughout the study, the calf gained six pounds and was able to recognize its keepers and sleep at regular intervals. The pumps operated without mechanical problem over the course of the study. The most promising success the calf had was running on the treadmill for 40 minutes with no sign of exhaustion. The left and right pumps increased in response to increased oxygen need without any external adjustments, and the calf's breathing remained normal. The calf demonstrated overall improved quality of life and overall improvement of metabolic functions. While this study had promising results, the calf was euthanized on day 48 due to a glitch in the left axial pump. Although the results of the study were promising to the extent of the device's success, the fact remains that the calf only survived 48 days, demonstrating that the device is a long way from being considered a viable replacement for the heart (Frazier et al. 2009).

CONCLUSION

Based on numerous studies that have been conducted, it is evident that the development of an artificial device that will completely replace the failing heart is still in its early stages. The various problems associated with the device prevent it from being considered a viable long-term solution for replacement of a failing heart. Although there is no current long-term solution for the problems associated with conventional heart transplants, the future for patients in end stage heart failure looks bright. Over the next few decades, researchers hope to perfect the model of the total artificial heart to the extent that it will be a long-term solution for those in need of a new heart. Additionally, successes associated with left ventricular assist device implantation as a temporary bridge, aiding the failing heart until a real heart is available for transplant, are allowing for more devices to receive FDA approval, subsequently leading to an increased number of implantations. Therefore, these devices should be considered while weighing the options for a patient diagnosed with advanced stage heart failure.

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