Analysis on Left Ventricular Assist Devices in the 21st Century

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ABSTRACT
Heart disease is the leading cause of death for most of the racial and gender groups in America. One person dies every 36 seconds due to cardiovascular disease, which costs Americans around 363 billion dollars annually for medicine, healthcare service, and loss of laborers due to death. Although heart transplantation is the gold standard surgical approach in the treatment of cardiovascular disease, factors such as the shortage of donors, graft failure, right ventricular dysfunction, rejection, and neoplasms limited the accessibility and outcome of heart transplants. Hence, mechanical support devices are becoming more popular. As scientists are making rapid progress and innovations, including smoother textures and more compact size, the efficiency of left ventricular assist devices(LVAD) is substantially promoted. The paper will illustrate the data from several experiments and compare generations of LVAD that can prove the advancements of devices. Heartmate III is the most modern LVAD device in modern days. Its compact design and removal of the cable greatly enhanced the function of the device. Nevertheless, LVADs still have major complications, such as bleeding, right heart failure, and infection, which might be fatal to the recipients. In conclusion, LVAD is a viable way to deal with cardiovascular diseases, but still needs further studies to eliminate its side effects. The resources of the paper, including the graphs, data, analysis, are found in Google Scholar. The passage will discuss the advancements of generations of LVADs and the current constraints on them, and demonstrate the possible directions researchers can investigate and explore in the future.

Keywords: *Total artificial heart, ventricular-assist devices, cardiac disease, bionic surgery, bridge to recovery.*

1. INTRODUCTION

Before the emergence of left ventricular assist devices, patients with cardiac diseases were usually treated with organ transplantation. However, the success of organ transplantation "is limited by the complications of chronic immunosuppression, opportunistic infection, and the development of allograft coronary artery disease requiring retransplantation in 40% of patients by six years". [20] In addition to the numerous technical difficulties, the low availability is another serious problem. In the United States during 1991, 3797 patients were on the heart transplant waiting list. The median waiting period was 198 days, and 778 patients died waiting. [20] Due to the scarcity of organ donors and the intolerable pain during cardiac diseases, "artificial hearts present an alluring promise for a return to the normalcy, comfort, and productivity enjoyed by most healthy people." [16] Compared to organ transplantation, ventricular assist devices have longer duration, due to the higher "possibility of earlier intervention and rehabilitation and the avoidance of the risks associated with immunosuppression and of reject." [9] Most significantly, the availability of artificial hearts, unlike transplanted organs, "is limited only by the industrial capacity for production". [20] The improvements in "materials sciences, electrical engineering, biochemistry, enhanced biomaterials, robotics, tissue engineering and computing power have led to significant developments in medical bionics", [2] which makes artificial hearts a viable option for many patients suffering from cardiac diseases. Artificial hearts still present practical challenges that relate to power consumption, flow control system, monitoring and impeller system, and materials for internal surfaces of the devices. [16] As relevant studies have not yet referred to this research aspect, this paper will demonstrate the advantages and limitations of ventricular assist devices based on the designs of the devices and the clinical results from the users. To some extent, it hopes that the paper would predict the trends of

artificial hearts in the future and how scientists might approach the current technical problems.

2. ADVANTAGES OF VENTRICULAR ASSIST DEVICES

2.1 Basic Properties of LVADs

Left ventricular assist devices are mechanical pumps that "take over the function of the damaged ventricle and restore normal hemodynamics and end-organ blood flow". [6] Many patients are ineligible for heart transplantation due to medical history or aging, and the long waiting line also makes transplantable organs inaccessible. Thus, artificial hearts can be a life saving choice. The ventricular assist devices include "extracorporeal membrane oxygenation, univentricular and biventricular extracorporeal nonpulsatile devices, extracorporeal and implantable pulsatile devices, and the total artificial heart". [6] There are two groups of patients that need those devices: First, patients who need ventricular assistance to allow hearts to rest and recover. Second, patients with long term or serious heart disease. Their cardiac abilities are not expected to recover to normal level, so they "require mechanical support as a bridge to transplantation". [9]

2.2 First Generation of LVADs

As the National Institutes of Health (NIH) established the artificial-heart program in 1964, "various circulatory-support devices have been developed for short-term use in patients with end-stage heart failure." [18] Short term appliance of artificial hearts in patients awaiting transplantation "normalizes hemodynamics, improves end-organ dysfunction and exercise tolerance, allows patients to be sent home, and provides a reasonable quality of life, with a relatively low incidence of major adverse events". [18] From 1998 to 2001, a clinical experiment was conducted, in which 68 patients received left ventricular assist devices, and 61 received optimal medical management. Based on Kaplan Meier survival curves, the survival percentage of patients who received left ventricular assist devices at one year was 52% as shown in Figure 1. It is much higher than the survival percentage of the medical-therapy group, which is 25%. The survival percentages at two years were 23% and 8%, respectively. Median survival was 408 days in the device group and 150 days in the medical therapy group. [18]

The first generation of left ventricular assist devices(LVAD) are represented by two systems, ThermoCardiosystems Heartmate 1205 VE device and the Novacor N100. Both devices are implanted through a median sternotomy with an inflow cannula inserted into the left ventricular apex and an outflow tube anastomosed to the ascending aorta. The pumping chamber is placed within the abdominal wall. [6] Both devices have backup mechanisms to ensure the support without the need of reoperation if the devices fail. The native hearts will continuously offer systematic support until the device is repaired. Even if the motor device fails, "the single-pusher-plate device can be pneumatically activated with a hand-held portable pump". [9] Device failure is one of the major causes of patients' death, but the two systems can address this problem to a certain extent. Another noteworthy advantage of HeartMate 1205 VE is the "use of sintered titanium to create texture on all blood contacting surfaces of the pump except the smooth titanium impeller". Such surfaces have facilitated "the growth of a stable, adherent biological lining that lowers thromboembolic risk with only platelet modifiers such as aspirin". [8] The clinical results of Novacor N100 on a 54 years old man with a history of dilated cardiomyopathy and contraindications was successful. The patient completed NYHA class I, drove a car, and traveled abroad for vacation, which proves the durability and value of Novacor N100 as it substantially improved the patient's living quality and increased his lifespan. [7]

Patients with LVAD demonstrated considerable physical improvements on multiple perspectives. At the tissue level, the contraction of heart muscles "was noted to have resolution of force decline with high-frequency contraction after the surgery compared with before". [11] Because of the presence of LVAD, heart muscles have greater magnitude of convulsion, enhanced relaxation, and more active responses to beta agonists. The abnormal enlargement of and the death of heart cells due to injury or failure of blood supply also tremendously declined. Many investigations showed reduction in "number of wavy fibers and contraction band necrosis in both dilated and ischemic cardiomyopathy". [11]

2.3 The third generation of LVADs

Implant number	Study duration (days)	Pump flow (L/min)[a]	Plasma free hemoglobin (mg/dl)[a]	Pump temperature (°C)[a]	Pump temperature rise (°C)[a]	Notes
1	40	5.3 ± 0.6	7.8 ± 1.6	—	—	Electively terminated
2	27	4.3 ± 1.1	5.8 ± 1.3	40.9 ± 0.5	—	Electively terminated
3	59	4.0 ± 0.5	5.6 ± 2.4	40.3 ± 0.5	—	Electively terminated
4	42	4.0 ± 0.6	5.3 ± 2.4	40.1 ± 0.3	1.4 ± 0.2	Electively terminated
5	27	5.7 ± 1.1	5.3 ± 4.7	40.5 ± 0.4	1.2 ± 0.3	Terminated due to pneumonia
6	49	5.4 ± 0.5	5.1 ± 1.9	40.3 ± 0.8	1.2 ± 0.4	Electively terminated
7	61	3.2 ± 1.1	6.7 ± 2.4	—	—	Electively terminated, kinked outflow graft
8	~100	5.5 ± 1.5	6.6 ± 2.5	—	—	Ongoing
9	2	—	—	—	—	Terminated due to

Figure 1 Summary of cumulative HeartMate III left ventricular assist device in vivo study data, the HeartMate III: Design and In Vivo Studies of a Maglev Centrifugal Left Ventricular Assist Device.

Now, mechanical design of Heartmate III, the third generation pump, already achieved an optimal pumping performance experimentally. [12] Since "motor function and magnetic levitation are achieved in a single, integrated unit incorporated with all control electronics in the pump's lower housing", heartmate III performs efficiently and compactly. [8] Heartmate III is expected to "maintain an ample and straightforward flow path to minimize hemolysis and thrombus formation". [12] When the 6 Heartmate III made by Thermo Cardiosystems Inc. were implanted sequentially in 9 calves, the result showed that the pump flows from 8 out of 9 studies were in the targeted range, which proved the feasibility of this device.[12] Heartmate III has several outstanding features. It has high portability and mobility due to its small size. The application of the device does not require anticoagulation. [17] It not only has a "magnetic bearing which eliminates all friction wear", but also "single-fault–tolerant redundancy of all implanted electronic components which ensures uninterrupted performance in the event of any single failure that may occur, affording an opportunity for remedy". [8] In order to reduce the wire number, the control circuitry has been concatenated in the pump, thus promoting system reliability. Furthermore, "the cable has been attached to the pump with a hermetic connector, facilitating modular replacement and separating pump reliability from cable reliability". The detachable cable "permits eventual modular upgrade from a percutaneous system to a fully sealed, transcutaneously powered system". [8] "The large gaps above and below the rotor to wash surfaces outside of the main flow path" are designated to minimize the possibility of "thrombogenesis and hemolysis".

Because of the values and enormous positive clinical results. Heartmate III gained approval from the FDA. Many FDA recognized LVADs systems, with the "access to the resources and infrastructures established", [3] started the mass production of the pump and the peripheral hardwares concurrently. The rapid progress of Heartmate from "concept, through design, and into animal studies" is a great encouragement to researchers and patients with cardiovascular diseases, and people can expect LVAD to develop into a dependable device and a "viable commercial endeavor" in the near future. [3]

3. LIMITATIONS OF VENTRICULAR ASSIST DEVICES

3.1 Pre-surgical complication

However, left ventricular assist devices have challenges and limitations. Selection of patients is a crucial factor that determines the outcome of the implementation. Patients with "preexisting mitral stenosis or aortic regurgitation may require correction of

the valvulopathy before implantation of the device". [9] Patients with inoperable coronary artery disease may "continue to have angina without adverse hemodynamic effects" [9] after the implementation of the device. Worse, "right ventricular ischemia and myocardial injury soon after implantation of the device can cause right-sided heart failure, resulting in decreased flow to the left ventricular assist device." [9] Patients with cardiomyopathies may continue to have atrial and ventricular arrhythmias. Patients with intracardiac septal defects "should be repaired at the time of the implantation of the device to avoid the right-to-left shunt and subsequent oxygen desaturation that would be created by the sudden reduction in left filling pressures". [19]

3.2 Sub-surgical complication

There are also many complications after the implementation. Based on all the English papers on PubMed conducted from January 2007 through June 2016 involving HeartMate II (HMII) and HeartWare, ischemic stroke, "including intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH) and subdural hematoma (SDH) and intracranial hemorrhage(SDH)", "occurred in 9.8% (or 0.08 EPPY) and roughly a third of patients died after ischemic stroke and nearly two-thirds died after ICH". [5] The median mortality rate for LVAD related diseases is "31%". In the study, the overall "rates of both ischemic stroke and ICH in LVAD patients exceed those of non-LVAD patients receiving similar antithrombotic regimens". [5] "Bleeding, right-sided heart failure, air embolism, and progressive multisystem organ failure" are the common causes of "early morbidity and mortality" after placement of LVADs." [9]

3.2.1 Hemorrhage

LVAD recipients are more likely to have bleeding, or hemorrhage, than the general population, "and of greater severity, requiring an average of 2-4 units of packed red blood cells per admission". Based on the historical statistics, "15%-61% of the patients may develop GI hemorrhage after LVAD transplant". [10] Numerous factors can cause hemorrhage: "preoperative coagulopathy due to hepatic dysfunction, poor nutritional status, and antibiotic therapy; cardiopulmonary-bypass–induced thrombocytopenia and platelet dysfunction; and the extensive nature of the surgery, which requires median sternotomy, cardiac mobilization (often in patients who have had previous cardiac surgery), and extensive dissection of the abdominal wall to create a pocket for the pump". [9] In other words, the cause can be exogenous, endogenous, intrinsic properties of the machines, or the predisposing condition of the patients, or a combination of multiple factors. [10]

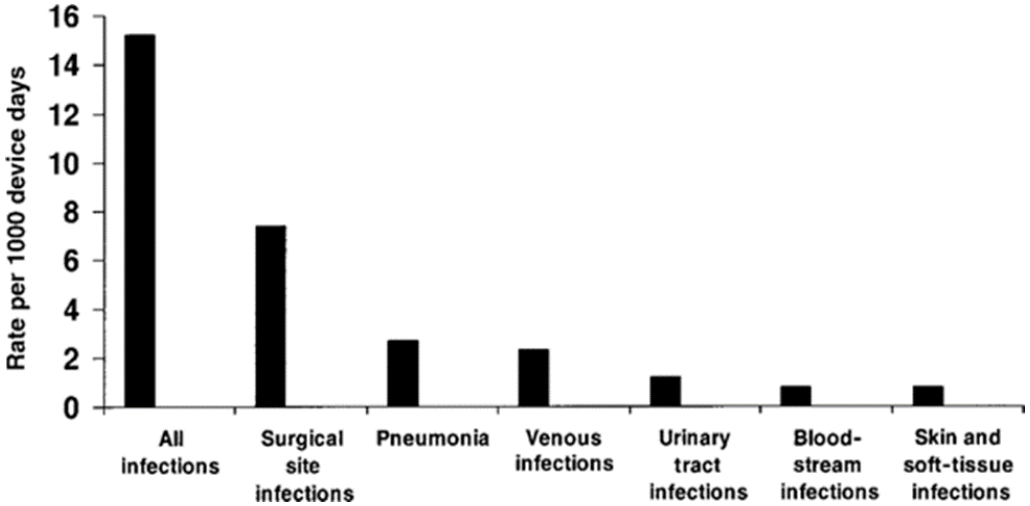

Figure 2 Rates of nosocomial infections among 24 patients who underwent left ventricular assist device implantation, Nosocomial Infections in Left Ventricular Assist Device Recipients.

3.2.2 right heart failure

Another implication of LVAD operation is right heart failure, which complicates 20%-50% of the cases. [1] Unfortunately, the development of right heart failure is often "sudden and unpredictable". [6] Overt signs of right heart failure may not show up until actual activation of the LVAD, "when considerable hemodynamic imbalance occurs between the failing right ventricle and the now-supported left ventricle". Anatomically, "mechanical unloading of the left ventricle by the LVAD causes bowing of the interventricular septum away from the right ventricle". Theoretically, LVAD improves diastolic compliance. The successful implantation of LVAD means the output of the right ventricle and the LVAD work should be in equilibrium. However, "if peak left ventricular pressure is reduced, the interventricular septum tends to bulge into the left ventricle." [6] Supposedly, the pulmonary capillary wedge pressure, right ventricle systolic pressure, and pulmonary artery pressure will decrease. Nonetheless, the position of interventricular septum may shift after the operation,

impairing the efficiency of right ventricular contractility. [1] Moreover, since LVAD promotes forward flow to the systemic circulation, it may "increase venous return beyond the capacity of the right ventricle", [6] leading to tricuspid annulus distortion. [1]

3.2.3 infection

Thirdly, recipients of LVADs are prone to infections.[13] The first type of infection is nosocomial infection, occurring "as a result of the patient's prolonged hospitalization, immobilization, endotracheal intubation, suboptimal nutritional status, and need for multiple intravascular and bladder catheters". [9] There are three main causes of nosocomial infections: The foremost reason is that all the FDA approved LVAD devices have "a transcutaneous line that carries the electrical cable and air vent to the battery pack and electronic controls". The drive line breaches the "normal cutaneous barrier against infection and serves as a major portal of entry for pathogens". [13] The second cause is that recipients of LVADs are usually critically ill, which weakens their immune system. Many of them are also "malnourished with multiple invasive supportive devices". [13] The last cause is the use of broad spectrum antimicrobial therapy, which is "often empiric, prophylactic, or for treatment of infections in critically ill patients". Many pathogens that developed resistances to these antimicrobial agents may cause nosocomial infections. The second type of infection is device related infection, which can be divided into driveline infection and pump pocket infection. Driveline infections "occur along the percutaneous lead which connects the LVAD motor to its external power source". [15] Pump-pocket infections "occur within the recess that is developed within the abdominal cavity to house the LVAD". [15] Obviously, the long drive line and compliance chambers will cause infections. Patients with high obesity and metabolic syndrome are more susceptible to infection. End-stage heart failure will also predispose recipients of LVADs to device-related infection, "due to poor nutritional intake, specific metabolic imbalances, as well as elevated serum TNF-α." [15]

4. CONCLUSION

The paper illustrates the data from several experiments and compares generations of LVAD that can prove the advancements of devices. The paper finds that LVAD is a viable way to deal with cardiovascular diseases, but still needs further studies to eliminate its side effects. As shown in this paper, LVADs had positive impacts on many recipients by improving their physical and thereby mental condition and saved the time of waiting for transplantable hearts and medical fees for patients. Nonetheless, the advantages of LVADs are still constricted by the possible implications, such as infection and right heart failure.

As is seen from the trend, the number of recipients of LVAD will grow exponentially in the future, and numerous third generation devices are in pre-clinical trials presently. The increased use of LVADs may benefit patients with end-stage heart diseases and waiting for heart transplantation, because the hemodynamic value of mechanical assistance may convert terminally ill patients into qualified heart-transplant recipients. [9] As those patients can return home to wait for heart transplants, the costs of hospitalization and medication will reduce. With the support of LVADs, the survival rate and possibility of returning to normal lives are more accessible after heart transplants may increase.

The passage is completely based on the research results from previous studies, which means the author did not conduct any experiment or survey. Some of the experiments the author used are from a decade ago, and some investigations included limited numbers of subjects or had short periods. One study is a retrospective analysis that targeted patients who received LVADs and worked backward to clarify the indications for insertion, which is not as accurate as the data obtained from a prospective and clinical trial. [6]

In the future, researchers should focus on several points to ensure the success rate of LVADs. Recipients should be selected meticulously based on previous medical history, age, and current physical condition. Next generation sequencing and whole-genome single nucleotide polymorphism array technology can also help doctors to identify individuals at risk before the LVAD implantations. [15] Hospitals need constant and long term inspections and timely medical therapies (angiotensin-converting enzyme inhibitors,b-blockers) on the patients to ensure a sustained recovery. Modification of the device is crucial, and scientists should aim at minimizing the volume and weight and eliminating any extraneous component of the devices. LVAD operations still have formidable difficulties, but the clinical results and experiments elucidated the great potential of this technology. Inevitably, LVADs will become more reliable and prevalent in the future.

ACKNOWLEDGMENTS

The author cannot express more gratitude to her professor Mr. Farina, teaching assistant Jun Ye, and essay professor Min Han for their dedication and commitment. Their patience and experiences guided me through choosing and narrowing down topics and editing the essay. The writer is also really grateful to Vassar College, as its website provides abundant high quality resources for her to explore and select.

In addition, the writer would like to pay special regards to her parents, Fang Li and Zhong Pan, for their economic support and encouragement throughout the

long research process. Their assistance is invaluable and precious to the author.

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