Ming Yang *Editor*

Artificial Hearts

Technology and Therapy Management

Springer

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Foreword

With the aging of global population and rising prevalence of poorly controlled risk factors, cardiovascular disease has become the leading cause of death worldwide. It is reported that there are more than 26 million heart failure patients in the world. Although most of them can be treated by medication and surgery, some end-stage heart failure patients need special treatment, such as heart transplantation, ventricular assist therapy, and so on. In recent decades, heart transplantation has become the gold standard for the treatment of end-stage heart failure, but the donor is seriously insufficient, and there is an urgent need for alternative treatment. Ventricular assist devices are undoubtedly one of the most promising treatment methods.

Fuwai hospital, the largest cardiac center in China, is committed to providing effective treatment for patients with heart failure who cannot benefit from conventional treatment. We have experienced the first generation of artificial heart products such as BVS 5000, AB 5000, MEDOS, Novacor, etc., to the development and clinical trials of the third generation of suspended artificial heart, such as CH VAD, etc. I have demonstrated that VAD implantation is an alternative choice for end-stage heart failure patients. Also data from western countries show that the number of VAD implants in the world is increasing, the quality of life of patients has been greatly improved, and the life span has been extended.

However, so far, none of the artificial heart products is perfect. In clinical application, the serious complications of artificial heart, such as infection, thrombus, pump failure, and so on, perplex clinicians, patients, and researchers.

Common understanding is that we need new device with better hemodynamic performance and blood compatibility to reduce the occurrence of adverse events. As an expert in the field of artificial heart research, Professor Ming Yang has been devoted to the development of artificial hearts for nearly 20 years. In this book, *Artificial Hearts: Technology and Therapy Management*, editor Ming Yang and the book's contributors provide a more comprehensive knowledge, including the basis and principle of artificial heart technology, basic technology, design, evaluation, and management of latest developments. In particular, the designs related to adverse events were discussed and possible solutions were proposed.

I appreciate professor Yang's contribution in this book, and I trust that cardiologists, healthcare professionals, engineers, and patients will all benefit from this book.

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March 31, 2020

Preface

It is my great pleasure and honor to publish this book entitled *Artificial Hearts: Technology and Therapy Management*.

Heart failure is the inability of the heart to pump sufficient blood to the body, leading to disability or death. Currently, patients with end-stage heart failure refractory to medical treatment are often considered for heart transplantation. However, donor organ availability is limited, and many patients die awaiting transplantation. In the effort to mechanically assist failing hearts, the use of implanted artificial heart supports has evolved from its initial function, as bridge to transplantation or bridge to recovery, to an increasingly more common-use destination therapy for end-stage heart failure. Artificial hearts are machines that are capable of replacing or assisting the pumping action of the heart for prolonged periods. Artificial hearts can be classified into total artificial hearts (TAHs) and ventricular assist devices (VADs). Implantation of a TAH requires removal of both of the patient's ventricles. However, the entire heart remains in the body when a VAD is used to support either the right or the left ventricle. VADs are now becoming an important option for the care of heart failure, and the clinical application of artificial hearts has been extended from America, Europe, and Japan to other countries such as China. Fuwai Hospital, China's largest cardiovascular hospital, recently reported successful application of VADs. However, the postoperative mortality after artificial heart implantation is still high and significantly depends on various device-related complications. Therefore, artificial heart including technologies and therapy management has now become a major concern and hot topic for researchers, surgeons, technicians, and heart failure patients to look for a better clinical result.

I have started my study on ultrasonic motors for cardiac assist devices when I was a research fellow at the University of Leeds, UK, from 2002 to 2005. Initially, my research focused on the development of ultrasonic devices for direct compression cardiac assist devices. After joining Shanghai Jiao Tong University, China, in 2005, I moved on to the research and development of implanted blood pumps driven by ultrasonic motors, in which water cooling and double traveling waves are proposed to operate ultrasonic motors continually with a potential long duration. The purpose

is to develop a small size blood pump that has improved biocompatibility and long operating life. I will share the development of this blood pump in the last chapter of this book.

Through nearly 50 years of continually evolving artificial heart technologies, the implanted artificial hearts such as ventricular assist devices have become more mature. Since the technology and therapy management of artificial heart is an interdisciplinary field, including surgery and engineering, many chapter authors with diverse expertise contribute to the book chapters to present a comprehensive introduction to artificial heart technologies and therapy management for readers.

The following chapter authors contribute to this book.

Prof. Chua Leok Poh from Nanyang Technological University and Dr. Su B.Y. from National Heart Research Institute Singapore present thorough evaluation techniques related to computer fluid dynamics and particle image velocimetry.

Prof. Po-Lin Hsu and Ms. Tingting Wu from Soochow University, China, provide a thorough review of the challenges existing in current technologies of heart assist devices.

Prof. Cunyue Lu, Dr. Huan Huang, Prof. Shiyang Li, and Prof. Ming Yang from Shanghai Jiao Tong University and MD. Guang Yang, Head of Wuxi Mingci Cardiovascular Disease Hospital, take the reader through the development of volume displacement pulsatile pumps again to uncover the possible way to reduce severe adverse complications and improve perfusion for end organs.

Prof. Yu Wang and his colleagues from Dalian University of Technology, Dalian, China; Ms. Zhehuan Tan from the University of Melbourne, Parkville, VIC, Australia; Prof. Palaniappan Sethu from the University of Alabama at Birmingham, Birmingham, AL, USA; and Prof. Ayman S. El-Baz and Prof. Guruprasad A. Giridharan from the University of Louisville, Louisville, KY, USA, examine the literatures and present the basis of artificial heart technologies and rotary blood pumps.

Prof. Wei Wang and Ms. Lu Han from Shanghai Children Medical Centre, Shanghai, China, introduce the topic related to total artificial hearts.

Prof. Xufeng Wei from Wuxi Mingci Cardiovascular Hospital, Wuxi, China, and Yixin Cui from Xijing Hospital, Xian, China, provide important insights into the mechanisms of heart failure.

Prof. Ming Yang from Shanghai Jiao Tong University and Prof. Yan Zhang from Beijing Fuwai Hospital introduce the evolution of artificial heart technology.

Prof. Yan Zhang from Beijing Fuwai Hospital provides a comprehensive introduction to the selection of VADs in terms of the pump technologies, assistant time and specific considerations relating to the patients.

Dr. Yueh-Ting Chou from Wuhan Asian Heart Hospital, Wuhan, China, presents therapy management related to patient assessment and management of adverse events and complications.

There are 11 chapters in this book.

Chapter 1 provides an introduction to artificial heart, history of artificial heart, classification of artificial hearts, and the development trend of artificial hearts. The purpose is to give an overview of artificial hearts.

Chapter 2 describes the pathophysiology of heart failure, including definition, mechanism, diagnosis, and management of heart failure. The purpose of this chapter is to introduce heart failure pathophysiology, which will help to understand the design, advantage, or disadvantage of artificial hearts.

Chapter 3 entitled "Basis of Artificial Heart Technologies" briefly introduces and describes significant technical characteristics of all the main artificial hearts mainly based on their flow profiles.

Chapter 4 entitled "Artificial Heart: Rotary Pump" introduces centrifugal and axial flow pumps in design, performance, and comparisons in their clinical applications.

Chapter 5 introduces the technology related to volume displacement pulsatile pump, including the principle, design, performance, and limitations of volume displacement pump. Although volume displacement pulsatile pumps have little clinical application now, this physiology pulsatile flow produced by variable displacement volume pump has benefits of less possible blood damage and better perfusion for end organs, which merit further research and development in future.

Chapter 6 entitled "Total Artificial Heart" is about the total artificial heart, where they are needed, how they are designed, and their performance and limitations.

Chapter 7 entitled "Evaluation of Artificial Hearts" focuses on the main artificial heart evaluation procedures such as modeling based on computational fluid dynamics and the experimental validation of particle image velocimetry.

Chapter 8 entitled "Selection of Artificial Heart Devices" introduces the criteria for the selection of artificial heart devices according to the characteristics of each device and the condition of patients.

Chapter 9 entitled "Therapy Management of Artificial Heart" provides an overview of the current implantable rotating left ventricular assist devices, patient selection, surgical overview, and postoperative management strategies.

Chapter 10 entitled "Challenges of Artificial Heart Technologies" examines adverse events associated with implantation and its interaction with the patient circulation system.

Chapter 11 entitled "Innovation Updates for Biocompatible Ventricular Assist Devices" focuses on the innovation updates of biocompatibility to reduce severe adverse complications, including ultrasonic motor actuating pump and non-contact blood compression assist devices.

I hope that the readership will understand the pathophysiology of heart failure, technologies related to artificial hearts, practical aspects of device selection, implantation, and management, and learn of advances in this field that may affect their daily practices and possible studies in future. Perhaps more importantly, readers will develop insights into how high technology has evolved into the future artificial hearts, which could replace or assist the pumping action of the heart without causing harm to blood and remaining organs.

I gratefully acknowledge all those who contributed to this book. Special thanks go to Dr. Azzam Ahmed, a former Postdoc fellow in Shanghai Jiao Tong University, for his skillful assistance in the book preparation; and Ms. Yajie Zhao, the former librarian in the Library of Shanghai Jiao Tong University, for her skillful assistance

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Shanghai, China Ming Yang
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Chapter 1
Introduction to Artificial Hearts

Ming Yang and Yan Zhang

Abstract Artificial hearts are machines that are capable of replacing or assisting the pumping action of the heart for prolonged periods. Artificial hearts can be classified into total artificial hearts (TAHs) and ventricular assist devices (VADs). Implantation of a TAH requires removal of both of the patient's ventricles. However, the entire heart remains in the body when a VAD is used to support either the right or the left ventricle or both. The technology of artificial hearts continually evolves with overall survival of VADs reaching 80% at 1 year and 70% at 2 years. The chapter will introduce what is artificial heart, history of artificial heart, classification of artificial hearts, and the development trend of artificial hearts. The purpose is to give general description on artificial hearts.

Keywords Artificial heart · History · Evolution · Trend

1.1 Background

1.1.1 General Introduction

Heart failure is a complex clinical syndrome that suggests the efficiency of the heart as a pump is impaired. The overall prevalence of heart failure is rising because of population aging and increasing rates of obesity [1]. Overall around 2% of adults have heart failure [2]. More than a half million adults in the USA have been diagnosed with advanced heart failure (HF), in which the symptoms of heart failure can no longer be managed by medication and lifestyle changes. The cost of heart

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failure in the USA is substantial. By 2030, direct medical costs are expected to reach US$53 billion and indirect costs will reach US$17 billion [3].

Over the past three decades, the pharmacological management of HF has undergone tremendous progress, with the currently recommended regimen capable of reducing HF-related mortality by 63% [4]. However, a small proportion of patients, estimated 200,000–250,000 people in the USA, will progress despite optimal medical therapy and require advanced treatments with cardiac replacement therapy [5]. Heart transplantation is the gold standard option for these patients [6], but the available donor hearts are limited, in which only ~ 2800 patients underwent a heart transplantation over the last year in the USA. Thus, the development of left ventricular assist device (LVAD) technology has come as a timely alternative to bridge these patients for heart transplantation or as the destination therapy. Over the past decade, over 20,000 patients have been supported by LVADs either as a temporary substitute or definitive alternative to heart transplantation [7].

1.1.2 History

While the concept of mechanical circulatory support can be traced back several hundred years, it was the heart-lung machine in 1953 that allowed heart opening surgery possible, arousing further interests to develop mechanical circulatory devices [8]. By the mid-1960s, the first successful clinical use of a left ventricular assist device was performed at the Texas Heart Institute, where an air-driven pump was implanted to support the left ventricle in several patients [9].

When the first heart transplantation was performed on December 3, 1967 [10], the mechanical circulatory devices and cardiac transplantation have been becoming intimately intertwined forever. Then next breakthrough came with the development of the intra-aortic balloon pump and its initial clinical introduction to improve coronary blood flow and systemic circulation in 1968 [11]. And it was 1969 that the total artificial heart was first used to bridge for heart transplantation [12]. Unfortunately, the first era of heart transplantation and the clinical use of mechanical circulatory devices ended shortly because of a lack of donor organs and poor outcomes related to rejection and infectious complications [13]. However, the introduction of the immunosuppressive agent cyclosporine in the early 1980s revived clinical use of cardiac transplantation by overcoming previous rejection-related complications [14]. The lack of donor organs continued bringing the use of mechanical circulatory support devices back to the clinical arena. In 1982, a pneumatically actuated total artificial heart (TAH), the Jarvik 7, was implanted as a permanent device [15]. In 1983, to prevent ischemia and compartment syndrome provoked by intra-aortic balloon pump placed in the femoral artery and aorta, another breakthrough came with the development of enhanced external counterpulsation (EECP), which is a noninvasive treatment that has been proven to alleviate anginal symptoms and improve quality of life in patients with coronary artery disease (CAD). Multiple clinical trials have demonstrated a wide range of benefits

derived from EECP therapy including diminishing the frequency of anginal episodes and requirement for nitrates [16].

Although all these mechanical circulatory support devices can assist the diseased heart partially or fully, most of them are only used for short-term assistance. Because of the need to serve as a bridge for the heart transplantation or as the destination therapy, this book chapter will focus on the total artificial heart and ventricular assist devices for the long-term support.

1.1.3 Classification

Artificial hearts, which include total artificial hearts (TAHs) and ventricular assist devices (VADs), are machines that are capable of replacing or assisting the pumping action of the heart for prolonged periods. Implantation of a total artificial heart requires removal of both of the patient's ventricles. However, the entire heart remains in the body when VADs are used to support either the right or the left ventricle or both. Hence the TAHs and VADs need to be addressed separately since their application and progress in development are significantly different.

1.1.3.1 TAHs

The TAH is designed to replace the heart and requires excision of the native heart for placement of the device. On 4 April 1969, a TAH was first implanted in a human by Denton A. Cooley at Texas Heart Institute, Houston, TX, USA. Although supported with the device for 64 h until the transplantation performed, the patient died 32 h after transplantation [17]. In 1982, the first implantation of Jarvik 7 TAH was performed in a patient with end-stage ischemic HF, who lived for 112 days with the device [18]. Although Jarvik 7 heart trials were suspended by the FDA in 1990 [19], the device resumed with different names after extensive technical refinements, and received CE mark approval in 1999. In 2004, it became the first TAH approved by the FDA for use as a bridge to heart transplantation [20]. The devices have subsequently been implanted in more than 1300 gravely ill patients, around 80% of whom have been successfully bridged to heart transplantation [21]. Although many efforts have been made to improve the performance of TAH, the prospect of a totally implantable, permanent mechanical heart-replacement device still seems very far off [22].

1.1.3.2 VADs

As 75–85% of patients demand associated with assisting a weakened heart rather than replacing it, ventricular assist devices (VADs) came into the development [12]. VADs are connected in parallel to the native heart and pump all or part of

the normal stroke volume, which enables heart functionality restoration with increasing coronary perfusion, unloading excessive cardiac pressure and volume, and reducing myocardium tension, cardiomyocyte hypertrophy, and chronic ischemia [23]. Unlike TAHs, the native heart is left in place allowing potential recovery of native heart function and possible removal of the device, as well as maintaining the native heart neural control mechanisms [12]. VADs can be further classified into two major categories: pulsatile devices (PF-VAD) and continuous-flow devices (CF-VAD).

In the early days of cardiac surgery, cardiopulmonary bypass (CPB) machines were developed to provide non-pulsatile flow to avoid complex structure of a suitable pulsatile system [24]. As experience gained with non-pulsatile systems, the non-pulsatile perfusion was clinically acceptable in short periods [12]. However, the human circulation is a pulsatile system, and the impact of non-pulsatile flow has been implicated in severe systemic pathophysiology consequences, such as liver dysfunction [24]. Therefore, the long-term VAD has started with pulsatile devices, such as Thoratec HeartMate IP/VE/XVE [25], Novacor [26], and EXCOR [27]. These devices usually have a pumping chamber with inflow and outflow one-way valves. The pulsatile pump such as Heartmate XVE could achieve low anticoagulation regimens and rare thrombus formation inside the pump, but it has large size and relatively low reliability [28]; the pulsatile pump such as Novacor has a less complex driving mechanics, longer operation times of 5–6 years, and a synchronized operation mode, which allows for optimal unloading of the heart and optimal coronary perfusion because of the resulting counter-pulsation mode [29], but it has high rates of thromboembolism, including strokes [30]; The Berlin Heart EXCOR VAD system consists of a paracorporeal air-driven diaphragm blood pump, cannulae that connect the pumps to the heart chambers and the great vessels, and an electro-pneumatic driving system. The blood-contacting surfaces of the pump and the tri-leaflet polyurethane valves have been coated with heparin [31]. In the REMATCH trial of pulsatile devices ended in 1999, 129 patients with NYHA class IV HF, 1-year survival was 52% in patients who received the LVAD, compared with 25% in those who received medical management only, and 2-year survival was 24% vs. 8%, respectively [32].

Comparing these pumps, it is found that the pneumatic driving blood pump such as EXCOR VAD is usually paracorporeal. However, the electromagnetic force driving blood pump could be implanted. They may exhibit different features as shown in Table 1.1, a simple structure such as Novacor VAD leading a longer duration, and a precise motion control with a cam such as HeartMate XVE having rare thrombosis. However, all these implanted pulsatile pumps have a large size which needs for abdominal implantation, preventing the clinical use [33].

To solve the size challenges posed by positive-displacement pulsatile pumps, one possible solution is to select rotary blood pumps. In 1986, implantable rotary blood pumps started with animal studies, resulted in the first clinically used continuous-flow pumps [34, 35]. The first human implantation of the HeartMate II was performed in November 2003 [36]; since then, more than 19,000 HeartMate II® pumps have been implanted in more than 185 countries. Overall, 1-year survival is

Table 1.1 Comparisons of implanted VAD

Implanted VAD	Example	Actuator	Size/Weight	Duration	Biocompatibility
Pulsatile	HeartMate XVE	Complex: rigid titanium housing divided in half by a flexible diaphragm.	112 mm in diameter 58 mm in height 1255 g	2 years	Rare thrombus formation inside the pump
		Powered by low-speed torque motor through a cam			Asynchronized with native heart
	Novacor	Less complex: a seamless, smooth surfaced polyurethane sac	160 mm in length, 130 mm in width, 65 mm in thickness	6 years	Thromboembolism Neurologic complications
		Powered by a solenoid			Synchronized with native heart
Continuous	HeartMate II	Simple: Has only one moving part, the rotor assembly	Diameter: 43 mm Length: 81 mm Weight: 281.3 g	8 years	Frequent adverse events of bleeding, stroke, and pump thrombosis
		Driven by an external power source			
	HeartMate III	A centrifugal pump that is fully magnetically levitated	Diameter:69 mm Height:30 mm	–	Better survival at 6 months
					Fewer pump thrombosis
		A programmed asynchronous pulse			No difference in rates of GI bleeding

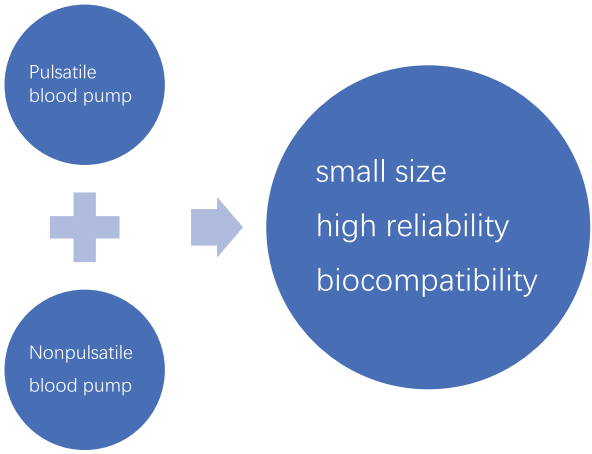

Fig. 1.1 The concerns for developing ventricular assist devices

more than 80%, and several patients have survived for more than 8 years [37]. The newest HeartMate 3 (Abbott, Abbott Park, IL, USA) is developed with fully magnetically levitated impeller, wider blood flow gaps, and programmed asynchronous pulse. Results from the short-term cohort have showed infrequent need to replace the HeartMate 3 due to pump thrombosis. But the complications such as stroke, bleeding, right-sided heart failure, and functional capacity, have no obvious improvements [38].

In the development of heart assist devices, there are debates on the pulsatile versus non-pulsatile flows [24]. However, from a practical point of view, the debate of pulsatile and non-pulsatile flows could not help much to the development of VADs, but only conceal the underlying problems. As shown from Table 1.1, the pulsatile pumps such as HeartMate XVE could achieve low anticoagulation regimens and rare thrombus formation inside the pump but the pulsatile pumps such as Novacor exhibit a high rate of thromboembolism [28–30]; on the other side, the pulsatile pumps such as Novacor have longest duration up to 6 years, which is close to the rotary pumps such as HeartMate II [29, 37]. These results suggest that pulsatile pumps cannot guarantee the prevention of blood trauma, and they do not mean short duration either. Perhaps, a more accurate concern for the development of VADs would be how to achieve small size and high reliability and biocompatibility simultaneously. As shown in Fig. 1.1, this concern could be further explained in that small size would make the device easy implanted with reducing infections, and the high reliability would suggest the potential of long-term support; the biocompatibility indicates VAD's capability of coexistence with blood or heart without causing harm. In terms of coexistence with blood, the biocompatibility of VADs is associated with biological reactions and material reactions due to the material contacting with the blood, and blood trauma caused by flow dynamics [38, 39]. In terms of coexistence with heart, the biocompatibility of VAD is associated with synchronization and even coordination with native heart, avoiding complications such as right heart failure due to the left ventricle effect of the left VADs [40].

1.2 Current Status

Although VADS and TAHs are different in functions, they are same in terms of pump technologies which are either positive-displacement or rotary blood pumps. The main difference is the requirement of balance between pulmonary and systemic flow in TAHs. To avoid duplicate contents, this chapter will introduce the status and future directions of VADs.

1.2.1 Achievements

In the implanted heart assist devices, electromagnetic motors are used to convert electrical energy to mechanical energy in order to create motion, and the general rule is that electromagnetic motors run most efficiently at the highest speeds. Therefore, rotary pumps could be developed with high efficiency and reliability, whereas pulsatile pumps such as HeartMate XVE have less efficiency and low reliability because of the need for a cam to produce reciprocal motion when driven by electronic motors. In the recent years, the LVAD landscape has rapidly evolved away from volume-displacement pulsatile technology and toward continuous rotary pumps [41]. This shift is clearly shown in the eighth annual report of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), which stated in 2017 that 95% of implants are continuous-flow devices. Overall survival continues to remain 80% at 1 year and 70% at 2 years [42]. The increasing use of these rotary pumps in the clinical applications is based on their multiple advantages such as smaller size and improved durability, as well as the desirable outcomes of enhanced survival with less morbidity. Comparing to pulsatile pumps, these small size pumps have one more major advantage in that they can use in underserved patient populations, including women and some children [43].

1.2.2 Adverse Complications

Although rotary VADs have significantly improved survival and functional capacity for majority of patients, an unacceptably heavy burden of adverse events has slowed down this therapy's expansion and even appeared to plateau during the most recent era [42, 43]. According to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), the most common adverse events within the first year of pump implantation are bleeding, infection, thrombosis, and stroke. One-year survival free of any major adverse events is only 30%. These adverse events frequently lead to hospital readmission with rising costs [44].

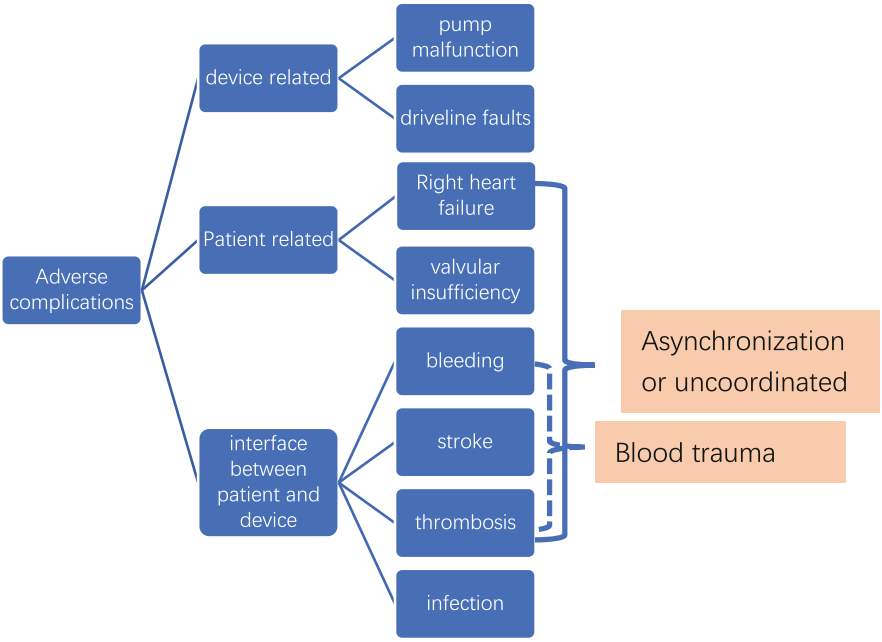

Fig. 1.2 Adverse complications of continuous VAD

As shown in Fig. 1.2, adverse complications can usually be classified into three broad categories [44]. There are those intrinsic to the pump and its constituents. Then there are those that are solely patient-related and develop because of the liability of the native heart. Finally, there are those that arise because of the pump–patient interface. From a technological point of view, these adverse events are further attributed to the blood trauma and coordination with native heart in the VAD.

The first category is related to the pump and its constituents, including pump malfunction, controller faults, and driveline faults. Since electronic motors and related materials are quite mature technology now, the failure of the pumps is rare now [37].

The second category is those that are solely patient-related but indirectly developed because of asynchronization or uncoordinated with the native heart, such as valvular insufficiency, and right ventricular failure.

Valvular insufficiency: Shortly after the adoption of continuous-flow left ventricular assist devices (CF-LVAD) therapy, it was noted that the most proximal portions of the vascular system—the aortic valve and aorta—were susceptible to unique changes that were not observed in patients with pulsatile flow left ventricular assist devices (PF-LVADs). The developments of de novo as well as worsening of existing aortic valvular regurgitation are known complications of CF-LVAD therapy [45]. The postulated mechanisms for the progression of aortic regurgitation with CF-LVAD therapy include the lack of aortic valve opening leading to commissural fusion of the aortic valve leaflets [46].

Right ventricular failure: The incidence of right ventricular (RV) failure after continuous-flow LVAD implantation is approximately 20–40%. Aside from underlying RV dysfunction which may precede LVAD insertion, excessive LV unloading due to LVAD pump over-speed can cause a leftward ventricular septal shift that distorts RV geometry and adversely affects RV function. Leftward interventricular septal shift reduces the efficiency of RV contraction. Furthermore, increasing systemic blood flow by a newly implanted LVAD can overload the RV with increased venous return [47].

The third category is those that arise from the pump–patient interface, such as acquired von Willebrand disease, infection, stroke, and pump thrombosis.

Bleeding: Bleeding is prevalent in CF-LVAD patients associated with the nearly ubiquitous development of acquired von Willebrand disease [48], which causes heavy bleeding or bleeding that will not stop. The risk of bleeding of CF-LVAD is typically multifactorial likely due to a combination of exogenous factors such as anticoagulation and antiplatelet therapy, endogenous causes such as fibrinolysis, and intrinsic properties of the devices such as the effect of the LVAD on endothelium, platelets, and von Willebrand Factor (vWF) [49]. For example, Von Willebrand factor (VWF) is a protein in the blood that helps it clot. The acceleration of blood through the CF-LVAD impeller creates shear forces that cause the large multimeric forms of von Willebrand factor (vWF) to unfurl, and be split [50]. The resultant vWF particles are too small to adhere to sites of vascular trauma or to bind platelets. The resultant coagulopathy aggravates bleeding from arteriovenous malformations that arise in the mucosal surfaces of the nose and gastrointestinal track. The mechanism is thought to be directly related to the lack of pulsatile blood flow, increased shear, and oxidative stress at a microvascular level. The absence of pulsatility might produce ischemia in these areas or might perhaps lead to greater venous distensibility within preexisting arteriovenous malformations, predisposing them to bleed [51]. From a technological point of view, it is found that the effect on von Willebrand factor (vWF) is related to blood trauma, and the absence of pulsatility is associated with the synchronization with native heart.

Stroke: Patients on lifelong support are concerned about their risk of experiencing stroke. These neurological events, which can lead to disability, loss of autonomy, or death, are the only serious adverse events encountered more frequently with CF-LVAD than with pulsatile pumps [52]. However, it remains unclear as to whether pulsatile arterial pressure may be protective of strokes while on LVAD therapy due to better preservation of vascular endothelial function [53]. The risk factors for strokes include infection, gastrointestinal bleeding, and device thrombosis [53]. Together, thromboembolic and hemorrhagic strokes occur with an incidence of 0.19 events per patient year, but the former is more common and the latter is more likely to be disabling or fatal. It has been reported that 97% patients who had undergone CF-LVAD explanation for heart transplantation or recovery since 2011 had at least one cerebral microbleeds [54], which is also associated with the blood pressure because maintaining a mean aortic blood pressure below 90 mmHg could reduce the incidence of hemorrhagic strokes by 50% [53]. From a technological point of view, maintaining a mean aortic blood pressure below 90 mmHg is related

to the coordination of a VAD with native heart; the gastrointestinal bleeding and device thrombosis are associated with blood trauma.

Thrombosis: Up to now, no single specific cause could be able to explain the jump in thrombosis rates in clinical trials, but several contributing factors have been proposed [55]. For example, CF-LVAD may damage red blood cells, platelets, and circulating factors through multiple mechanisms including shear injury, surface texture, and pump heating. These blood–device interface activates the hematologic, inflammatory, and immunologic systems, thereby promoting thrombosis, which is reported to occur in 5–8% of cases with continuous-flow LVAD [56]. The other factors include surgical and medical management decisions intentioned to minimize bleeding, but resulting in unintended thromboses [55]. Furthermore, the stasis of blood in the aortic root can lead to aortic root thrombosis because LVAD unloads left ventricle and decreases flow through the aortic valve. The source of the thrombus may have grown inside of the pump or come from the left atrium or left ventricle [57]. From a technological point of view, blood–device interfaces are related with the blood trauma, and the stasis of blood in the aortic root is caused by the VAD's non-coordination with native heart.

Infection: As smaller continuous-flow VADs have replaced larger pulsatile flow devices, the rate of infections has decreased in some extent. But the infection remains one of the most common complications in VAD patients, leading to hospital readmission in VAD patients [58]. VAD-related infections may be found to drive-lines, pump pockets, bloods, or device endocarditis [56]. For example, all VADs have a driveline penetrating the body percutaneously to receive electrical power supply, and percutaneous site infection may begin with the disruption of the barrier between the skin and driveline, where immobilization of the percutaneous drive line is essential at the exit site [56].

Apart from the infection, it is found that the adverse events can be mainly attributed to both non-coordination between VAD and the native heart, and blood trauma produced by VAD, which suggest that reducing the blood trauma and increasing the coordination with native heart would be the keys to reduce adverse events of VADs therapy.

1.2.3 Current Progress

Despite the huge advancements in VAD system manufacturing, majority of these concerns remain, due to directly connecting to the physical configuration of the available VADs; therefore, by taking into consideration of all these limitations, most of these researches concentrate on the approaches to reduce adverse complications caused by the blood trauma and low pulsatility.

1.2.3.1 HeartMate 3

One newest LVAD is the HeartMate 3 (HM3), which is a centrifugal pump with fully magnetically levitated impeller to eliminate wear and heat generation [39]. The HM3 also has wider gaps between the impeller and the pump housing for minimal shear stress on blood components, which may reduce blood cellular trauma [59]. The internal and external portions of the VAD's blood-contacting surfaces are textured with sintered titanium microspheres for establishing a biologic interface between the VAD and blood, preventing thrombus formation [28]. Finally, the pump has a programmed asynchronous pulse with every 2 s, which is designed to reduce stasis within the device and increases washing of the impeller, potentially decreasing rates of device thrombosis [60]. Comparing the centrifugal-flow pump HM3 with the axial-flow HeartMate II (HM2), the first report from the clinical trial including 294 patients followed for 6 months following device implantation has verified that the HM3 group had better survival with 86.2% at 6 months, free of disabling stroke or reoperation for pump thrombosis, than the HM2 group with 76.8% [61].

1.2.3.2 Bionic Vortex Flow

The next possible way to reduce the adverse events is to reduce blood trauma inside the VAD. Current continuous-flow VAD designs generate non-physiological blood flow patterns, imparting supraphysiologic shear stress to circulating platelets, ultimately activating the blood hemostatic response. As a result, patients are prone to develop thromboembolic complications, mandating lifelong antithrombotic regimens and leading to severe complications [62]. Device design optimization for reducing shear-induced blood damage is essential for improving device thromboresistance. Hence one target is to mimic the blood flow pattern in the left ventricle because it does not produce blood trauma induced by blood flow dynamics. To this end, an asymmetric inflow and outflow channel arrangement with a 45° intersection angle with respect to the blood chamber is proposed to approximate the vascular structure of the aorta and left atrium on the left ventricle. In this pulsatile pump, both the particle image velocimetry and the computational fluid dynamic results show the development of a persistent vortex during the cardiac cycle, realizing quasi intra-ventricle vortex flow patterns in a pulsatile VAD [63]. Since the biologic interface between the VAD and blood in Heartmate XVE could achieve low anticoagulation regimens and rare thrombus formation inside the pump, the technology combination of biologic interface and bionic vortex flow could have the potential to avoid possible post-implant thromboembolic complications in future.

1.2.3.3 Non-Blood Contacting Device

In the current VADs, the blood is removed from the heart, and then pumped into the aorta. The contact between blood and artificial surfaces induces the risk of thromboembolic events, necessitating long-term blood-thinning medications for patients with VADs. Hence another possible solution is to develop non-blood contacting VADs. Based on twisting and the circumferential actuators, Roche et al. developed an implanting non-blood contacting device. Soft robotic techniques are used to develop a tethered implantable sleeve that can provide circulatory support for patients with compromised heart function, augmenting cardiac function by closely coordinating with the native heart, instead of disrupting it. This sleeve does not contact blood, avoiding the need for anticoagulation therapy or blood thinners, and reducing the complications such as clotting and infection. The actuators are in a layered helical and circumferential fashion, mimicking the orientation of the outer two muscle layers of the mammalian heart. The feasibility of this soft sleeve device for supporting heart function is verified in a porcine model of acute heart failure [64].

1.2.3.4 Piezo-Hydraulic Pumps

From the actuating point of view, electronic motors are more suitable for the development of rotary blood pumps in terms of small size, reliability, and efficiency. However, natural selection of human favors pulsatile blood flow, and high speed rotation of the impeller may impart supraphysiologic shear stress to the blood components, inducing blood trauma. To reduce this risk of adverse events, one possible solution is to look for new actuating technology that is well suited for intimate interactions with the blood and heart. To this end, Valdovinos et al. evaluated piezoelectric hydraulic pumps as drivers for pulsatile pediatric ventricular assist devices. Because piezo-hydraulic pumps are high power density motors, pulsatile pediatric ventricular assist devices could be theoretically miniaturized with minimal loss in power output. The feasibility of using piezo-hydraulic pumps in pulsatile pediatric ventricular assist devices is investigated by incorporating an existing piezo-hydraulic pump into a ventricular assist device driver to drive a pulsatile pediatric 30-mL stroke ventricular assist device. The driver was tested at heart rates ranging from 50 to 110 beats per minute in an in vitro mock circulation to characterize its performance. The maximum drive pressure was 33 kPa with a peak flow rate of 6 L/min against a 10 kPa back pressure. These results compare well to commercially available systems that output between 25 and 40 kPa drive pressure and flow between 0 and 10 L/min against 10–16 kPa pressures [65].

1.3 Future Directions

The tremendous clinical advances have been made in heart assist devices over the past 60 years, and in recent years the major advantages have occurred as VAD technologies have moved away from pulsatile VADs to continuous-flow VADs [66]. However, continuous-flow VADs have remained associated with adverse complications, such as gastrointestinal bleeding and arteriovenous malformation [67]. Therefore, the trend of future development for VADs will move forward to a reduction in adverse events and minimizing negative patient–device interactions [68]. As shown in Table 1.1, it would be very hard to avoid blood trauma when rotary impeller is adopted in VADs. Therefore, the soft actuating technology has been proposed to actuate VADs in replicating the heart motion to avoid the possible blood trauma [64, 69]. These results suggest that the actuator of VADs will determine the size, reliability, and the pumping process, which is crucial to the blood flow dynamics and synchronization with native heart. Hence, the actuating technology will be a key to develop a VAD with small size, high reliability, and low rates of complications. Since VADs are used to assist the diseased heart, the biocompatibility of VADs is also major concern [70]. Furthermore, improving the patient quality of life will also be a key for the development of VAD. For example, the investigation of control strategy could improve the potential of myocardial recovery, and the utilization of transcutaneous energy transmission system could avoid driveline infections. That is, future directions for VAD techniques will focus on the investigations for the actuating technology, the biocompatibility, and the way to improve the quality of life as shown in Fig. 1.3.

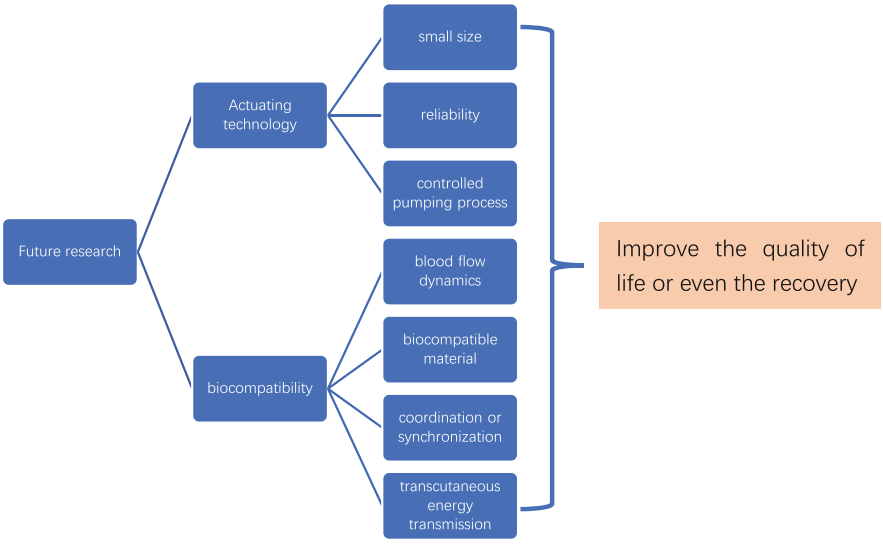

Fig. 1.3 Future directions of VAD development

1.3.1 Actuating Technology

As seen from Table 1.1, the existing cam in Heartmate XVE provides a precise control on ejection process of the blood pump, minimizing the blood trauma caused by blood dynamics but inducing a large size and limited reliability [28]; the existing solenoid in Novacor provides a simple structure, having longest duration up to 6 years but losing a precise control on the pumping process and inducing thromboembolism [29, 30], so does as the rotary impeller in HeartMate II [37]. These results suggest that actuating technology has a vital role in determining the features of VAD. This could be further explained as the actuators of VAD determine the structure, shape, and performance of the VAD. For example, standard electronic motors are commonly used to offer an effective way of continuously operating pumps, fans, compressors, conveyors, etc. at fixed speed. That is, the electromagnetic force actuated CF-LVAD can be developed with smaller size, high reliability and efficiency. However, the non-physiological blood flow patterns produced by CF-LVAD restrict the coordination between the CF-LVAD and a pulsatile human circulation, causing severe impacts on the circulation and trauma to blood. Hence, investigation on the actuating technologies would be priority to develop a VAD with small size, high reliability, and low rates of complications. To achieve a unification of small size, high reliability, and low rates of adverse events within one VAD, the desired characteristics of an ideal actuator would be light weight, small size, high reliability, fast dynamic response, accurate speed and position control, enough force, and silent operation. With this ideal actuator technology, a VAD would be able to implant with small size and light weight while coordinating with human circulation system. The possible approach to look for new actuators could be achieved by investigating on the novel configurations or design optimization of electromagnetic forces such as increasing gaps between the impeller and the pump housing in Heartmate 3 [60], or even exploring new actuation methods of various physics, chemistry, and biology. Some new progresses of existing actuation methods such as piezo-hydraulic pumps, and piezoelectric ultrasonic motors are warranted for further investigations [71].

1.3.2 Technology for Biocompatibility

The biocompatibility of VADs is associated with blood trauma caused by non-physiological blood dynamics such as high shear stress area, adverse events caused by non-coordination between the VAD and heart, and the material reactions caused by the blood contact with artificial surface. This could be explained in two aspects. In the first aspect, the technology of producing physiological blood flow is associated with VAD blood flow pattern mimicking that in the ventricle. The reason is that blood flow pattern in the ventricle is the result of a long-term natural evolution, which has the merits with minimal blood damages. In the second aspect,

coordination technology consists of synchronization and matched assisting blood volume with the diseased heart. The benefits of coordination can be demonstrated from intra-aortic balloon counter-pulsation (IABP), in which diastolic inflation and systolic deflation of intra-aortic balloon increase coronary blood flow and decrease the afterload, translating into augmentation of oxygen supply and lowering of oxygen demand [72]. Coordination could be further explained as the needs of physiological controllers for patient well-being, including the integration of sensors that will allow the pump to adapt to different perfusion demand [33, 66]. For the material reactions caused by the blood contact with artificial surface, the future investigation on novel surface structuring and endothelialization should lead toward enhanced device hemocompatibility and needs to be verified in vivo [66].

1.3.3 Improve Quality of Life

Improving the quality of life is mainly associated with reduction of adverse events and the way for myocardial recovery. One important issue is to reduce the infections. Since most infections start as superficial driveline infections and progress over months to become deep tissue infections [73], one more future investigation will be adaptation and integration of transcutaneous energy transmission technology to avoid the risk of infection due to drivelines. By the way, this transcutaneous energy transmission system will additionally increase the freedom of movement [33, 66].

The most effect way to improve the quality of life is to obtain the reverse remodeling and myocardial recovery. Since the long-term VAD supports have induced the largest degree of reverse remodeling among heart failure therapies, further research may focus on the analysis of human tissue after a period of VAD support. These analysis results will be very important for optimization design and control of VAD for reverse remodeling and myocardial recovery to increase the opportunity of explanting the VAD in future [74]. As stem cell therapy and VAD support are both known to improve perfusion and contractility in ischemic heart tissue, the combination of LVAD support and stem cell therapy may have potential with synergistic effects greater than either of single therapy [75], increasing the opportunity for myocardial recovery.

1.4 Conclusion

Since continuous-flow VADs can provide meaningful increases in survival, functional capacity, and quality of life, they have now become the mainstay for the care of heart failures. However, adverse complications, such as gastrointestinal bleeding and arteriovenous malformation, have remained in continuous-flow VADs. Therefore, reduction in adverse events has become the major directions for future development of VADs. Future innovations may concentrate the optimization actuating

technology, improvement of biocompatibility, and enhancement of the quality of life. Ideally, a VAD with small size, high reliability, physiological blood flow, coordination with native heart, and super blood compatibility artificial surfaces will be able to develop effective destination therapies with longer patient survival times and improved quality of life.

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Chapter 2
Mechanisms of Heart Failure

Xufeng Wei and Yixin Cui

Abstract Heart failure (HF) is an end-stage manifestation of various heart diseases and a major cause of death in patients with heart disease. Morbidity increases with age, and mortality and hospitalization remain high. This chapter will introduce definition, mechanism, diagnosis, and management of heart failure. Through the description of the pathophysiology of heart failure, to understand the current world's cutting-edge treatment technology. Whether it is chronic heart failure or acute heart failure, it is a challenge for doctors in this era to propose effective treatment methods based on symptomatic treatment. From the traditional single drug treatment gradually to more challenging mechanical treatment evolution. In this chapter, the current effective, feasible and high survival rate treatment methods are briefly listed.

Keywords Heart failure · Pathogenesis · Mechanism and Diagnosis · Management

2.1 Introduction

This chapter will introduce definition, mechanism, diagnosis, and management of heart failure. The description of the pathophysiology of heart failure is helpful to understand the current world's cutting-edge treatment technology.

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2.2 Definition

Due to myocardial contraction and/or diastolic dysfunction, cardiac output is absolutely or relatively reduced, that is, the function of cardiac pump is weakened, so that the pathological process cannot meet the needs of the body metabolism. The main manifestations are venous congestion caused by tissue ischemia and blocked venous return.

There are many causes of heart failure, including myocardial lesions caused by viruses and bacteria, myocardial ischemia and hypoxia, severe vitamin B1 deficiency, and cardiac overload, including pressure overload and volume overload. In the presence of these basic causes, there are some other inducements, such as systemic infection, acidosis, hyperkalemia, arrhythmia, pregnancy, and childbirth, which may lead to heart failure.

2.3 Pathogenesis of Heart Failure

Reduction of cardiac output is a key link in the pathogenesis of heart failure. There are various compensatory mechanisms to prevent the decrease of cardiac output when the heart is damaged by etiology. When heart failure occurs, there are mainly the following compensatory methods.

2.3.1 Compensatory Response In and Out of the Heart

2.3.1.1 Contraction-Related Protein Destruction

Myocardial necrosis, severe myocardial ischemia, myocarditis, cardiomyopathy, and other cardiac diseases cause myocardial degeneration, necrosis, and fibrosis, resulting in a large loss of myocardial contractile protein, leading to a significant reduction in myocardial contractility.

In vivo and in vitro factors trigger pre-existing death processes within cells, which then lead to death causes the myocardial cell quantity to reduce, causes the heart failure.

2.3.1.2 Cardiac Energy Metabolism Disorder

Reasons and mechanisms of energy generation barriers:

Hypoxia and coronary heart disease can cause myocardial ischemia and hypoxia. Myocardial hypoxia can lead to the obstacle of aerobic oxidation, which leads to the decrease of ATP production and myocardial contractility, while myocardial

ischemia can reduce the production of ATP, but increase the accumulation of metabolites to cause acidosis. Due to insufficient thiamine pyrophosphate production caused by vitamin B1 deficiency, pyruvate oxidative decarboxylation disorder occurs in the body, which further causes ATP production to go down the well, thus reducing myocardial contractility.

Energy utilization barrier: Because the body's hydrolysis of ATP is reduced, it cannot provide enough energy to reduce myocardial contractility. The utilization of ATP energy in myocardium is decomposed by ATPase in myosin head. The excessive hypertrophy of the myocardium will lead to the decrease of myosin head/tail ratio and the relative insufficiency of myosin enzymes, weaken the activity of ATPase and decrease the ability of utilizing ATP, resulting in the decrease of myocardial contractility.

2.3.1.3 Systolic Coupling Disorder Caused by Myocardial Excitation

The main causes include dysfunction of sarcoplasmic reticulum uptake, storage and release of Ca2+ caused by myocardial hypertrophy, extracellular Ca2+ influx disorder in hyperkalemia, cardiac hypertrophy, acidosis, and troponin-Ca2+ binding disorder. In a word, acidosis caused by various reasons decreases calcium influx in sarcoplasm and decreases calcium concentration in cytoplasm during contraction due to calcium release disorder, coupled with excitation-contraction decoupling caused by troponin and Ca2+ binding disorder, and decreases myocardial contractility.

2.3.1.4 Moderate Cardiac Hypertrophy Is a Powerful Compensatory Method

However, cardiac hypertrophy, hypertrophic myocardium due to several levels of unbalanced growth, cannot sustain normal function, heart failure will occur. The unbalanced growth of hypertrophic myocardium is manifested in the following aspects.

The increase of myocardial weight over the increase of cardiac sympathetic nerve significantly decreased the distribution density of cardiac sympathetic nerve and further led to the decrease of norepinephrine content in myocardium. Causes the myocardial contractility to reduce.

The increase of myocardial mitochondria lagged behind the increase of myocardial cell volume, and the level of oxidative phosphorylation of mitochondria decreased, resulting in insufficient energy production.

Myocardial capillary hyperplasia lags behind the growth of myocardial cell volume; or microvascular proliferation can correspondingly, but due to contraction, compression, and narrowing, result in poor myocardial microcirculation perfusion, hypertrophic myocardium ischemia, and hypoxia.

The decrease of myosin ATPase activity hinders energy utilization. The decrease of the proportion of myosin head and the change of the proportion of three isoenzymes (the decrease of V1 with high activity and the increase of V3 with low activity) promoted the decrease of myosin activity. Myocardial hypertrophy exceeds the limit and reduces contractility.

The ratio of surface area to weight of hypertrophic cardiomyocytes decreased significantly, and sarcoplasmic reticulum treated calcium dysfunction, resulting in decreased Ca2+ influx and calcium release.

In conclusion, the above unbalanced growth leads to heart failure. These are the first mechanisms of heart failure, most of which are caused by heart failure. Heart failure was once defined as a decrease in cardiac output caused by decreased myocardial contractility. However, diastolic changes of myocardium are considered to be an important mechanism of heart failure.

2.3.2 Ventricular Diastolic Dysfunction

The main manifestation of heart failure is a decrease in cardiac output, which depends on the contractility of the heart and the volume of blood in the heart. The latter is affected by ventricular diastolicity. Decreased ventricular diastolic function can also lead to heart failure.

2.3.2.1 Delayed Ca^{2+} Reset

As has been said before, the initiating factor of myocardial diastole is the reduction of calcium ions in the cytoplasm to the original level at repolarization, i.e., the release of calcium from cells into the sarcoplasmic reticulum. This requires the use of calcium pumps and energy supply. Therefore, when myocardial ischemia and hypoxia occur, ATP supply decreases, activity of sarcoplasmic reticulum and membrane Ca^{2+}-ATPase decreases, and the concentration of [Ca^{2+}] in cytoplasm cannot be rapidly lowered, thus delaying myocardial relaxation.

2.3.2.2 Dysfunction of Actin-Globulin Complex

Normal cardiac diastole requires not only the dissociation of calcium from troponin, but also the dissociation of actin-globulin complex. This is also a process of energy consumption. Therefore, when myocardial ischemia and hypoxia occur, ATP supply decreases, forcing the actin-globulin complex to dissociate, and the myocardium is in a state of continuous contraction.

2.3.2.3 Reduction of Ventricular Diastolic Potential Energy

During cardiac contraction, a diastolic potential energy can be produced to facilitate ventricular repositioning due to changes in ventricular geometry. The better the contraction of the heart, the better the diastolic potential energy. In addition, filling perfusion of coronary artery is also an important factor to promote ventricular diastole. Therefore, the decrease of cardiac contractility or coronary artery occlusion leads to the decrease of diastolic potential and the decrease of myocardial diastolic potential.

2.3.2.4 Decreased Ventricular Compliance

Ventricular compliance refers to ventricular dilatability. If the ventricular compliance decreases, the pressure required to increase the same volume of the ventricle is greater than that required in normal condition. The main reasons leading to the decline of ventricular compliance are: internal factors such as thickening of ventricular wall and/or changes in composition of ventricular wall, and external factors such as pericarditis and pericardial tamponade.

2.4 Mechanism and Diagnosis

Maintaining normal blood circulation requires the pump function of the heart, a certain volume of blood, and a good state of vasodilation and contraction. Cardiac output can reflect cardiac function. If normal cardiac output is maintained, three conditions are needed: (1) Good myocardial contractility to ensure that blood can pump out of the heart; (2) A certain amount of blood in the heart, which is affected not only by the total volume of blood, but also by the dilatability of the heart, that is, diastolic coordination; (3) Systolic and diastolic coordination of all parts of the heart. Heart failure is one of the three obstacles mentioned above. Good myocardial contractility ensures that blood can pump out of the heart.

Human circulation includes pulmonary circulation and systemic circulation. Pulmonary circulation is the flow of blood from the right ventricle into the pulmonary artery, gas exchange in the pulmonary capillaries, and through the pulmonary vein into the left atrium. Systemic circulation is the flow of oxygen and blood from the pulmonary vein into the left atrium, which further flows into the left ventricle, pumps into the aorta, supplies blood to various systems and organs throughout the body, and finally flows back to the right atrium through the superior and inferior vena cava.

From the perspective of hemodynamics, the clinical manifestations of heart failure can be divided into three categories: pulmonary circulation congestion, systemic circulation congestion, and insufficient cardiac output. Among them,

pulmonary circulation congestion is the most characteristic. We mainly introduce pulmonary circulation congestion.

Pulmonary circulation congestion: Left heart failure can lead to pulmonary circulation congestion. The main manifestation of pulmonary circulation congestion is dyspnea.

Systemic circulation congestion: Systemic circulation congestion is mainly the result of heart failure or right heart failure. The main manifestations were venous system filling, systemic edema, and visceral hyperemia.

Insufficient cardiac output can lead to insufficient tissue perfusion. Specific manifestations are: pale skin caused by decreased blood flow; weakness, insomnia, and lethargy resulting from reduced blood supply to muscle tissue and the central nervous system; and decreased urination; in severe cases, cardiogenic shock may occur.

Heart failure is the quintessential cardiovascular syndrome of aging that results from common cardiovascular conditions in older adults in conjunction with age-associated changes in cardiovascular structure and function. To a large extent, heart failure is a geriatric syndrome in much the same way that dementia, falls, and frailty are geriatric syndromes. The incidence and prevalence of heart failure increase strikingly with age and make heart failure the most common reason for hospitalization among older adults. While outcomes for older adults with heart failure have improved over time, mortality, hospitalization, and rehospitalization rates remain high.

It is necessary to conduct a comprehensive and detailed medical history inquiry and examination. The most common cause of heart failure is coronary heart disease, which is caused by hypertension. In addition, there are also some valvular diseases, alcoholic cardiomyopathy, perinatal cardiomyopathy, arrhythmic cardiomyopathy, and so on. Infection is the most common cause of heart failure, usually in patients with underlying heart failure. Heart failure is aggravated by cold. Secondly, rapid infusion or inappropriate reduction of diuretics in patients with chronic heart failure can lead to aggravation of heart failure. Physical strength, mental overload, or delivery of pregnant women are all causes of heart failure. Detailed inquiry removes incentives as soon as possible. Based on the analysis of symptoms, objective evidence, etiology, and inducement, a comprehensive clinical evaluation of patients with heart failure is made, and appropriate treatment options are given.

Acute heart failure (AHF) refers to acute attack or aggravation of left ventricular dysfunction caused by decreased myocardial contractility, increased cardiac load, resulting in acute cardiac output, increased pulmonary circulation pressure, increased peripheral circulation resistance, resulting in pulmonary circulation congestion and acute pulmonary congestion, pulmonary edema and accompanied by tissue and organ irrigation. Left ventricular failure is the most common clinical syndrome of insufficient injection and cardiogenic shock. Acute heart failure can be acute exacerbation or sudden onset on the basis of the original chronic heart failure. Most patients before onset have organic cardiovascular disease, which can be manifested as systolic heart failure or diastolic heart failure. Acute heart failure is often life-threatening and must be urgently rescued.

Classification of chronic heart failure is divided into heart failure with reduced ejection fraction and mainly includes heart failure with decreased ejection fraction and heart failure with preserved ejection fraction.

Patients usually have typical symptoms and signs of heart failure, and left ventricular ejection fraction is less than 40%. With symptoms and signs of heart failure, left ventricular ejection fraction was normal or slightly decreased, and left ventricular was not significantly enlarged. Left ventricular ejection fraction (LVEF) was more than 50%. There were related structural heart disease and/or diastolic heart dysfunction. Echocardiography showed no valvular disease and excluded pericardial disease, hypertrophic cardiomyopathy and limitation. Systemic cardiomyopathy, etc.

Diagnosis should meet the following conditions: (1) symptoms of heart failure during exercise or rest; (2) evidence of cardiac insufficiency rest; (3) better clinical response to the treatment of heart failure. Right heart failure should be differentiated from pericardial effusion, constrictive pericarditis, liver cirrhosis, and nephrogenic edema.

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Chronic heart failure refers to the aggravation or end stage of patient's heart disease [1], which will lead to the decline of patients' ventricular pumping function. Traditionally, the main way to treat the disease is to use cardiotonic agents, diuretics, or vasodilators to intervene in patient's disease, although the above-mentioned treatment methods can be used. In the short term to improve the adverse symptoms of patients, the long-term effect of application is indeed limited, so the clinical field has been committed to the study of the treatment of the disease [2]. ACEI is known as angiotensin converting enzyme inhibitor. Its main components are enalapril, ramipril, captopril, perindopril, and benazepril. Beta-blockers mainly include carvedilol, bisulol, and metoprolol. Aldosterone receptor antagonists mainly include epristone and spironolactone. The recombinant human brain natriuretic peptide mainly includes novobin and nesiritide [2]. With the continuous improvement of medical technology, there are more and more ways to treat heart failure. The treatment of heart failure patients by ACEI, beta-blocker, aldosterone receptor antagonist, and adequate human brain natriuretic peptide is conducive to improving the clinical efficacy, improving the clinical discomfort symptoms and improving the quality of life of patients. The curative effect is remarkable.

2.5 Management

At present, the activation of neuroendocrine system leading to myocardial remodeling is a key factor in the occurrence and development of heart failure, including sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS). Based on the neuroendocrine mechanism of heart failure, the current treatment of chronic heart failure is to improve neurohormonal abnormalities and prevent myocardial remodeling. More new drugs for chronic heart failure, such as ARNI, tovaptan, levosimendan, and ivabradine, have made up for many clinical treatment deficiencies. Most of the clinical trial population of chronic heart failure is heart failure patients with decreased ejection fraction. Next, I will briefly summarize the drug treatment. The neuroendocrine mechanism of heart failure is the basis of classical drugs. New drugs are available. In addition, new drugs such as the following are still in clinical trials, which will bring more choices for the treatment of heart failure. Heart failure is the end stage of various cardiovascular diseases with complex pathogenesis and high mortality. How to reduce the mortality rate of heart failure patients, reduce the hospitalization rate, improve the long-term prognosis, improve the quality of life, and so on are long-term problems faced by medical workers.

Specific suggestions for implementing the new process of chronic systolic heart failure are as follows:

(a) The time when ACEI and beta-blockers began to be used: In the past, it was emphasized that diuretics should be used to eliminate fluid retention before adding them. The new guidelines remove this requirement. For mild to moderate edema, especially for hospitalized patients, it can be used with diuretics at the same time.
(b) The priority of the use of ACEI and beta-blocker: The priority of beta-blocker and ACEI has always been the focus of attention, but the priority of the two drugs is not important, the key is to use them together as soon as possible.
(c) Form “golden triangle” as soon as possible: Avoid hypotension, hyperkalemia, and renal function damage.

Renewal of treatment concept of chronic heart failure.

(a) Sodium Limitation
Restriction of sodium intake may not necessarily benefit patients with stable heart failure. Normal diet can improve prognosis. Patients with grade III–IV congestive symptoms and signs of cardiac function are beneficial. Patients with acute attack of heart failure accompanied by volume overload usually need to limit sodium intake <2 g/d.
(b) Water Restriction
Severe hyponatremia (blood sodium < 130 mmol/L), liquid intake should be < 2 L/d. Routine fluid restriction in patients with mild to moderate symptoms may not be beneficial.

For acute heart failure, loop diuretics such as furosemide and torasemide are preferred. Thiazide diuretics can be used in patients with mild fluid retention and hypertension. At present, there is a new diuretic—tovaptan, which is an antagonist of vasopressin V2 receptor. It has the characteristics of no drainage and no sodium excretion. It has a very good effect on refractory heart failure and intractable edema. Indications include routine diuretic resistance, hyponatremia, and intractable edema.

(a) Digoxin

Indications (Class IIa, Class B): Diuretics, ACEI (or ARB), beta-blockers, and aldosterone receptor antagonists have been used, but symptoms persist; LVEF <45%; patients with atrial fibrillation with rapid ventricular rate are particularly suitable.

Application method: 0.125–0.25 mg/d, the dosage of elderly or renal impaired patients was reduced by half, and it should not be easily discontinued. NYHA level I should not be used.

(b) Ivabradine

Beta-blockers also have the effect of slowing heart rate, but at the same time, they also inhibit sympathetic excitation and reduce myocardial contractility.

Indications: In HF-REF patients with sinus rhythm, ACEI (or ARB), beta-blocker, and aldosterone receptor antagonist were used, and the recommended dose or maximum tolerable dose was reached. Heart rate was still more than 70 beats/minute. Continuous symptoms (NYHA class II-IV) could be considered to add ivabrail (class IIa, class B).)

Heart failure is the end-stage manifestation of various heart diseases and one of the main causes of death of heart disease patients [3]. With the increase of age, the incidence of heart failure is increasing. Despite the continuous improvement of drug treatment, the morbidity and mortality rate are still very high [4]. In recent years, more and more clinicians pay attention to the non-drug treatment of heart failure. Surgical methods are increasingly innovative. Medical interventions are constantly introducing new auxiliary devices. Genetics and stem cell technology bring new hope for its treatment [2]. In this chapter, the current status and progress of surgical operation, interventional therapy and related gene and cell therapy for heart failure are briefly introduced. (1) The main surgical treatments of ischemic heart failure include coronary artery bypass grafting and left ventricular angioplasty; (2) The surgical treatments of idiopathic dilated cardiomyopathy include partial left ventricular resection and dynamic cardiomyoplasty; (3) Ventricular assist devices and artificial hearts belong to mechanical assist devices; (4) Transplantation; (5) Heart initiation; Beat therapy has become a new treatment for patients with slow arrhythmia and severe heart failure. (6) Cell transplantation for heart failure is to inject autologous bone marrow stem cells or skeletal muscle cells into coronary artery, or to inject them into the epicardium or subepicardium by thoracotomyinto. After transplantation, these cells further differentiate into cardiac myocytes, reconstruct myocardial tissue, replace scar connective tissue, restore the contractile and diastolic function of myocardial tissue, and improve the overall cardiac function [2, 4–7].

Heart transplantation is currently an effective treatment for end-stage heart failure, but its application is limited due to the serious shortage of donors and other reasons. In recent years, mechanical circulatory support devices, including aortic balloon counterpulsation, ventricular assist devices and total artificial heart, have developed rapidly. Whether it is acute heart failure caused by surgery or end-stage chronic heart failure caused by various heart diseases, it will pose a huge threat to patient's lives and aggravate the burden of health care system. With the rapid development of economy and the continuous improvement of cardiac surgeon team's technical level, mechanical circulatory support devices have been widely used in transitional treatment before heart transplantation for end-stage heart failure or permanent replacement therapy for heart transplantation patients.

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Chapter 3
Basis of Artificial Heart Technologies

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Abstract An artificial heart or a ventricular assist device (VAD) is a critical treatment option for the patients with end-stage heart failure (HF). Due to the paucity of donor organs, it is considered as the standard clinical therapy for most heart transplant recipients while drug therapy has little effect on them. To date, significant advances have been made for artificial heart and VAD technologies over the past five decades. Currently, there are a wide array of artificial hearts and VADs available and under development, and they are implanted on the left, right, or both ventricles of the patient's heart. In general, artificial hearts can be classified according to varying aspects such as their operating features (first, second, and third generation), supporting duration (acute, chronic), flow profiles (pulsatile and continuous), and implantation form (extra-, para-, and intracorporeal). While these devices have different housing structures, actuation mechanism, design, and performance, they provide hemodynamic support. Progressive generations of devices have iterated to improve various aspects such as size, weight, blood-flow pattern, material, drive and control, and power supply. This chapter briefly introduces and describes significant technical characteristics of all the main artificial hearts and VADs mainly based on their flow profiles.

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3.1 Introduction

Heart failure (HF) is one of the most common diseases. It has high incidence and is also the serious and terminal stages of various heart diseases. In recent years, the prevalence of HF is growing with over 20 million patients globally. The incidence of HF is increasing by two-million patients annually [1]. Heart transplantation may be the best treatment for end-stage HF patients, with the estimated half-life of nearly 10 years. While heart transplant patients are on immune suppression medication to minimize rejection, they have a good quality of life. However, heart transplants have plateaued in recent years (5000 transplants/year globally [2]) and due to the shortage of donor organs, qualified recipients need to wait years for a matching donor heart [3]. It is estimated that the number of patients died exceed 20% after about 6 months on the transplant list. To overcome this limitation, mechanical circulatory support (MCS) devices have been developed as a treatment option for end-stage HF patients to provide sufficient physiological perfusion [4].

Since 1960s, the development of artificial heart technologies has been an active area in the USA and Europe. Artificial hearts have become a foundation for the care and management of patients with advanced congestive HF or end-stage HF. Having successfully demonstrated clinical use as bridge to transplant (BTT) therapy in HF patients, artificial hearts have also been used for different device strategies such as destination therapy (DT), bridge to recovery (BTR), or bridge to decision (BTD) [5, 6]. As an effective option for end-stage HF patients, there are other classifications for artificial heart technologies. They can be classified and categorized by configuration of device (left ventricular assist device—LVAD, right ventricular assistant device—RVAD, and biventricular assist device—BiVAD), drive mechanism (pneumatic and electric), support duration (short-term vs long-term), implantation position (extracorporeal vs intracorporeal), pump flow pattern (pulsatile flow vs continuous pump), etc. While these artificial hearts have different structure, working mechanism, design, and performance, they still have some common elements. All devices are currently powered by Li-ion batteries, which typically provide adequate power density for at least 4–6 h of support. Data and power transfer usually takes place through a driveline, which has to be maintained to minimize infections. Fully implantable systems have been developed, but requires a coil and an internal battery to be implanted. The ideal device has to be small enough to reduce surgical invasiveness, has to be reliable for prolonged support, reduce blood trauma, and has to be hemo- and biocompatible. This chapter provides an overview of the technical characteristics and challenges of various types of MCS devices with different pump flow profiles, which are clinically applied and currently under development.

3.2 Pulsatile Flow Pumps

The first generation of implantable artificial hearts was the pulsatile blood pumps, which can generate pulsatile flow rates and pressures by mimicking the working function of the natural heart. They are either pneumatically or electrically driven. These pumps are characterized by their large size, heavy weight, and a large external drive unit that limited mobility of patients [7]. They were used as LVAD, RVAD, or BiVAD. Examples of typical pulsatile pumps include Heartmate XVE, BVS5000, AB5000, Thoratec PVAD/IVAD, Berlin Heart Excor, Novacor, etc.

3.2.1 Thoratec HeartMate XVE

The HeartMate XVE (Thoratec Corporation, Pleasanton, CA, USA) has been developed from the discontinued implantable pneumatic (IP) [8] and vented electric VE pumps [9, 10]. The XVE is a pulsatile blood pump, which actuates a push slab. The push slab connects to a special diaphragm that is flexible to generate pulsatile flow directing from the left ventricle (LV) to the ascending aorta [11]. There are valves in the paths of inlet and outlet to prevent retrograde flow. HeartMate XVE was electrically powered to move the pusher plate, while HeartMate IP was pneumatically driven. HeartMate XVE also has two rechargeable batteries and a belt-like controller as the wearable components to support approximately 6-h power [8]. Compared to the pneumatic driver, the electric driver reduced the size of wire that passes through the skin to around ∅12 mm, without using the externally compressed air source [8].

HeartMate XVE sizes ∅55 × 170 mm and weighs 1150 g, which cannot be implanted in patients whose body surface areas (BSA) are no larger than 1.5 m^2. It can provide full support cardiac output as high as 10 l/min with 120 beats per minute (bpm). Moreover, the blood contacting surface is made of sintered titanium, which reduced the requirement for anticoagulation therapy [12] and reduced stroke rates. The drawbacks of this device included large device size that necessitated implant in the abdomen and limited durability.

3.2.2 BVS5000

The BVS5000 (it has not been promoted any longer) is a pulsatile artificial heart. It can provide support for left-, right-, or both ventricles. The whole BVS5000 contains a dual-chamber blood pump, a drive console, and various cannulae [13]. The left atrial (LA) cannula is placed through LA appendage or dome, while the right atrial cannula is placed through right atrial appendage or mid-free wall [14]. There is a woven Dacron graft with the length of 14 mm for the arterial cannula. To prevent

bleeding, each cannula has an exterior Dacron velour sleeve [14]. The extracorporeal blood pump (volume is 660 ml and weight is around 1700 g) is suspended through an IV-type pole with a clamp [15]. The pump has two chambers for filling and pumping, each of which has a polyurethane bladder with the volume of 100 ml, meaning that the pump casing is plastic, visible for the chamber contents.

BVS5000 is actuated by a user-friendly, fully automatic, and pneumatic drive console. Systole and diastole percentages of the pump can be automatically regulated by the control system, in order that the changes in preload and afterload can be compensated by maintaining a constant stroke volume (SV) that is around 80 ml [14]. It automatically regulates the pumping flow rate to provide physiological perfusion up to 5 L/min. The size of drive console is 610 × 560 × 845 mm, with the weight of approximately 82 kg [15]. The operation of the drive console is based on either alternating-current or internal battery power, consuming the mean power of 280 w. The drive console also has a safety backup system for the microprocessor and a foot pump for completely manual operation [14]. A backup battery is automatically activated to support the device for up to 1 h in case of lost alternating-current. If the microprocessor-based system fails, a fixed pump rate is implemented by the hardware-based backup system. If a complete console failure happens, the foot-operated pump allows continued assist until a backup console is available [16, 17].

3.2.3 AB5000

The AB5000 (it has not been promoted any longer), a pulsatile artificial heart, is designed as an improvement over the BVS5000. It is comprised of a pneumatically driven and paracorporeal blood pump, a fully automatic cannula, and a vacuum-assisted console [18]. The cannulation is similar to the BVS5000 system, the inflow cannula with different sizes of 32F, 36F, or 42F is placed into the atriums or ventricles, while the outflow cannulation with 10 mm or 12 mm grafts is connected to the aorta or pulmonary artery [18]. Its blood sac (volume is 100 ml) has two flexible and polyurethane trileaflet valves and is designed into the transparent blood chamber.

The AB5000 device is a rigid chamber, houses a polyurethane bladder, and is made of different materials such as polycarbonate, epoxy, aluminum, and titanium [8]. It has dimension of 155 × 80 × 60 mm and a weight of 300 g, which is lighter than the BVS5000. The total extracorporeal system volume is no more than 200 ml. The fixed rate mode is set to automatically regulate the device by maintaining the SV as 70–80 ml. In addition, the dimension of the drive console measures 584 × 305 × 737 mm, weights 43.5 kg while the weight of the portable cart is negligible, and the maximum power consumption is 250 w [15].

3.2.4 Thoratec PVAD

The Thoratec paracorporeal VAD (PVAD) (Thoratec Corporation, Pleasanton, CA, USA) consists of a pulsatile pump, the prosthetic ventricles, cannulae implanted into the atrium or ventricle as inflow and artery as outflow, and a console that is pneumatically driven [19]. It is a short or medium term device, used as left-, right-, or biventricular support, providing up to 6.5 l/min cardiac output with the maximum heart beats of 100 bpm. In order to assist the LV or LA, the inflow cannulation is performed from the LV apex, or the LA appendage through the interatrial groove [19]. In contrast, cannulation is performed from the right atrium to the pulmonary artery to assist the right heart. The outflow cannula is attached to a 14-mm polyester graft, and connected to the ascending aorta [19].

The chamber and cannulae are made from Thoratec's BPS-215 M polyurethane elastomer as the combination of two polymers [19]. One of the two polymers is used to provide thromboresistance, while the other provides extensive strength and life [20]. The Thoratec PVAD's volume is about 320 ml, weight is around 420 g, and dimension is 125 × 80 × 60 mm. Its effective SV is 65 ml and cannula inner diameter at ports is 16 mm [21]. Note that there may be some issues for daily movement of patients implanted with the Thoratec PVAD, since it is placed out of the body and near to the abdomen.

The Thoratec PVAD can be operated with either a Dual Drive Console (DDC) weighting as 231 kg with 40 min battery life, or a lighter one with the weight of only 9.8 kg as the portable Thoratec TLC-II driver [15]. The console is operated with a pulse-like fashion to control the pneumatic pressure and vacuum such that the pump can be filled or empty. Asynchronous (fixed rate), synchronous (timed to patients' heart rates), and volume mode (full-to-empty variable rate) are the control modes of the console [22, 23]. In most cases, the volume mode is recommended for the patient support. It can automatically regulate the heart rate and thus the flow rates based on venous return and the requirements of the body [19].

3.2.5 Thoratec IVAD

The Thoratec IVAD (Thoratec Corporation, Pleasanton, CA, USA) is an intracorporeal and pulsatile artificial heart, which is pneumatically actuated and can allow the patient to have a normal life out of the hospital, meaning that mobility is improved [24]. In comparison to the PVAD, the IVAD has smaller size as 120 × 80 × 50 mm, the volume as small as 252 ml, the weight as light as 339 g, and has the same inner diameter of cannula and SV [21]. This device allows implantation in patients whose weights are ranged 40–100 kg or with a BSA larger than 1.3 m^2. Furthermore, the valves and other materials used for the IVAD are similar to those for the PVAD, except that the chamber housing of the IVAD is

fabricated with titanium alloy to allow for improvement of external surface biocompatibility, the transcutaneous driveline is longer, while the cannulae are shorter [24].

Same as the PVAD, for hospitalization purpose, the IVAD also can be driven with the Thoratec DDC [25], which independently controls the left and right side pumps for the purpose of biventricular support. There is a variety of control parameters used to adjust the pumps, including the operation modes (asynchronous, synchronous, and the commonly used volume mode), vacuum pressure, ejection drive pressure and time, and pumping rates. Thoratec can also offer a TLC-II portable driver as mentioned previously, which allows for the patient to be discharged home [26]. Unlike the DDC, the TLC-II only has two control modes such as volume and asynchronous [25].

3.2.6 *Berlin Heart Excor*

The Berlin Heart Excor (Berlin Heart AG, Berlin, Germany) (Fig. 3.1) is a pulsatile artificial heart to deliver the cardiac output as high as 10 l/min with 150 bpm. It is designed to assist left, right, or both ventricles, and comprised of a paracorporeal pump, a pneumatically driven system, and silicone cannulae with different diameters anastomosed to the atrium and ventricles as inflow and artery as outflow [27]. The Excor adult blood pump has different pump volumes of 50, 60, and 80 ml, while the pediatric pump has smaller sizes as 10, 25, and 30 ml [27]. The blood pump has a transparent polyurethane housing allowing for visual inspection, and a triple layer membrane is used to separate the blood chamber and an air chamber [28]. Blood pumps with trileaflet valves are made of polyurethane, while blood pumps with bi-leaflet valves are made of carbon. All surfaces of the pump including the trileaflet inlet and outlet valves are coated with a Carmeda bioactive surface coating to improve the blood compatibility [28].

Fig. 3.1 The Berlin Heart Excor (left), IKUS driving unit (middle), and mobile driving unit (right)

The driving unit IKUS, weighing as 93 kg [15], is used for the Berlin Heart Excor blood pumps sized as 10, 25, and 30 ml. It can generate as high as 300 mmHg systolic pressure and as low as −100 mmHg diastolic pressure, and overcome issues for the high resistance of the small bore cannulae at high pumping rates as necessary [27]. In addition, it can still work for 30 min with the battery if power failure occurs. In comparison, the Excor mobile driving system weighs only 9 kg, which allows for free mobility, and can be used for adult-sized pump to produce pressures less than 250 mmHg.

3.2.7 Novacor LVAD

The Novacor pump (Novacor Division, Baxter Healthcare Corp., Oakland, USA) is an implantable pulsatile artificial heart. The blood pump is electromagnetically actuated, housed with a lightweight shell, and made of a special sac, which is polyurethane, one-piece, and seamless [29]. The sac has dual push slabs, which can collapse the sac when they are powered in order to propel blood. Through a percutaneous lead, the pump is connected to either a control console or a controller, which are extracorporeal or wearable, respectively [29]. Dacron fabric grafts are connected to the LV apex and ascending aorta for inflow and outflow, respectively. With size of ∅60 × 145 mm, weight of 1000 g, and maximum SV of 70 ml, the pump can provide physiological perfusion of up to 10 l/min.

The three components of the Novacor pump, including compact controller, battery, and backup battery, have been suitably miniaturized as the wearable system [30]. The new version of the above components has been significantly smaller and weigh only about 3 kg. The battery packs are capable of being carried in a bag or by a small bedside monitor, or tied to the waist belt [31]. The batteries can support patient's mobility up to 6 h.

3.2.8 Intra-Aortic Balloon Pump

The intra-aortic balloon pump, IABP (Maquet, Fairfield, NJ, USA), (Fig. 3.2) is a special type of artificial heart. It is a percutaneous counterpulsation device, which can enhance myocardial oxygen perfusion and indirectly increase physiologic perfusion [32]. Due to its working mechanism, it could also be considered as pulsatile artificial heart. IABP has four important components, including a cylindrical polyurethane balloon that is extremely lighter compared to most LVAD, RVAD, or BiVAD, residing in the aorta, approximately 2 cm from the left subclavian artery [33], a fiber-optic or polyethylene catheter, a transducer, and a console unit [34]. The size of the IABP catheter, displayed on the IABP catheter box, is related to the patient's height. Based on the IABP brochure, the recipients were implanted with an appropriate IABP with the sizes varying from 30 to 40 mL. In general, the majority

Fig. 3.2 IABP (left) and control unit (right)

of the recipients (up to 70%) received a 40-mL balloon, the length of balloon is around 260 mm [35].

The IABP console transfers gas in a cylinder (including helium and carbon but usually helium) via a pneumatic system into the balloon using varying timing modes. Some important components of the console contain a valve unit allowing delivery of the gas and a monitor system that can acquire aortic pressure and electrocardioram. The control unit can analyze electrocardiogram to send a trigger signal, in order to implement timing of balloon inflation and deflation by controlling the valve unit, which can open the valve to deliver the gas or close the valve to stop the gas [32]. In addition, take the console unit named Maquet Datascope CS 3000 IABP as an example, the size of console unit on cart is ~110 cm∗57 cm∗43 cm, weighing as up to 40 kg, while the weight of the monitor is more than 4.0 kg. For its power supply, the main voltage is 100–120 VAC ± 10% or 220–240 VAC ± 10%. The sealed lead-acid internal battery can last about 3 h with 24 VDC.

3.3 Continuous Flow Pumps

Continuous flow rotary blood pumps (RBP) now have been accepted for the clinical short−/long-term use in mechanical circulatory support treatment. These pumps are smaller in size and can be implanted in the pericardial space. They are more durable as they do not have valves or many moving parts compared to traditional pulsatile flow pumps [8]. Continuous flow devices are more efficient, use less power, and have a smaller diameter drivelines compared to pulsatile flow devices. Continuous flow pumps provide sufficient physiological perfusion for patients as partial or full support through a rotating impeller, contained within the housing. With different

types of the impellers, continuous flow pumps are classified as axial flow (AF) RBP, centrifugal flow (CF) RBP, or mixed flow (MF) RBP. Continuous flow pumps are mainly considered as the second generation of MCS devices. They have been approved for destination therapy with support durations exceeding 5 years in patients [36]. The primary disadvantage of continuous flow pumps is the reduction of pressure and flow pulsatility which has been associated with adverse events in patients including hemorrhagic strokes, arteriovenous malformations, and compromised end-organ functions, etc. Examples of typical continuous flow pumps for both second and third generations contain DeBakey, Jarvik 2000, Heartmate II, Heart III, HVAD, HeartAssist 5, CentriMag, etc.

3.3.1 DeBakey

As the second-generation implantable AF pump, the DeBakey (MicroMed Technology, Houston, TX, USA) is made of titanium and electromagnetically actuated, consisting of three main components: a miniaturized AF impeller, a clinically used data acquisition (DAQ) system, and an external controller. The pump's diameter is 35 mm, length is 76 mm (about the size of an AA battery), and weight is 95 g. The impeller's rotational speed is between 7500 and 12,500 rpm and can produce flow rates of 10 l/min as maximum. The priming volume of the pump is 25 ml. There is no significant wear or failure after 2-year use due to the mechanical blood-immersed bearings [31]. Median sternotomy is the common way of implanting the pump. The inflow cannula, made of titanium, is implanted into the LV apex via a core, while the outflow cannula is anastomosed to the ascending aorta [31].

With the size of 4 × 6 in., the external controller is used to monitor pump parameters such as speed, flow, current, power, battery status, etc., and it can also display audible and visual alarms. It is comprised of a controller module, a battery charger, and battery packs [37]. The battery packs are connected to the controller module to drive the pump, and the controller is connected to the DAQ system for power, which is low and ranged from around 9 to 12 w [37].

3.3.2 Thoratec HeartMate II

The HeartMate II (Thoratec Corporation, Pleasanton, CA, USA) is a second-generation AF and implantable pump, mainly used as a LVAD. It is made of titanium and the pump volume is 63 ml. The cannulation of HeartMate II is the same as that of DeBakey. It provides sufficient physiological perfusion of up to 10 l/min. The impeller's rotational speed usually ranges between 6000 and 15,000 rpm, and with 9000 rpm it can generate satisfied pressures and flows [38, 39]. It uses a brushless DC motor to provide rotation [8]. The spinning of the pump generates kinetic energy to force blood into the ascending aorta via the outflow graft, thus supporting the sick

heart. This small pump sizes ∅81 × 43 mm approximately equal to the dimension of a D-cell battery and weighs 281 g.

The pump is electrically powered and its control and power are supplied via a percutaneous lead. The lead is connected to a controller, and the controller is connected to the batteries that can be rechargeable and last up to 12 h before recharging, or to an external power module [40]. The controller can be set manually or fixedly, to regulate the pump speed, show alarms, and hold various device failure events for future analysis [41]. Patients can usually wear the controller and batteries.

3.3.3 Jarvik 2000 Flow Maker

The Jarvik 2000 (Jarvik Heart, Inc., New York, NY, USA) is a second-generation AF pump. This pump can be used for the purpose of full support and long term. It is comprised of an implantable pump, a DC power supply, a percutaneous power cable, a controller, and a 16-mm outflow graft. It is surgically implanted from the LV cavity to the aorta (ascending or descending) [38], and it is also designed to minimize the mechanical support, reduce risk and redundancy in its function, and provide best chance of myocardial recovery for the patients. The size and weight are ∅25 × 55 mm (equal to the size of a C-battery) and 85 g, respectively, and the pump volume is 30 ml. Its welded titanium shell resides in a direct-current impeller. The only moving part of Jarvik 2000 is the small and spinning titanium impeller, which is assisted at each end by tiny blood-immersed ceramic bearings [8], and delivers flow rates of usually 3–7 l/min with the pump speed ranging from 8000 to12000 rpm [39]. In fact, the impeller can pump blood from the heart at up to 9.5 l/min. However, there is slight reverse flow of 0.35 l/min [42].

The Jarvik 2000's external controller has a user-friendly control interface. The controller is designed with ease of use in mind. Based on the patient's different levels of activity, the clinicians and patients can manually regulate the pump speed with the numbered dial on the controller. The pump speed could be turned up for more flow rates when exercising and down for less flow rates for having a rest. The controller provides broad range of speeds to make flexible selection of pump speed for clinicians and patients, but narrow enough range to prevent unexpected or unsafe events. The 12-v DC power supply can be supported by either lithium-ion or lead-acid batteries [43].

3.3.4 HeartAssist 5

The HeartAssist 5 (Medgadget, LLC, Eugene, OR, USA) is a second-generation AF pump, but this miniaturized and long-term used pump is still under investigation. It is a refinement of the DeBakey LVAD. The implantable HeartAssist 5 is easy to operate, externally monitored and controlled. It is designed to characterize pulsatility

delivery, making the blood vessels continuously feel a normal pulse generated by the heart itself. Sizing ∅30 × 71 mm and weighing only 92 g, this pump provides direct measurement of cardiac output using the ultrasonic flow probe externally clamped the cannula. The pump usually delivers the cardiac ouput of 5–6 l/min with the pump speed of 10,000 rpm. In contrast, with the maximum speed of 12,500 rpm, it may provide flow rates of over 10 l/min.

The electromagnetically driven pump is made of titanium and plastic, supported with dual mechanical pivot bearings (front and back), whose lifetime is no less than 2 years [8]. Thrombus formation is an issue with the earlier iterations of this device. To reduce the incidence of thrombus information, Carmeda biocompatible coating has been used on the blood contacting surfaces.

3.3.5 Berlin Heart Incor

The Berlin Heart Incor (Berlin Heart AG, Berlin, Germany) (Fig. 3.3) is an implantable and third-generation AF pump and made of titanium alloy. Same as the previously mentioned continuous flow pumps, it is also surgically implanted from the LV to the aorta. However, the difference is that the impeller is completely suspended with the active electromagnetic bearings, residing in each end of the

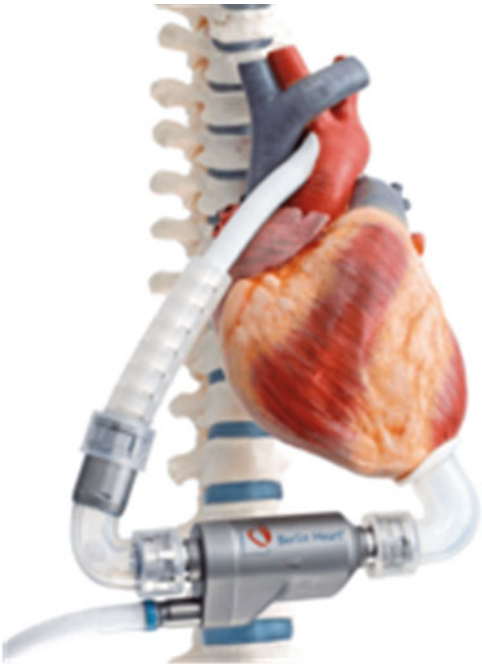

Fig. 3.3 Berlin Heart Incor

rotor that is passively forced for radial tilting and movement [8]. Its size, weight, and volume are ∅30 × 120 mm, 200 g, and 30 ml, respectively [44].

With the fixed inflow inducer and outflow diffuser, this pump generates cardiac output of 5 l/min with the speed of 8000 rpm, while it provides flow rates of 7 l/min at 10000 rpm as maximum [39]. The power consumption is between 2 and 4 w, and the pump does not generate any significant amount of heat with more than 90% motor efficiency and power consumption of less than 4 w [44]. The magnetic bearing of the pump is used to measure the rotor position and control the pump speed [45]. All blood contacting surfaces of the pump are heparin coated by the Carmeda process [46].

3.3.6 *DuraHeart*

The DuraHeart (Terumo Corporation, Shibuya, Tokyo, Japan) is an implantable and third-generation CF pump to support LV [47]. It uses the contact-free impeller suspension technology [48]. With a direct coupled magnetic driving system, the impeller is driven by an external brushless DC motor with the pump speed between 1200 and 2600 rpm, to support physiologic perfusion as high as 10 l/min. This pump sizes ∅72 × 45 mm, and has the volume and weight of 196 ml and 540 g, respectively [49]. Blood trauma is likely to be mitigated due to its magnetic bearing characteristic and relatively large clearance gaps (250 μm) [38]. In addition, titanium is used to design the blood contacting surfaces and housing. Pump thrombosis can be effectively prevented due to the covalently bonded heparin coating [38]. Furthermore, if the magnetic bearing failure happens, a backup hydrodynamic bearing with a spiral groove can be used between the rotor and motor such that non-contacting suspension still can be provided. The power requirement is 15w, while 9 w for magnetic suspension [31]. Two batteries and a controller form the outside kit, whose total weight is 2250 g.

3.3.7 *HeartWare HVAD*

The HeartWare HVAD (HeartWare Inc., Framingham, MA, USA) (Fig. 3.4) is an implantable and third-generation CF pump, which is the most widely used centrifugal pump to date. HeartWare HVAD is the first LVAD with the noninvasive and off-pump surgical technique [50]. It can be placed not only on left, but also on both ventricles [51, 52]. A tapered thrust axial bearing can generate hybrid passive hydrodynamic and magnetic forces, which can completely suspend the impeller [50, 53]. So far the device is smallest (displacement volume is 50 ml [15]) and lightest (145 g) centrifugal flow pump in clinical use. The dual flat axial flux motor,

Fig. 3.4 The HVAD pump

providing a level of redundancy, achieves impeller rotational speeds as low as between 1800 and 4000 rpm to deliver physiological perfusion of 10 l/min as maximum [53]. The stable impeller levitation is achieved via the uninterrupted and adequate hydrodynamic forces ensured by the lower pump speed. The blood contacting surfaces, made of ceramic-titanium, are used to limit the pump thrombus. There is no mechanical contacting point inside the pump, which can be considered as wearless [40], eliminates friction and heat generation, and enables improved device duration [41].

A microprocessor-based controller (~13 cm × ~10 cm × ~5 cm; weight less than 0.4 kg) [54], a battery charger, lithium-ion battery packs AC and DC adapters, and a monitor form the external components of the HVAD. The controller is connected to the pump through a percutaneous driveline. It can operate the pump, monitor pumping status, manage power function, and provide diagnostic information, etc. [54]. After being fully charged, the battery can provide 4–6 h of support. The power consumption is about 4.5 w [15]. While power failure happens, the battery inside the controller will generate an audible alarm. Moreover, the touch-screen monitor can be used to display system performance information and adjust the operating parameters [54].

3.3.8 HeartMate III

The HeartMate III (Thoratec Corporation, Pleasanton, CA, USA) is a CF pump and has the similar implantation technology compared to HeartWare HVAD [55, 56]. It weighs 220 g and sizes ∅35 × 69 mm with displacement volume of 195 ml. The HeartMate III has a magnetically levitated rotor and the related blood-flow paths are large, in order to reduce shear stress as much as possible [57]. The inflow cannula is inserted into the LV, and the pump is placed in the pericardial cradle [57], which can achieve less invasive pump implantation without the cardiopulmonary bypass method [58]. The rotational speed is between 2000 and 5500 rpm, to provide flow rates of up to 10 l/min.

The pump is driven by an external power source via a driveline, which consists of the pump cable extends from the pump through the skin and the modular cable connects the pump cable to the system controller. In addition, the pump can be powered with the controller and the power module, the mobile power unit connected to an AC electrical outlet, or two 14-v lithium-ion DC batteries. The power consumption is up to 4 w. With the dimension of 12.7 cm × 3.5 cm × 8.0 cm and weight of 336 g, the system controller acts to monitor system performance and communicate with the implanted pump.

3.3.9 CentriMag

The CentriMag (Levitronix Technologies Inc., Framingham, MA, USA) is a third-generation, extracorporeal, and CF pump, which is operated electrically and has the similar implantation technology as HeartWare HVAD [59]. The rotor is disposable and the cannula size is varying. The housing is made of polycarbonate and it can fit a 1.7-kg external and magnetic motor that adjusts the pump speed and radial rotor position [15]. The pump weighs 1700 g, with the priming volume of around 30 ml. Its length is 82 mm, and the diameter is 100 mm. The pump is magnetically levitated to provide cardiac output of up to around 10 l/min, while the pump speed ranges from 1500 to 5500 rpm.

A driving console weighs 6.6 kg and connects to the motor, is used to regulate the pump speed while using 120 w of power. Therefore, this large drive console significantly limits patients' mobility. Also based on its short-term support, this device does not have the advantages as the other third-generation pumps have, for example, the improved supporting durability and lifetime.

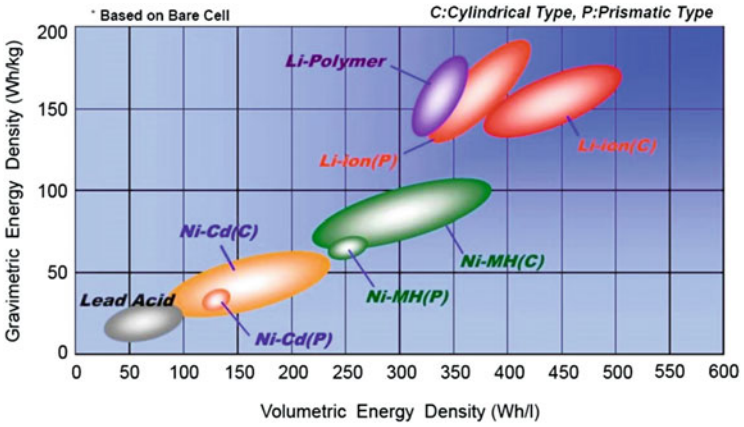

Fig. 3.5 Comparison of energy density in battery cells

Power Supply The artificial hearts require to be powered either through an electrical outlet or through batteries. Battery technology has evolved from early generation lead acid, NiCd, and NiMH batteries that were heavy with low energy densities (Fig. 3.5, Table 3.1). Currently, ambulatory artificial hearts are powered using Li-ion batteries (Fig. 3.6), which have energy densities of 90–190 Wh/kg and retain 80% of capacity after 1000 charge/discharge cycles. Greater power densities coupled with higher efficiency artificial hearts have enabled ambulation of patients. Current Li-ion batteries can power the artificial hearts from 4 to 8 h and patients usually carry a spare battery.

Drivelines and fully implantable systems: Pneumatic drivelines needed to be larger to shuttle air without a big drop in pressure. Electrical actuation reduced the diameter of drivelines. Despite reduced diameter, driveline infections are common. A primary cause of adverse events associated with these devices is infections at driveline exit sites [60]. Even with new tunneling and surgical techniques [61, 62], dressing protocols [63], specialized training [64], novel materials [65], the infection rates remain high (6% [60] - 92.5% [66], with most reports in the 14%–38% range [67, 68]. The current treatments for driveline infections include debridements, antibiotics, packing, and re-tunneling the driveline, which are not always successful [69]. Device explant or exchange is the definitive treatment but it is highly expensive and increases the risk of mortality [70]. Several wireless power and data transmission systems based on radiofrequency and electromagnetic transcutaneous energy transmission systems (TETS) have been developed [71–76]. However, most of these systems have low energy transfer efficiency, generate heat, and have a low depth of penetration. Furthermore, a small internal battery needs to be implanted with TETS. This internal battery can only be charged and recharged for a finite number of cycles (~1000 cycles), which necessitates a surgical replacement of the internal battery approximately every 2 years. Due to these limitations, all current artificial hearts use drivelines.

Table 3.1 Specifications by battery chemistry (https://www.epectec.com/batteries/cell-comparison.html)

Specifications	Lead Acid	NiCd	NiMH	Li-ion		
				Cobalt	Manganese	Phosphate
Specific energy density (Wh/kg)	30–50	45–80	60–120	150–190	100–135	90–120
Internal resistance (mΩ)	<100 12 V pack	100–200 6 V pack	200–300 6 V pack	150–300 7.2 V	25–75 Per cell	25–50 Per cell
Life cycle (80% discharge)	200–300	1000	300–500	500–1000	500–1000	1000–2000
Fast-charge time	8-16 h	1 h typical	2-4 h	2-4 h	1 h or less	1 h or less
Overcharge tolerance	High	Moderate	Low	Low. Cannot tolerate trickle charge		
Self-discharge/month (room temp)	5%	20%	30%	10%		
Cell voltage (nominal)	2 V	1.2 V	1.2 V	3.6 V	3.8 V	3.3 V
Charge cutoff voltage (V/cell)	2.40 Float 2.25	Full charge detection by voltage signature		4.20		3.60
Discharge cutoff voltage (V/cell, 1C)	1.75	1.00		2.50–3.00		2.80
Peak load current Best result	5 C 0.2 C	20 C 1 C	5 C 0.5 C	>3 C <1 C	>30 C <10 C	>30 C <10 C
Charge temperature	−20 to 50 °C −4 to 122 °F	0 to 45 °C 32 to 113 °F		0 to 45 °C 32 to 113 °F		
Discharge temperature	−20 to 50 °C −4 to 122 °F	−20 to 65 °C −4 to 149 °F		−20 to 60 °C −4 to 140 °F		
Maintenance required	3–6 months (topping charge)	30–60 days (discharge)	60–90 days (discharge)	Not required		
Safety requirements	Thermally stable	Thermally stable, fuse protection common		Protection circuit mandatory		
In use since	Late 1800s	1950	1990	1991	1996	1999
Toxicity	Very high	Very high	Low	Low		

Fig. 3.6 Inspired Energy NH2054 Li ion battery

3.4 Summary

Artificial hearts and VADs are the mechanical blood pumps that support the native ventricles to pump blood. They are primarily categorized as pulsatile flow pumps and continuous flow pumps. Pulsatile flow pumps are constructed with one/dual pressure membrane chambers. They are powered by rechargeable batteries and large consoles that restricted mobility of the patients. However, pulsatile pumps and associated accessories are larger in size, less durable and less efficient and hence are no longer implanted commonly. Continuous flow pumps are smaller in size, with fewer moving parts, lower power consumption, and greater durability. The controller and batteries are portable and facilitate ambulation of patients. Table 3.2 shows an overview of different artificial hearts associated with their specifications.

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Table 3.2 Overview of different artificial hearts associated with their specifications

(Manufacturer) Device	Size (mm/ml)	Weight (g)	Flow profile	Material	Drive mechanism	Power (w, h, or v)
(Thoratec) HeartMate XVE	∅55 × 170 mm	1150	Pulsatile	Sintered titanium	Electrically driven	6 h
BVS5000	660 ml	1700	Pulsatile	Polyurethane	Pneumatically driven	280 w
AB5000	155 × 80 × 60 mm	300	Pulsatile	Polyurethane	Pneumatically driven	250 w
(Thoratec) PVAD	125 × 80 × 60 mm	417	Pulsatile	Polyurethane elastomer	Pneumatically driven	–
(Thoratec) IVAD	120 × 80 × 50 mm	339	Pulsatile	Titanium alloy	Pneumatically driven	–
Berlin heart AG Berlin heart Excor	–	–	Pulsatile	Polyurethane	Pneumatically driven	Several hours
(Novacor) Novacor LVAD	∅60 × 145 mm	1000	Pulsatile	Polyurethane	Electromagnetically driven	6 h
(MicroMed technology) DeBakey	∅35 × 76 mm	95	Continuous	Titanium	Electrically driven	12 w
(Thoratec) HeartMate II	∅43 × 81 mm	281	Continuous	Titanium	Electrically driven	12 h
(Jarvik Heart) Jarvik 2000	∅25 × 55 mm	85	Continuous	Titanium	Electrically driven	12 v DC
Medgadget (HeartAssist 5)	∅30 × 71 mm	92	Continuous	Titanium	Electrically driven	–
Berlin heart AG Berlin heart Incor	∅30 × 120 mm	200	Continuous	Titanium alloy	Magnetically levitated	2–4 w
(Terumo corporation) DuraHeart	∅72 × 45 mm	540	Continuous	Titanium	Magnetically levitated	15 w
(HeartWare) HVAD	50 ml	145	Continuous	Ceramic-titanium	Magnetically levitated	4.5 w
(Thoratec) HeartMate III	∅35 × 69 mm	220	Continuous	Titanium	Magnetically levitated	4 w
Levitronix (CentriMag)	∅82 × 100 mm	1700	Continuous	Polycarbonate	Magnetically levitated	120 w

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Chapter 4
Artificial Heart: Rotary Pump

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Abstract Over the past two decades, rotary blood pumps (RBPs) have gained clinical acceptance and market share due to their smaller size, and increased efficiency and durability compared to pulsatile blood pumps. RBPs constitute the second and third generations of the artificial hearts. As a continuous flow system, RBP augments perfusion and provides sufficient systemic perfusion for patients, while reducing ventricular work. RBP can unload the native ventricles continuously as partial or full support device. RBP consists of a rotating impeller, which is enclosed in a housing. The impeller can be mainly classified into axial flow (AF) and centrifugal flow (CF), though mixed flow (MF) pumps have also been developed. The Archimedes screw was used to design the AF pumps, where the direction of blood flow is parallel to the central axis of the impeller. Most AF RBPs belong to second-generation pumps and can operate at speeds of 7000–50,000 rpm. In comparison, CF pumps have a flow direction that is perpendicular to the central rotational axis of the impeller. Centrifugal pumps typically are larger in diameter, smaller in length, and have higher hydraulic efficiencies and the speeds are lower than those of AF pumps. Axial and centrifugal pumps are suspended using physical bearings, hydrodynamic bearings, or are magnetically levitated. This chapter will

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introduce AF and CF pumps in design, performance, and the comparisons in their clinical applications.

Keywords Artificial hearts · Rotary blood pumps · Axial flow pumps · Centrifugal flow pumps

4.1 Introduction

Artificial hearts are gaining widespread acceptance in clinical practice as a treatment option for the patients with advanced heart failure (HF) as the bridge to transplantation (BTT) [1], recovery (BTR) [2], decision (BTD), and as the destination therapy (DT) [3]. Over the past decades, the use of rotary blood pumps (RBPs) as the newer generation of implantable artificial hearts has far surpassed the use of pulsatile blood pumps. With a rotating impeller enclosed in the pump housing, RBPs provide partial or full assist for the patients. Based on the direction of pump flow with respect to the axis of the rotating impeller, RBPs that generate non-pulsatile continuous flow are classified as axial flow (AF), centrifugal flow (CF), and mixed flow (MF) pumps. The concept of AF pumps is from the Archimedes screw where the direction of blood flow is along the central axis of the impeller. The inlet and the outlet are along the same axis. Flow straighteners and diffusers can be incorporated into the AF pumps to reduce turbulence and improve mechanical efficiency. Examples of some AF pumps include the DeBakey left ventricular assist device (LVAD), Javik 2000, Heartmate II, etc. In CF pumps, the blood is sucked into the central inlet and the blood is expelled through an outlet that is perpendicular to the central rotational axis of the impeller. The centrifugal force due to the rotation of the impeller is used to expel the blood through the outlet. Examples of some CF pumps include Heartmate III, HVAD, HeartAssist 5, etc. In the MF pumps, the flow of fluid through the impeller is in different directions. MF pumps that are currently under development include the DP2 pump [4]. AF pumps predominantly constitute the second generation of artificial hearts, while CF and MF pumps are categorized as third-generation devices. The durability of RBPs makes them suited for long-term use, with reported implant durations in excess of 5 years [5]. The third-generation devices reduced the mechanical contact and suspended the rotating impeller with magnetic or hydrodynamic forces in order to extend pump durability as long as 10 years [6, 7].

Axial and centrifugal blood pumps have many advantages over pulsatile pumps due to their simpler design with less moving parts, higher mechanical efficiency, and ease of clinical use. Importantly, RBPs are smaller and can fit in the thoracic or pericardial space, which obviates the need to create a large surgical pocket and enables easier implantation [2, 8]. Pulsatile pumps are seldom implanted currently as RBPs have higher mechanical reliability and durability due to the simpler design [2, 9]. In addition to the smaller device size, the drive accessories and the battery packs are often smaller than pulsatile pumps due to the higher mechanical efficiency

of RBPs. The design of RBPs enables higher patient mobility and improves quality of life of patients.

The average pump flow rates are comparable between RBPs and pulsatile devices, but RBPs significantly diminish aortic pressure and flow pulsatility. Successful clinical outcomes post-RBP implantation have been reported in numerous studies. Major adverse events for patients with RBPs include percutaneous lead infection, stroke, postoperative bleeding, right HF, etc. [10], which have been associated with diminished pulsatility due to RBPs support [11–13]. Other adverse events that have been attributed to RBPs include aortic valve insufficiency, arteriovenous malformations, gastrointestinal bleeding, hemorrhagic strokes, and valve fusion [14, 15]. RBP patients have a higher survival rate compared to pulsatile pumps and survival rates varied with different types of RBPs [16, 17].

This chapter will introduce some typical axial and centrifugal flow pumps in design, performance, and their clinical applications.

4.2 Axial Flow Pumps

AF RBPs are smaller in diameter and the pump speed ranges from 6000 to 50,000 rpm. Most AF RBPs are considered as the second-generation devices. The characteristics of contact impeller suspension and stationary guide vanes may increase probability of thrombus formation especially in the areas of recirculation and stagnation [6]. Furthermore, many studies have reported that the typical lifetime of the AF pumps is approximately 5 years.

AF pump rotates similar to the propeller rotating and it is considered as an auger (Archimedes screw), which pushes the fluid against the resistance force in the outlet part to overcome the difference between preload and afterload [18]. The increasing pressure head curve of AF pumps is steep with a non-linear reduction in flow. In addition, the relationship between current and flow of AF pumps is also non-linear. These non-linear relationships reduce the accuracy of flow estimation with AF pumps. The design and unique features of AF pumps are presented next.

4.2.1 MicroMed DeBakey

The DeBakey pump (MicroMed Technology, Houston, TX, USA) has components including an AF titanium pump, a clinical data acquisition (DAQ) system, a controller, and a patient home support system. The pump's length is 3.0 in., diameter is 1.2 in., and weight is 95 g. The DeBakey with its small size can offer treatment to HF patients with smaller body sizes such as women or even children [19]. It is electromagnetically powered through a small, flexible, and percutaneous cable, and the incidence of infection has been reduced compared with the larger devices.

The design of this device is simple because the only moving part is the rotating impeller. This device can produce the cardiac output (CO) as high as 10 l/min [20]. The controller as an external system is used to monitor pump parameters such as speed, flow, current, power, and battery status, and display information for visual and audible alarms. It mainly contains a controller module (with the size of 4 × 6 in.), battery packs, and a battery charger [21]. The battery is used to power the pump, and the DAQ system can also be used for power by connecting it to the controller. The power is as low as from around 9 to 12 w [21].

4.2.2 Jarvik 2000

Jarvik 2000 (Jarvik Heart Inc., New York, USA) is an AF and electrically powered pump. It is surgically implanted through left thoracotomy, midline sternotomy, and subcostal approach for long-term use. Due to the size of ∅25 × 55 mm (like the C-cell battery), the volume of only 25 ml, and the weight of 85 g, this small pump can be used to support right ventricular function as right ventricular assist device (RVAD) and bi-ventricular functions as bi-ventricular assist device (BiVAD) for the patients with different sizes and weights [22]. Those implantation strategies and its small size may allow it to be implanted in the patients who are not qualified for other LVADs. With the pump speed between 8000 and 12,000 rpm, Jarvik 2000 can generate CO as 3–7 l/min with the an energy requirement of 4–8 w [23], while the pump speed is reduced to 6000–10,000 rpm during RVAD support [24], even significantly smaller than HeartMate II. Inside the sealed pump housing there is a brushless electromagnetic DC motor to power the impeller [6]. The impeller is supported using ceramic bearings and housed in a welded titanium shell, and is made of neodymium-iron-boron magnet [25].

Except for the pump, the remaining parts of the whole system consist of an external pump speed controller, a 16-mm outflow graft, a DC power supply, and the percutaneous power cable [26]. The rotational pump speed is regulated using a speed control circuit with modulated pulse width. The 12 v DC power is provided by the lithium-ion or lead acid batteries [27].

4.2.3 Thoratec HeartMate II

HeartMate II (Thoratec Corporation, Pleasanton, CA, USA) is an AF pump with the axial rotor as the only moving part. The primary system contains a RBP, a system driver, portable batteries, and power supply. This pump generates kinetic energy and tangential velocity to the blood flow to produce a pressure rise across the pump [28]. The pump's inflow cannula is anastomosed to the LV apex and outflow cannula is anastomosed to the ascending aorta. To curve around a central shaft, the HeartMate II has an internal titanium rotor with helical blades.

The pump can produce sufficient flow rates of up to 10 l/min for the patients with the rotational speed usually operating between 6000 and 15,000 rpm. The pump is powered by an electrically powered motor, which is connected through a percutaneous driveline from the right side of the abdomen. The controller is connected to a percutaneous lead to power and control the pump. The rechargeable batteries can last up to 12 h before recharging and are worn by patients or installed to an external power module [29]. Furthermore, there are two settings (manual and fixed) for the controller to regulate pump status, display alarms, and save any device malfunctions for future analysis [30].

4.2.4 HeartAssist 5

The HeartAssist 5 (Medgadget, LLC, Eugene, OR, USA) is a second generation AF pump but still under investigation. It is also the latest DeBakey LVAD for long-term support but miniaturized. The HeartAssist 5 is easy to operate, externally monitored and controlled. It is designed to characterize pulsatility delivery, making the blood vessels continuously feel a normal pulse generated by the heart itself. Sizing ∅38 × 71 mm and weighing only 92 g, this pump provides direct measurement of cardiac output with an ultrasonic flow probe clamped on the outflow cannula without having to estimate. With the pump speed of around 10,000 rpm, the pump can usually provide physiologic perfusion of 5–6 l/min. In contrast, with the maximum speed of 12,500 rpm, it may provide flow rates of over 10 l/min.

The electromagnetically driven pump is made of titanium and plastic, supported with dual mechanical pivot bearings (front and back), whose lifetime is no less than 2 years, and combined with the flow straightening inducer and stationary outlet diffuser [31]. Moreover, in order to reduce the incidence of thrombus information, Carmeda biocompatible coating has been applied to the blood contacting surfaces, but negatively influenced the earlier iterations of this device.

4.2.5 Impella

The Impella (Abiomed, Danvers, MA, USA) (Fig. 4.1) is a micro-axial and transvalvular pump [32] and also considered as MF pump [6]. It is the short-term circulatory support for both LVAD and RVAD. Currently Impella has several available generations, mainly including Impella 2.5, Impella 5.0, Impella CP, Impella LD, etc., with different specifications [33]. Impella 2.5 and CP are percutaneously implanted from the femoral artery into the LV with the sheaths of 12-Fr and 14-Fr, respectively. In comparison, Impella 5.0 is implanted from the axillary artery into the LV [34], through a surgical incision with a sheaths of 21-Fr [33]. The Impella is mainly comprised of a catheter-mounted miniature AF pump. Particularly, the pigtail-like structure in the upper portion of the Impella, which is attached in the

Fig. 4.1 The Impella (left) [35] and controller (right) (https://www.abiomed.com)

single cannula mentioned above and a pump pressure monitor, makes it as stable as possible while implanting into the LV. Impella is in conjunction with the automated controller, which weights as around 12 kg and operates on its internal battery for at least 1 h while being fully charged. More importantly, the controller provides a smart interface in order to monitor and control the function of the Impella catheter.

The Impella can draw blood from LV to the aortic root to perform functions at inflow and outflow sites. The Impella can enhance mean arterial pressure, unload LV, myocardial work, and oxygen consumption, and it can also be used with VA-ECMO [32]. Different types of Impella can generate varying flow rates as non-pulsatile. Impella 2.5 generates physiologic perfusion as high as 2.5 L/min, while impella CP increases physiologic perfusion up to between 3 and 4 L/min, and Impella 5.0 increases flow rates up to 5 L/min. In addition, Impella 2.5 and CP can be temporarily used for no more than four days, while Impella 5.0 and LD can be temporarily used for no more than 2 weeks.

4.2.6 MVAD

The MVAD (HeartWare, Framingham, MA, USA) (Fig. 4.2) is miniaturized transapical AF pump [36]. It has displacement volume of only 20 mL while weighing as 78 g [37]. Due to the small size and short inflow cannula, MVAD is able of putting into LV as pericardial implantation. The outflow graft is made of gel-impregnated polyester with the length of 10 mm. The driveline's length is 70 cm and it is thin with diameter of only 3.5 mm [38]. With the polyurethane outer sheath and in the extruded silicone, three encapsulated wires form the driveline. In the exit part, the improvement of wound healing can be provided using a polyester velour sleeve that also partly covers the driveline [38]. The impeller of MVAD is made of platinum alloy, and it is operated with a wearless and hybrid suspension system [39, 40]. This suspension system can implement hydrodynamic and passive

Fig. 4.2 The MVAD pump

magnetic forces. Furthermore, the magnetic force between impeller and stator can provide axial stiffness, while on the impeller surface the hydrodynamic thrust bearings generate the radial forces [39, 40]. The MVAD has two flow paths. The primary path is through the impeller channels, while the secondary path is through the radial gap between the inner pump housing and the impeller [39, 40].

Except for the pump, the MVAD components also include controller, battery, power, and monitor. The dimension of the water-resistant and wearable controller is 9.6 × 4.8 × 8.4 cm with the weight of 0.43 kg including the pigtail driveline [38]. The touchscreen as the user interface can show information such as MVAD status and parameters, battery status, and alarm. Inside the controller there is a lithium-ion battery, which can support the MVAD close to 1 h. When the external power source is on, the internal battery will be recharged. Furthermore, the controller was designed with different control algorithms such as flow estimation, suction detection and response, pump pressure algorithm, and qPulse cycle [38].

The rotational impeller of MVAD can provide pump pressure head to direct blood from the LV to the aorta. It can reduce LV work and promote aortic valve performance [41]. Usually with the pump speed between 8000 and 18,000 rpm, it can provide flow rates ranging between 1 and 7 L/min with mean arterial pressure of around 75 mmHg [37]. An animal study shows that with the MVAD speed between 14,000 rpm and 16,000 rpm and power of 3.5–6 w, MVAD can provide flow rates as 3.5–5.0 L/min, close to the normal physiological perfusion but with little hemolysis (pf Hgb 0–30 mg/dL [36]).

4.3 Centrifugal Flow Pumps

CF RBPs have larger diameter, smaller length, lower pump speed, and higher hydraulic efficiency compared to the AF pumps. CF RBPs are often considered as the third-generation pumps that have hydrodynamic or magnetic bearing forces to completely suspend the impeller [6]. This technology can avoid component wear,

reduce infection rate and noise emission, etc. for better patient outcomes [42], and potentially have device lifetime of approximately 5–10 years.

Centrifugal blood pump rotates like a disk spins with blades. The blood is tangentially thrown out of the blade tips due to the centrifugal force [18]. For the centrifugal blood pumps, typically the pressure head curve is flatter than the AF pumps. With a narrow-range change in the differential pressure across the pump, centrifugal pumps operate over a wide-range change in blood flow. Centrifugal pumps are superior to the axial pumps for suction avoidance at low level flow. CF RPBs also have a more linear relationship between flow rates and pump current, which enable reasonable estimation of pump flow rates when the viscosity of the blood is taken into account.

4.3.1 HeartWare HVAD

The HeartWare HVAD (HeartWare Inc., Massachusetts, MA, USA) (Fig. 4.3) is a miniature CF pump with magnetic levitation technology usually as the LVAD support. The pump weighs 145 g and operates at a speed of 1800–4000 rpm to generate CO as high as 10 l/min. To improve device durability, the impeller is suspended using a hybrid hydrodynamic and passive magnetic thrust bearing with the titanium-ceramic housing. The dual motor stators are used for the improvement of device reliability. The stators are independently driven and have separate cables, passing via the fatigue-resistant percutaneous driveline with diameter of 4.2 mm [43].

The pump's small displacement volume is approximately 50 ml, capable of being implanted in the pericardial cavity [21]. Therefore, it doesn't require extensive abdominal dissection for device implantation. Surgically implanted via the LV

Fig. 4.3 The HeartWare HVAD

apex, the inflow cannula of HVAD is made of titanium, its outer diameter is 21 mm, and length is 25 mm [43]. During surgery, a titanium frame and a Dacron polyester suture ring form a sewing ring that is screwed onto the inflow cannula to secure the myocardial interface of this device.

The controller can estimate flow rates using the pump intrinsic electrical current and impeller rotational speed, and a clinically determined blood viscosity value. The flow estimations derived from the speed and power in HVAD are accurate and reliable enough for clinical use. HVAD also has a programmable hematocrit setting for accurate flow estimation. A 4.5 w power is delivered through either a 12-v DC supply, an AC power supply, or two rechargeable batteries with the supporting duration of up to 12 h.

4.3.2 CentriMag

The CentriMag (Levitronix LLC, Waltham, Massachusetts, USA) is a centrifugal pump with magnetically levitated technology, eliminating friction and wearing during operation and requirement for mechanical bearing, therefore reducing the risk of hematological damage and improving support durability. It is designed for temporary extracorporeal support. One of the key advantages of the CentriMag is its portability and versatility [28]. Another advantage is that it can be attached to cardiopulmonary bypass cannulas. This device is widely used in patients with allograft failure, postcardiotomy shock, and refractory HF after acute myocardial infarction, and right HF with existing LVAD [44]. To minimize blood-related complications, the impeller of this short-term solution works during a contact-free condition.

The CentriMag mainly contains a pump, a magnetic motor, and a bedside controller. The pump propels blood with the rotary motion of a spinning impeller. The flow rates are close to 9.9 l/min and the support duration can be around 6 h. The pump housing has a magnetically levitated rotor. An external electric processor is adopted to electronically regulate the magnetic field to control the radial rotor position and speed [45]. The bearingless pump without mechanical contact reduces the incidence of hemolysis and thrombus formation.

4.3.3 HeartMate III

The HeartMate III (Thoratec Corporation, Pleasanton, CA, USA) is an implantable CF pump [46, 47]. It weighs 220 g and sizes $\varnothing 35 \times 69$ mm. The HeartMate III has a magnetically levitated rotor with large paths for the blood flow in order to minimize shear stress, reduce overall blood trauma, and maximize hemocompatibility. Moreover, pulsatile flow is feasible and stasis can be minimized because its pulse mode is optional [48]. This technique can reduce detrimental effects on blood components

[48]. The characteristics of implantation for the pump and cannulae are similar to the HVAD [49]. The rotational speed is between 2000 and 5500 rpm, to support physiological perfusion as high as 10 l/min.

The main internal part of HeartMate III is the CF RBP, while the main external components are a controller and batteries. The small external (system) controller can control and monitor system operation. The driveline consists of the pump cable, which extends from the pump through the skin, and the modular cable, which connects the pump cable to the system controller. The pump can be powered with the power module, the mobile power unit connected to an AC electrical outlet, or two 14-v lithium-ion DC batteries. The power consumption is up to 4 w. With the dimension of 12.7 cm × 3.5 cm × 8.0 cm and weight of 336 g, the system controller acts to monitor system performance and communicate with the implanted pump.

4.3.4 DuraHeart

The DuraHeart (Terumo Corporation, Shibuya, Tokyo, Japan) is a third-generation CF pump but uses an axial magnetic bearing to assist sick LV with a contact-free impeller suspension technology [50]. With a direct coupled magnetic driving system, a brushless DC motor as the external part drives the pump. DuraHeart can support physiologic perfusion up to 10 l/min at the pump speed between 1200 and 2600 rpm. Its volume is 196 ml, weight is 540 g, and size is ∅72 × 45 mm, respectively [51], and blood trauma is likely to be mitigated due to its magnetic bearing characteristic and relatively large clearance gaps (250 μm) [52]. In addition, titanium is used to design both blood contacting surfaces and housing. Thrombosis events inside the pump can be effectively prevented due to the covalently bonded heparin coating [52]. Furthermore, if the magnetic bearing failure happens, a spiral groove hydrodynamic bearing can be used into the titanium housing between the rotor and the motor as a backup such that non-contacting suspension still can be provided. The total weight of the controller and two batteries is 2250 g. The power requirement is 15 w, while 9 w for magnetic suspension [25].

4.4 Comparison of Clinical Applications between Axial and Centrifugal Pumps

In spite of the increasing number of axial and centrifugal flow RBPs for HF patients based on revolutionary advances in technologies, there are various clinical applications and outcomes among current RBPs. In general, although RBPs seem to have better clinical applications and performance than pulsatile flow pumps, complications and adverse events related to the RBPs therapy have also been observed. Some of the most commonly studied and reported major complications and adverse events

following RBPs implantation include driveline infections, pump thrombosis, gastrointestinal bleeding, ventricular arrhythmia, right HF, etc.

From November 1998 to December 1999, DeBakey was implanted in 19 end-stage HF patients at six clinical centers in Europe [20]. There are more than 200 patients who received DeBakey implantation until August 2003. In a study with the first 110 patients with DeBakey, the average support duration was 63 days and 25 patients died postoperatively due to sepsis or multi-organ failure [53]. The DeBakey pump has been approved by CE and received FDA approval in 2004 for DT clinical trial in the USA [25]. The overall performance is satisfied and only 6.3% of perioperative bleeding events was found [54]. Another study reported that in one of five patients after being implanted with DeBakey for less than 2 months, microembolic signals and some transient ischemic attacks were detected [55]. In a small study, none of nine patients had pump thrombosis events although one died due to LV thrombus [56]. Other studies showed that the level of interleukin-6 was higher in the patients with DeBakey compared to that with pulsatile pumps [57].

Jarvik 2000 was approved by CE for BTT, BTR, and DT in 2005 and by FDA for BTT in 2012, respectively [58]. The first clinical implant trial for Jarvik 2000 was in April 2000 for around 360 patients and no device failure happened [59]. For BTT patients, the traditional exit from the subcostal margin had been chosen, while for DT patients there was a low risk of infection observed, partly because of a small post-auricular pedestal for power delivery [60]. The hemodynamic function of patients improved significantly. Two days after implantation, for example, 52% reduction in pulmonary capillary wedge pressure and 43% promotion in average cardiac index were observed [53]. However, in 2018, Class 2 of Jarvik 2000 recall happened for a potential external cable damage [61]. Furthermore, a study found that 14% GI bleeding events occurred [62]. Similar GI bleeding events (15%) was found in BTT patients with HeartMate II [63]. Studies for maintaining sufficient physiologic perfusion with Jarvik 2000 for over 6-month support were also reported [64, 65].

HeartMate II was initially applied in clinical trial in 2000. It was approved by FDA for BTT in 2008 and DT in 2010, and by CE for BTT and DT in 2005, respectively [58]. To date, the number of patients implanted with HeartMate II is about 10 times more than any other RBP, which have greater survival rate compared to the pulsatile pumps [3, 10], meaning that it is the most frequently used AF pump to date [3, 48]. Miller et al. reported that 133 advanced HF patients were implanted with HeartMate II for 180 days [10]. The principal outcomes among 100 out of 133 patients showed that the median support lifetime was 126 days, with a maximum duration of 600 days. After 6 months the survival rate was 75%, and after 12 months the survival rate was 68%. Heart function and quality of life were promoted after 3 months. Device thrombosis happened in only two patients, but studies have demonstrated that redesigning the pivot bearing area, optimization of pump position, and device exchange may reduce thrombus formation [5, 66, 67]. However, anticoagulation treatment could be limited in HF patients to get a lower INR between

1.5 and 2.0 [23]. The 281-patients clinical outcomes about HeartMate II were reported. After 18 months, around half of patients underwent heart transplant, one fifth of patients were alive with this device, another one fifth died, and 7 out of 281 patients experienced recovery of heart function. The survival rate for the remaining patients with the device was 82% at 180 days, 73% at 1 year, and 72% at 18 months [68]. However, the most common causes of death were stroke and sepsis, and the most frequent long-term complications were infection related to respiratory failure (26%), renal insufficiency (11%), and percutaneous lead (14%) [68]. Lok et al. reported the results for BTT, showing that the survival rates were 81%, 76%, and 68% at 1 year, 2 years, and 4 years, respectively [69]. The similar result of 1-year survival rate for DT was 73% with an obvious reduction in hemorrhagic stroke-related events [46].

A multicenter study showed the clinical results for 468 patients implanted with HeartMate II as a BTT. After a median support duration of 5 months, around half of patients have experienced BTT, 23% patients died, 2.6% patients' cardiac function recovered, and around one fifth of patients were alive with the device [31]. Another multicenter study showed that 22% of HeartMate II patients experienced infection, mainly due to driveline site and staphylococci pathogen [48]. Hasin et al. reported that bleeding predominantly in the gastrointestinal tract was the most common reason for patients' readmission [49]. Other adverse events included sepsis [61], impaired platelet aggregation [70], bleeding [71], and cardiac arrhythmia [72]. Kormos et al. reported that HeartMate II patients as a BTT resulted in 13% incidence of early right HF. Those patients had a 20% reduction in 1-year survival compared to the patients without right HF [73]. Lee et al. reported that 2 of 40 patients underwent right HF after HeartMate II implantation [74]. However, many hemodynamic parameters and indices related to right ventricle and pulmonary circulation, hepatic and renal functions during HeartMate II support as significant improvements were observed [75], even a decrease in pulmonary hypertension was also observed [76].

The HeartAssist 5 now has been approved in the USA for pediatric patients (BTT) and in Europe for both adults and kids for BTT in 2009 and BTR and DT in 2013, respectively [58]. The clinical trials were implemented in 1998 with more than 440 patients, significantly less than the number of patients implanted with the HeartMate II. However, HeartAssist 5 has automated noninvasive tracking of pump function and flow, which provides an extra tool for clinicians to help in the clinical assessment and management of patients [77]. Chiu et al. demonstrated that platelets flowing via HeartAssist 5 had clearly lower stress accumulation than HeartMate II [78]. In general, the clinical complications during HeartAssist 5 support included bleeding, thrombosis, and infections [61].

The Impella has been approved in Europe and the USA [79]. There are several clinical benefits of Impella especially for acute high-risk PCI and cardiogenic shock. For example, with the assist of Impella, the aortic pressure and systemic forward flow enhanced mean arterial pressure. Impella can obviously reduce LV loading and

LV end-diastolic pressure and improve peak coronary flow rates, resulting in the needed balance between supply and demand of myocardial oxygen [80]. It can also maintain central venous pressure around 10 mmHg to prevent suck-down events [81]. Clinical data also showed that Impella improved numerous hemodynamic performance for about half of 1 h after percutaneous implantation [32, 34]. However, there are also some contradictions and adverse events while clinically using Impella. Some complications have been reported such as severe peripheral arterial dysfunction, LV thrombus and septal defect, aortic stenosis, and backflow across the aortic valve. Other adverse events have also been observed, mainly including reduced platelet aggregation, mechanical hemolysis, even acquired von Willebrand syndrome, and some peripheral complications regarding femoral insertion, etc. [82]. Moreover, some clinical studies showed that increased cardiac output did not significantly reduce mortality for the patients [82–84].

To date, there is few clinical reports for the MVAD compared to its predecessor—HVAD, or HeartMate II. However, hemodynamic performance, biocompatibility, and hemocompatibility of the MVAD have been validated through some animal and pre-clinical studies [37–40]. There was a CE Mark interventional and clinical trial whose official title was a multicenter, prospective, non-randomized, and single-arm trial [37]. It has been implemented to assess the performance and safety of the MVAD for the patients with advanced HF. There were 60 patients enrolled in this trial at more than 10 sites from different countries such as United Kingdom, Germany, Austria, Australia, etc. to start this program for both short- and long-term use. The primary endpoint was survival at about half a year, while the secondary outcome would be survival at around 2 years. During the trial, the pump thrombus events were observed for 11 patients, but no stroke events found in any patient. The related full study summary will be published in the future.

The clinical trials of HVAD initiated in 2008 with more than 700 patients. CE mark and IDE BTT trial were attained in 2009 and 2010, respectively, and approved for BTT in 2012. The number of implants for centrifugal flow pumps is not as high as that for the axial pumps. However, now surgical implants for HeartWare HVAD have been obviously increasing in numbers, which is larger than many previous axial flow pumps except for HeartMate II [6]. To date, there were many clinical trials with HVAD. A multicenter study in Australia and Europe observed that the survival rate was 91% after half a year and 86% after a year [85]. The safety of this device was further evaluated extensively in 50 patients. After implantation of HVAD, the survival rate was 90%, 84%, and 79% after 6 months, 12 months, and 24 months, respectively. And among these patients, 40% of the patients underwent transplants, 8% of the patients received device explantation after myocardial recovery, and 34% of the patients were on the device support at 24 months. Moreover, 9 (18%) patients died due to multiple organ failure, hemorrhagic stroke, and sepsis ($n = 3$ for all events). The major adverse events included infection and bleeding [86]. In addition, some studies suggest that increasing the resistance of outflow graft [86] or running it at lower speed for right ventricular support may improve the hemodynamic

performance [87]. However, to date there is little data available to make detailed and authoritative conclusions. Moreover, a study reported that 6 out of 7 pediatric patients were successfully bridged to transplantation [88]. Since HVAD is implanted intrapericardially, it also allows implantation in a significantly higher percentage of women [89]. A comparison between HVAD and HeartMate II for 2-yeart survival rate has been conducted. Overall the results did not differ significantly between the two devices (60.2% vs. 67.6%) while the HVAD group decreased device failure requiring replacement and increased occurrence of stroke and sepsis [77, 90]. A low or non-pulsatile flow-related study for the RBPs (HeartWare HVAD or HeartMate II) reported that reduced pulsatility may lead to colonic mucosal ischemia with high shear stress [44], resulting in arteriovenous malformations, acquired von Willebrand disease, and gastrointestinal bleeding [5, 70, 71, 91]. Stulak et al. reported that HVAD had higher incidence of stroke than HeartMate II, but no significant difference in pump thrombus, GI bleeding, and infection between the two devices was found [92]. A study also concluded that the clinical limitations are the same as those for HeartMate III [61].

The CentriMag has been clinically used for salvage as a BTD [29, 30, 93–95]. The recommended duration of use was 30 days for CE and 6 h for FDA, respectively [77]. In the clinical use, however, CentriMag has been used for more than 3 months without increased adverse events [96]. Loforte et al. reported that the survival rates in 42 patients were 55% at 1 year and 24% at 2 years, respectively [97]. Moreover, heparin as anticoagulants has been usually used for the patients with CentriMag in order that bleeding can be delayed for about 2 days after implantation, and to maintain physiologic perfusion as about 4 l/min to prevent pump thrombosis and other thromboembolic events [98]. Another study showed that the mortality rate was 19% with CentriMag, 29 (68%) patients were returned home, 16 patients were implanted with this device for long-term use, and 10 out of these 16 patients successfully underwent heart transplant [99]. Studies also showed that the mortality rate of CentriMag patients as RVAD support after LVAD implantation was high [100], which was much higher as in-hospital mortality (74%) reported by Takeda et al. [101] compared to the patients with BiVAD support (24%). In addition, due to its large drive console and required prophylactic pump exchange every around 1 month [102], it was hard to discharge the patients from hospital. CentriMag-related major complications include infection, bleeding, respiratory failure, liver dysfunction, and hemolysis, etc. [94, 100, 103].

HeartMate III has been evaluated prospectively for BTT and DT indications [104]. In Europe, the HeartMate III clinical study has been conducted at 10 centers in 6 countries for BTT (54%) and DT (46%), respectively [104]. It was reported that 32-day mortality was 2% and the survival rate at half a year was 92%, higher than the expected one of 88% [105]. No thrombosis, exchanges, hemolysis events, or malfunctions in the pump were involved. More than 80% of the patients showed a significant improvement in cardiac function. The survival rate at 2 years has been increased from 76.2 to 82.8% by the key improvements including pumping

efficiency, mechanical reliability, and battery life, together with the refined implantation techniques [106]. A comparison was conducted between HeartMate III and HeartMate II for some clinical outcomes at 6 months and 2 years [107]. There was no obvious difference in death or disabling stroke rates, but the rate of pump malfunction in HeartMate III ($n = 1$) was less than HeartMate II ($n = 7$). However, some studies reported that HeartMate III had greater freedom from hemocompatibility-related adverse events than HeartMate II at 6 months [108] and 1 year [109], respectively. The incidence of pump thrombosis in HeartMate III was less compared to HeartMate II and HVAD [90]. The stroke risk was also reduced with HeartMate III compared with HeartMate II. In addition, bleeding, infection, arrhythmia, and stroke are the main limitations during HeartMate III support [61].

The clinical trial of the DuraHeart was initiated in 2004 and has been approved by CE in 2007. The number of device implants was only approximately 100 patients because the device is relatively large and it is not easy to implement inflow cannula placement. However, DuraHeart has the similar survival rates compared to HeartMate II, which was 77% at 1 year and 61% at 2 years, respectively, and the most common adverse events included right HF (27%), neurological complications (27%), and infection (18%) [47]. Other clinical complications are mainly hemolysis, thromboembolism, and bleeding [61]. Morshuis et al. reported that with DuraHeart, the incidence of suction was much lower than the axial flow pumps [110].

4.5 Summary

In this chapter, we introduced axial and centrifugal flow pumps in design and performance and compared their clinical applications and outcomes. The axial blood pumps are the second-generation artificial hearts, which have a single moving part (impeller) and do not require valves. AF pumps have rotors oriented to ensure that blood can accelerate in line with the rotor's axis. Due to the smaller size, they can be implanted in the thoracic cavity of patients with small body surface areas. The centrifugal and mixed flow blood pumps are the third-generation artificial hearts, with the axis of the inlet and outlet perpendicular to each other. Axial flow pumps can operate at the rotational speeds ranging from 6000 to 50,000 rpm. In comparison, centrifugal flow pumps are slightly larger in diameter and typically have higher hydraulic efficiency and lower pump speed range. In general, the axial flow RBPs produce higher flow rates with lower pressure rises at higher rotational pump speed, while the centrifugal flow RBPs generate higher pressures at lower flow rates and require, therefore, much lower pump speed. Both axial and centrifugal pumps can be clinically used for BTT, DT, BTR, or BTD. Different RBPs may have distinct clinical outcomes and adverse events despite having similar hemodynamic performance.

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Chapter 5
Artificial Heart: Volume Displacement Blood Pump

Cunyue Lu, Guang Yang, Huan Huang, Shiyang Li, and Ming Yang

Abstract Although the ventricular assist device landscape has rapidly evolved away from volume displacement pulsatile technology and toward continuous rotary pumps, adverse events such as gastrointestinal bleeding, stroke, and pump thrombosis force the engineers to look back the volume displacement pulsatile pumps again for the possible ways to reduce these severe adverse complications and improve perfusion for end organs. This chapter will introduce principle, design, performance, and discussions of volume displacement pump.

Keywords Pulsatile blood pumps · Principles and designs · Surgical techniques

5.1 Introduction

In North America only, it is said that there are more than five million adults with heart failure (HF) [1]. Since many patients with end-stage HF experience significant morbidity and mortality in the absence of advanced therapies, the demand for durable left ventricular assist devices (LVADs) has been increasing [2]. Up to now, continuous-flow left ventricular assist devices have revolutionized advanced heart failure treatment due to the smaller size, durability, and improved survival outcomes, and more than 22,000 patients have now received LVADs therapy [3]. The reported survival rates of patients with a LVAD were 80% after 1 year and 70% after 2 years [4]. However, continuous-flow LVADs have also been associated with certain complications such as nonsurgical bleeding, thought to be linked with decreased arterial pulsatility [5]. Therefore, clinical complications

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associated with continuous-flow VADs have renewed efforts to restore pulsatile flow [6, 7].

Pulsatility is one of intrinsic properties of the cardiovascular system, and the human cells are adapted to the cyclic changes of pressure and flow. At the cellular level, these mechanical forces of pulsatility constantly act on the various cellular signaling pathways, which affects endothelium regulation of vasodilation and vascular remodeling, including matrix deposition, programed cell death, smooth muscle cell proliferation, and atherosclerosis [5]. For example, it is reported that the frequency and amplitude of pulsatile flows are both directly associated with endothelial production of nitric oxide causing vasodilation [8]; The recent research also demonstrates how the reduced pulsatile pressure will decrease bradykinin-dependent vascular relaxation, reduce nitric oxide production, and increase vascular oxidative stress [5, 9]. Moreover, significant hemodynamic benefits of pulsatile VADs can provide superior left ventricle unloading with lower pulmonary pressures, and also induce more possibility of myocardial recovery than continuous VADs, possibly due to improvements in coronary flow [10]. Hence pulsatility is the desired feature for the VADs in coexistence with the cardiovascular system.

Since the human circulation is a pulsatile system, the long-term VADs have started with volume displacement pumps, mimicking the pulsatile flow of the native heart [11]. Generally, these devices consist of a sac, which is cyclically pressurized for periodic filling and emptying through inflow and outflow one-way valves. When operating in the fill-to-empty mode actuated pneumatically or electrically, these pulsatile VADs emulate the Frank–Starling response of a typical heathy hearts, aiming to reduce incidences of ventricular suction and pulmonary congestion [11]. However, the major downside of pulsatile VADs is relatively frequent complications such as device failure, thrombosis, bleeding, and infection. For example, the device failures are usually resulting from relatively complex structure and numerous moving components. Furthermore, volume displacement pulsatile pump usually has a large size due to the limit of the stroke and heart rate. But the large size prevents the clinical applications of pulsatile pumps because of requiring a large pump pocket or large percutaneous cannulas. Hence, the pulsatile VADs and continuous VADs are now in a dilemma. On one hand, human circulation is a pulsatile system. A pulse is required to coordinate with human circulation. However, the pulsatile devices are restricted due to relatively large size with a limited reliability or high thromboembolism, inducing severe complications such as device failure, thrombosis, and infection. Furthermore, pulsatile VADs also require a large body habitus, extensive surgical dissection, and large percutaneous vent lines. The clinical applications of pulsatile pumps have been accompanied with considerable morbidity, including infection, bleeding, and device failures [12]; On the other hand, continuous-flow VADs are simple with small size and high reliability and duration. They are capable of augmenting the circulation to meet the body's physiological needs, extending survival and improving quality of life. However, non-pulsatile flow restricts the coordination with a pulsatile human circulation, causing severe impacts on the circulation, and trauma to blood. Therefore, it is necessary to introduce and discuss volume displacement pumps again to look for the underlying mechanisms

causing these benefits and adverse complications. The purpose is to find the approach for development of VADs with low adverse complications and small size and high reliability.

This chapter is organized as follows. The second section presents the principles and designs of the pulsatile pumps. The third and fourth sections present performance and surgical techniques of the pulsatile pumps followed by Sect. 5.5 with discussions. Finally, the chapter will conclude with future considerations of volume displacement pumps.

5.2 Principles and Designs

Although the pulsatile flows can be produced by the modulation of rotation speed in the rotary pumps, the pulsatile flow generated by the motion of flexible diaphragm is conventionally called volume displacement pulsatile pumps. This conventional pulsatile pump consists of two parts, the blood chamber and the driving chamber, which are isolated by a diaphragm. In the driving chamber, the diaphragm is connected to the actuator, cyclically exerting external force to empty blood chamber, and then to fill the chamber with blood. In the blood chamber, one-way valves are placed at the inlet and outlet of the chamber to ensure unidirectional flow. Hence the principles of pulsatile pumps are mainly associated with the actuators, the artificial valves, the materials, and the operation modes, as shown in Fig. 5.1, which will be introduced below.

The pulsatile pumps could be electrically or pneumatically actuated. The electrically actuated pulsatile pumps can further be driven either by a torque motor or a linear actuator. When a torque motor is used, a movement converter is required to obtain pulsation. A movement converter such as a cam could provide precision control on the ejection process of the pulsatile pumps, which could prevent a sudden open and close of the artificial valves. When the biological valves are used, the pulsatile pump such as Heartmate XVE could achieve low anticoagulation regimens due to rare thrombus formation inside the pump [13]. However, the use of a

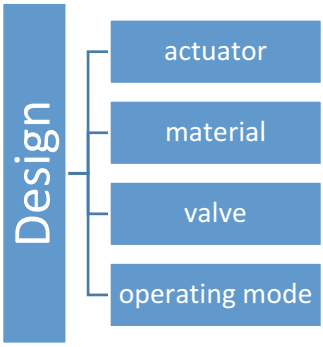

Fig. 5.1 The design principle of pulsatile pumps

movement converter is a stumbling block for miniaturization and high reliability due to numerous motion components; when a linear actuator is used without any movement converters, this pulsatile pump has a simple structure with high reliability [14]. The pulsatile pumps such as Novacor have longest duration up to 6 years [15]. But the solenoid in the Novacor is difficult to control the blood pumping process, which induces thromboembolism [16]. No matter the linear actuator or torque motor, the dilemma of current VAD technologies is associated with electromagnetic actuating principle, which prevents the high reliability and precision control on the blood pumping process simultaneously under current techniques. Hence a novel actuating technology needs to be explored when designing a pulsatile pump coexisted with the cardiovascular system without causing harm.

Usually, pulsatile pumps are known to induce blood trauma by the complicated flow field of artificial valves [17]. However, the pulsatile pump such as Heartmate XVE could achieve low anticoagulation regimens due to rare thrombus formation inside the pump [13], which suggest that the precision control of the blood ejection process and biological valves in the pulsatile pumps could be used to prevent the blood trauma [18]. The type of valves is either mechanical or biological design. A mechanical valve is expected to outlast the patient but requires anticoagulation, whereas a biological valve does not require anticoagulation but is subject to structural valve degeneration after 10 years [19]. However, the current lifetime of VAD therapy is below 10 years [2], which suggests that biological valves can meet the requirements of VADs. In other words, the biological valves should be selected when designing a pulsatile pump for a low rate of blood trauma.

The pulsatile pumps are manufactured from materials, which should have good properties regarding biocompatibility, mechanical, and thermal properties. The mechanical property is selected to guarantee the light weight and strength; thermal property is measured by thermal conductivity, which is designed to keep thermal balance, preventing the possible heat accumulation in the pulsatile pumps. The biocompatibility refers to the ability of the material coexistence with living tissues or organisms without causing harm. The available tests for the biocompatibility of the material are chemical characterization, cytotoxicity, hemocompatibility, implantation testing, irritation, sensitization, systemic toxicity, and so on [20]. For example, all blood-contacting surfaces of the HeartMateXVE, except the porcine valves, are textured for deposition of a stable biologic lining. The diaphragm is fabricated from polyurethane with an integrally textured surface for deposition of a tightly adhered fibrin/cellular matrix. In addition, metal components have blood-contacting surfaces of sintered porous titanium [21]. For the pulsatile pumps, the materials must be carefully designed in terms of biocompatibility, mechanical and thermal properties.

The pulsatile pumps can be operated in three different modes, which are asynchronous, synchronous, and fill-to-empty. In asynchronous mode, the pulsatile pumps eject the blood at a fixed frequency, regardless of the patient's heartbeat and the remaining blood volume in the chamber, which may result in premature closure of aortic valve with reducing stroke volume or late closure of aortic valve with increasing left ventricle afterloads [22]; In synchronous mode, the electrocardiogram of the patient triggers blood ejection to synchronize ejection with the

patient's heartbeat. When the pulsatile pumps are operated in counterpulsation under synchronous mode, the coronary perfusion could be enhanced to improve the possible heart recovery. Finally, in fill-to-empty mode, the blood volume ejected is coordinated with that filled, which ensures that the pump ejection matches venous return, avoiding possible right ventricle failure.

5.2.1 Pneumatic Pulsatile VADs

The pneumatically driven blood pumps are used mainly because they are inexpensive and simple to operate and control. Currently the pneumatically driven pulsatile VADs are used to provide either for the patients whose failed heart may be recovered after a short-term support or the long-term support for pediatric patients due to the small stroke volume such as 10, 12, 15, 25, or 30 ml [23]. Typical examples for pneumatic pulsatile VADs are BVS 5000 (ABIOMED BVS 5000™) and Berlin Heart EXCOR (extracorporeal VAD system Berlin Heart).

5.2.1.1 BVS 5000

The ABIOMED BVS 5000™ is used worldwide for temporary left, right, or biventricular support in patients with potentially reversible heart failure. It is the first heart assist device approved by the US Food and Drug Administration for the support of post-cardiotomy patients, and hundreds of patients have been sustained by the BVS 5000 since then.

The pump of BVS 5000 has two polyurethane chambers, an atrial chamber that fills with blood through gravitational force and a ventricular chamber that pumps blood by air-driven power. The atrial chamber is vented outside the patient. The ventricular chamber is connected to the power console. Two tri-leaflet valves separate the atrial and ventricular chambers. The pump can produce blood flow of up to 5 liters per minute. The console can support one or two blood pumps, which is fully automatic and compensates for changes both in preload and afterload. The left and right sides are triggered independently of each other [24].

5.2.1.2 EXCOR

EXCOR® is a mechanical, pulsatile ventricular assist device (Berlin Heart AG, Berlin, Germany), which is used for the short- to long-term support of the left and/or right ventricular pumping function. It is indicated for patients both children and adults with life-threatening diseases with severe heart failure after all conservative therapeutic options have been exhausted [25].

The EXCOR system includes paracorporeal, pneumatically driven polyurethane blood pumps, consisting of a blood chamber and an air chamber which are separated

by a multilayer flexible membrane. The air chamber is controlled by a driving unit with air in and out, which draw blood into the blood chamber and push it back into the body. To protect against thrombosis, all blood-contacting surfaces are heparin-coated, whose beneficial effect continued to be present after more than 90 days of VAD use [23, 26]. The EXCOR product range covers blood pumps and cannula of various sizes and types designed for both adults and young patients from newborns to adolescents. The choice of pump size is based on the weight of the patient. Specifically, the calculated pump flow for children is 120–150 ml/kg, and for adolescents, 100 ml/kg [27]. Since the inner surfaces of extracardiac pneumatic blood pump chambers are heparin-coated, no postoperative anticoagulation is given for the first 8–24 h. However, postoperative anticoagulation is started with intravenous heparin 24 h to keep the partial thromboplastin time 1.5–2.0 times the normal value. When the serum level is below 70% of normal, antithrombin III is replaced with subsequently aspirin and dipyridamole, which are guided by the results of platelet mapping by thromboelastogram TEG 5000 (Haemoscope Corp, Niles, IL). Later, low molecular heparin or oral warfarin is started. This systemic anticoagulation is trying to reduce the high rate of hemorrhage complications in the assist patients [26].

The clinical effect of the EXCOR can be found in a recent report published by Roland Hetzer et al. [27], in which the Berlin Heart EXCOR® has been implanted in 122 children (median age 8.64 years, range 3 days to 17 years) with heart failure between 1990 and 2013. The overall median duration of implantation is 63.6 (range 1–841) days. Fifty-six children eventually undergo orthotopic heart transplantation. Eighteen children have myocardial recovery and are weaned successfully. Forty-three patients died from loss of peripheral circulatory resistance, multiorgan damage, sepsis, or hemorrhagic or thrombotic complications.

5.2.2 Electromagnetic Motor Driving

The long-term VAD has started with pulsatile devices, such as Thoratec HeartMate IP1000/VE/XVE (St. Jude Medical, Inc., MN, USA) and Novacor (St. Jude Medical, Inc., MN, USA). Although volume displacement pulsatile pumps driven by electromagnetic motors are no longer in clinical use any more, the severe adverse complications in the current continuous blood pumps force the engineers to look back the volume displacement pulsatile pumps again for the way to reduce these severe adverse complications [4]. The reason is that the lessons learned from these volume pulsatile pumps may uncover the clues for the mechanism inducing these severe adverse complications. Since these implanted volume displacement pumps are either driven by a low-speed torque motor or a linear motor, this section will mainly introduce Heartmate XVE and Novacor.

5.2.2.1 HeartMate XVE

Left ventricular assist devices driven by electromagnetic motors are the most successful devices developed. Three types of HeartMate blood pumps have been developed: the pulsatile pump called HeartMate XVE, the axial flow pump called HeartMate II, and the maglev centrifugal pump called HeartMate III. The HeartMate XVE is a pulsatile pump, in which pump ejection requires one revolution of the torque motor. It can provide a stroke volume of 83 ml and generate pulsatile blood flow up to 10 l/min [28].

The HeartMate XVE left ventricular assist device is electrically powered and consists of a blood pump chamber and an electric torque motor driving a textured polyurethane diaphragm. The electro-mechanical driver is comprised of a low-speed torque motor and a rotary-to-linear motion converter. The torque motor comprises a stator, a magnet assembly that rotates inside it. The rotary-to-linear motion converter such as a cam converts the rotary action of the motor to the linear motion required by the blood pump. The magnetic rotor assembly contains two roller bearings. As the rotor turns, the roller bearings push up a pair of ramped cams connected to the pusher plate/diaphragm. As the driver bearing rotates, the cam/pusher plate is forced upward, ejecting blood from the chamber. As ejection is completed, the driver arrives at the terminus of the cam with no further pressure to the pump chamber, in which the pump chamber can be filled. To improve the biocompatibility, the blood-contacting surfaces of the pump chamber and its conduits are textured to promote the formation of a biologic neointima lining. Combining the precision control of the pusher plate and the use of biological valves and textured surface, anticoagulation is not required for most patients [21, 28]. The entire device is shown in cross section in Fig. 5.2 [21].

The weight of the HeartMate XVE left ventricular assist device is about 1255 g. The diameter of the pump body is about 112 mm. The nominal height of pump body

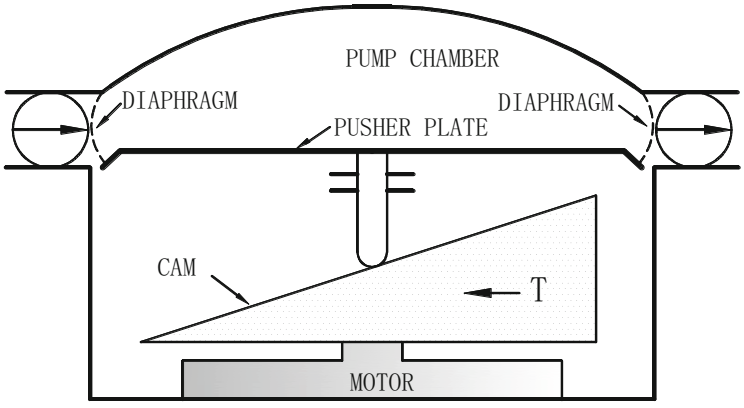

Fig. 5.2 HeartMate XVE LVAD (schematic design) [21]

is about 58 mm, and the nominal length is about 1016 mm. The power consumption the LVAD is 5–15 watts, and the operating voltage is 10–14 volts DC [21].

Electromagnetic motors are usually inefficient at low speeds because the reverse electromotive force (EMF) that counteracts the current is small. Therefore, at low speed, the efficiency of the motor becomes low and the heat of the motor is serious [14]. HeartMate XVE uses low-speed electromagnetic motors, which have the same drawbacks. Since a motion conversion mechanism is used to convert the rotary motion of the electromagnetic motor into a linear motion, the XVE LVAD contains cams and excessive mechanical parts compared with HeartMate II or HeartMate III, and thus has potential risks of low life caused by friction and wear, low efficiency, and high failure rate [28].

The clinical effect of HeartMate XVE can be found in a publication reported by Slaughter et al. This report introduced neurocognitive function and the frequency and incidence of neurologic events in 21 consecutive patients who were undergoing long-term support with the HeartMate XVE LVAD. It is found that the mean duration of LVAD support was 531 days (range, 55–1309 days), and no patients received anticoagulant therapy but aspirin with none experienced strokes or transient ischemic attacks. In the end, 20 patients were discharged from the hospital [29]. In a case report, Loumiotis et al. introduce a patient who is the recipient of a third-generation LVAD due to recurrent heart failure nearly one decade after successfully being bridged to recovery after implantation of a first-generation LVAD [30]; in another case report, Malehsa et al. describe von Willebrand syndrome which was observed in the patient implanted with HeartMate II axial flow device but not observed in the patient implanted with HeartMate XVE pulsatile ventricular assist device [31].

5.2.2.2 Novacor

The Novacor left ventricular assist system (LVAS; Baxter Healthcare Corporation, Novacor Division, Oakland, CA) was first successfully implanted in 1984 [32]. The Novacor VADs consist of a seamless smooth-surfaced polyurethane sac, two pusher plates bonding to the sac, and a solenoid exerting a linear action to the plates. When the plates are powered by a solenoid, the two pusher plates squeeze the collapsing sac, thus propelling blood from the pump. The actual control is located extracorporeally, where a percutaneous tube is tunneled from pump to console and exits the patient from the right abdominal quadrant. This percutaneous tube can deliver electric energy to the pump and return signals from transducers located at the pusher plates and solenoid, which provide information about energy usage, filling volumes, and pump output volume. Hence pump action with patient left ventricle can be synchronized, in which low left ventricular pressure and decreased myocardial oxygen demand can be achieved. A major principle governing pump timing is that it must be empty and ready to fill at the beginning of the left ventricular systole, and that pump ejection must always be complete prior to a subsequent left ventricular contraction. By the way, the patient population that can be implanted with Novacor

is somewhat limited because the device measures 16 × 13 × 6.5 cm, excluding some patients due to the surgical concerns [33].

In 2000, the clinical effects of Novacor have been reported by Banayosy et al. through the comparisons between Novacor N100 left ventricular assist system (Baxter Healthcare Corporation, Berkeley, Calif) and TCI HeartMate vented electric left ventricular assist system (Thermo Cardiosystems Inc., Woburn, Mass) [34]. It is found that there are no statistically significant differences regarding postoperative hemodynamics, organ recovery, out-of-hospital support, and survival to heart transplantation. Mean duration of support is 235.3 ± 210 days for the Novacor group and 174.6 ± 175 days for the HeartMate group, respectively. However, it is found that the neurologic complications occur significantly more often among the Novacor group, whereas the HeartMate group has a higher prevalence of infections and technical problems. Survival to transplantation is almost same for both groups, that is 65% for the Novacor group and 60% for the HeartMate group. Hence, more attention should be paid to the thromboembolism for the Novacor device and infection and reliability for the HeartMate device [34].

5.2.3 Piezo-Hydraulic Pumps

Although EXCOR® can provide for the short- to long-term support of the left and/or right ventricular pumping function for both children and adults with life-threatening diseases, the electric motor-driven air compressors are suitable to adult blood pumps but not to children blood pumps because these air compressors cannot provide the necessary pressure (40–46 kPa) at relatively high pulse rates needed for children (80–150 beats per minute (BPM) [35]. Therefore, new actuator approaches for pulsatile VADs should be pursued to increase pumping rate and to reduce the size of the drivers for pediatric devices. One approach is to utilize high-frequency piezoelectric actuators.

Piezo-hydraulic pumps (PHPs) consist of piezoelectric actuators driving a piston with valves to generate hydraulic power in the form of a pressurized continuous flow [36]. John Valdovinos studied the feasibility of using piezo-hydraulic pumps in pulsatile pediatric ventricular assist devices in 2013 [37]. A piezo-hydraulic pump was incorporated into a ventricular assist device driver to drive a pulsatile pediatric 30-mL stroke ventricular assist device as a proof of concept. The VAD is a blood chamber of EXCOR. The PHP uses Dexron IV hydraulic oil as the working fluid, which does not contact with the blood. The hydraulic cylinder converts the PHP flow to a linear mechanical stroke, while the four-way solenoid valve (SV08–40; Hydra Force Inc.) produces bidirectional actuation. The driver was tested at heart rates ranging from 50 to 110 beats per minute in an in vitro mock circulation to characterize its performance. The maximum drive pressure was 33 kPa with a peak flow rate of 6 L/min against a 10-kPa back pressure. The maximum mean flow rate from the ventricular assist device outlet was 3 L/min at 100 beats per minute operation. This small piezo-hydraulic pump may only need 5.8 W of electrical power to achieve

a 1.7-W output. These results indicate that it is not only feasible to use PHPs in pediatric VAD applications but they can also potentially lead to smaller drivers when operated at high frequencies [37].

5.3 The Performance

Hemolysis, the destruction of red blood cells, and thrombosis, clot formation, are fundamental problems related to the performance of the VADs. Pulsatile pumps are characterized by inlet jets that set up a rotational "washing" pattern during filling, and by strong regurgitant jets through the closed artificial valves that cause red blood cell damage and platelet activation [38]. Hence, the flow dynamics of volume displacement pulsatile pump must be one major concern in the design and evaluation. The pulsatile pump such as Heartmate XVE has rare thrombus formation but more thromboembolism for the Novacor device [34], suggesting that the precision control of blood flow dynamics and biocompatible material are both essential to reduce blood trauma.

The relationship of hemolysis and thrombosis to the fluid mechanics such as velocity, shear and wall shear rates, and turbulence is the major impetus for flow studies in blood pumps. However, neither phenomenon is completely understood. Usually, the design of the fluid mechanics in the blood pumps is mainly based on the trial-and-error improvements of thrombosis and hemolysis performance. It has been reported that wall shear rate should be above 500 s^{-1} to prevent clot formation on segmented polyurethane [39]; furthermore, there is a hemolysis potential curve, relating shear stress and exposure time to red cell, white cell, and platelet lysis. According to the hemolysis potential curve, blood cells can tolerate high stresses for short exposure times without hemolysis. For example, an exposure time of more than 0.1 ms at a shear stress of 10,000 dynes/cm^2 will produce red cell lysis same as that of 1500 dynes/cm^2 for times over 100 s [40].

5.4 Surgical Techniques

There are various kinds of ventricular assist devices (VADs) [41], and the processes and surgical techniques of device implantation are different according to the specific features of the device and the ways of being used in different clinical situations. Generally speaking, the surgical techniques can be classified into three categories: (1) short duration of support with extracorporeal implantation for recovery and transplant, (2) intermediate duration of support with paracorporeal implantation for recovery and transplant, (3) long duration of support with orthotopic implantation for transplant and destination treatment [46].

It is imperative that a thorough assessment be performed before and after anesthesia to ensure the hemodynamics. Transesophageal echocardiogram (TEE) should be performed to identify potential valvular problems or the presence of a patent foramen or intracardiac thrombi that need to be addressed at operation and is used to optimize pump speed while weaning from cardiopulmonary bypass after VAD implantation. Emphasis should be placed on the valve lesions of aortic and pulmonary regurgitation and tricuspid regurgitation that have a potential effect on VAD performance.

5.4.1 Extracorporeal Implantation

This kind of implantation is usually used for right ventricular assist and can be performed under the condition of cardiopulmonary bypass or without bypass or with ECMO support. The implantation is performed using a median sternotomy approach. Venous inflow for right ventricular assist device (RVAD) is provided by percutaneous femoral venous line. The femoral venous cannula is inserted percutaneously into the right atrium through the right femoral vein, and the position of the cannula is confirmed by transesophageal echo. Then the venous cannula is connected to the inflow cannula of VAD device. An 8–10 mm Dacro graft is used for the arterial return to the pulmonary artery. The graft is anastomosed end-to-side to the main pulmonary artery with a 5-0 polypropylene running suture, using a Satinsky side clamp. The outflow graft is passed transcutaneously through an opening on the right subcostal margin, or through a small skin incision on the left chest wall via the second interspace, where the outflow cannula of VAD device is inserted and the graft is tied tightly around the cannula outside the chest and secure firmly to the chest wall [47, 48].

5.4.2 Paracorporeal Implantation

This kind of implantation can be used for biventricular assist and is performed under the condition of cardiopulmonary bypass. The implantation is performed using a median sternotomy approach under transesophageal echocardiogram guidance. On the left side, the inflow cannula is implanted at the apex of the left ventricle, and the outflow graft is anastomosed to the ascending aorta. On the right side, the inflow cannula is implanted in the right atrium, and the outflow graft is anastomosed to the main pulmonary artery. All these four cannulae are passed transcutaneously through openings on the right subcostal margin, and connected to device by specific demand accordingly [49].

5.4.3 Orthotopic Implantation

This kind of implantation can be used for biventricular assist and is performed under the condition of cardiopulmonary bypass. The implantation is performed using a median sternotomy approach. The surgical preparation is similar to other cardiac operations, PA (pulmonary artery) catheter is routinely used for VAD implantation to assist with perioperative therapies including pulmonary vasodilator therapy as well as ionotropic and vasoconstrictor support. Because this implantation of left ventricular assist device is the most popular means of ventricular assist, the process of implantation will be described step by step as following.

5.4.3.1 Entry and Exposure

A standard sternotomy incision is performed to exposure. Pericardium is incised and the incision is carried to the left to several millimeters before reaching the diaphragm, where a T-shape incision is created toward the right and left [42, 45]. The incision to the left continues several centimeters above the phrenic nerve to expose the apex of heart [42, 44].

When a large profile device is implanted, it is necessary to create a pump pocket due to the size and structure of the device to optimize the flow and avoid compression of either ventricle. The pericardial reflection is divided laterally beyond the left ventricular apex [44]. The incision beyond the diaphragm requires dissection through subcutaneous tissue anterior to the posterior rectus sheath. The exposed part of diaphragm is cauterized as far as possible laterally [42, 44]. An ideal pump pocket is created when the incision is extended about 7 cm below the xiphoid process and deep enough to extend laterally under the costal arch [42]. With lower-profile device, dissection and division of pericardial reflection laterally beyond the left ventricular apex is sufficient to accommodate the device.

5.4.3.2 Tunneling of the Driveline

The process of tunneling of the percutaneous driveline is common to all devices and is done before administration of heparin to prevent bleeding in the rectus sheath. With the funneling device, the driveline is tunneled through the rectus muscle, exits the anterior rectus sheath, and continues in the subcutaneous tissue to the skin at the site along the anterior axillary line, approximately 2 cm below the costal margin on the right side. The woven polyester portion of the driveline should be completely buried in the subcutaneous tissue 1–2 cm from the skin exit site [42, 43].

5.4.3.3 Cardiopulmonary Bypass

After the administration of heparin, the cannulation sutures are placed for arterial and venous access. The position of aortic cannula should be weighed for leaving room for the outflow graft anastomosis and aortic root vent. A two-stage venous is used for venous drainage, and bicaval cannulation for venous return is necessary in the event either mitral or tricuspid valves or patent foramen ovale need to be addressed [42, 43, 45]. The procedure is performed on cardiopulmonary bypass on the beating heart.

5.4.3.4 Attachment of the Apical Cuff and Coring of the Apex Muscle and Insertion of Device

Once on full bypass, the heart is elevated and supported with moist sponge pad to expose the left ventricle and apex, the coring site of apex is identified on the distal anterior surface of the left ventricle, approximately 2 cm lateral to the left anterior descending artery. A stab incision is placed into the apex, a 16F Foley catheter is inserted into the left ventricle, and the balloon is inflated and retracted to lift the apex. The apical cuff is sewn onto the left ventricle apex before coring the left ventricle apex. For most devices 8–12 interrupted, pledgeted, horizontal mattress sutures are used in attachment of apical cuff. A Foley catheter is passed through the center of the coring knife, and the muscle is cored by gently retracting upward on the catheter. For some specific device, the Foley catheter is removed, the incision is extended to the edges of the center of the apical cuff, and a specific coring knife is inserted into the left ventricle, and the apical muscle is cored. The left ventricle is then inspected for thrombus and crossing trabeculae, which are excised as necessary [43–45].

The inflow cannula is then inserted into the left ventricle and secured to the apical cuff according to specific features of each device and the device is positioned with the outflow graft and driveline parallel to the diaphragm, and the screw on the cuff is tightened. The correct position of inflow cannula should be parallel to the interventricular septum and directed to the mitral valve. The apex of the left ventricle with the device is returned to its anatomic position, so that the inflow cannula is directed to approximate position. Deairing is accomplished by passively filling the heart and pump and elevating the apex and gently shaking the ventricle. The outflow graft is then distended, clamped, and trimmed to proper length [43, 45].

5.4.3.5 Outflow Graft Anastomosis

It is imperative to determine the appropriate length of the outflow graft. Graft of excessive length may lead to kinking of the graft, and conversely, a short graft may cause tension to anastomosis and lead to bleeding or obstruction. The graft should lie within the atrioventricular groove between the right atrium and right ventricle

[42]. Once the size is determined, the graft is occluded with a vascular clamp. The ideal site of anastomosis is distal to the sinotubular junction of the lateral aspect of the greater curvature of the proximal ascending aorta, preserving as much aorta as possible for later transplantation [44, 45]. A partial aortic occlusion clamp is placed on the site of aorta, and an incision should be made wide enough to accommodate the graft, and the anastomosis is performed with a 4-0 polypropylene suture in a running fashion [42, 44]. Once the anastomosis is complete, the vascular clamp on the outflow graft is temporarily removed to purge air from the system, then reapplied. With the HeartMate II device, the outflow connector is now engaged and tightened when the left ventricle is partially full, while allowing air to come out before completing the circuit [42].

5.4.3.6 Deairing and Weaning off Cardiopulmonary Bypass

It is important to place a vascular clamp on the outflow graft with continuous-flow device until output is initiated to prevent backflow of blood into the left ventricle. The deairing maneuvers include placing the patient in a Trendelenburg position, adding volume to the heart, and resuming ventilation [44]. An aortic vent needle is placed in the ascending aorta distal to the anastomosis site for air removal, and a needle is placed in the outflow graft proximal to the clamp to remove air from the graft [44, 45]. Air removal is a continuous process involving visual inspection of the right ventricle while observing overall hemodynamics on transesophageal echocardiogram.

After deairing is confirmed by transesophageal echocardiogram, administration of nitric oxide is started as well as combination of vasopressor and inotropic support to assist the right heart. The patient is gradually weaned from cardiopulmonary bypass. Once the flow is less than 2 L/min, the vascular clamp on the outflow graft is removed and the LVAD is started. The speed of the pump is gradually increased to allow for increased LVAD output and cardiopulmonary bypass is discontinued [43, 44]. Transition from cardiopulmonary bypass to LVAD support needs close communication between the surgeon, anesthesiologist, perfusionist, and LVAD operating team, and close attention to transesophageal echocardiogram monitor of the presence of air, inflow cannula position, right ventricular function, and septal motion. When the hemodynamics is appropriate, protamine is administered and the cannulae are removed. Close attention should be paid to ensuring satisfactory hemostasis. A patch of GORE-TEX membrane is sewn to either side of the pericardium to cover the heart and device for future reoperation [43, 44]. Standard mediastinal and pleural chest tubes are placed, and the sternum is closed with wires and the incision is closed in layers by suture. Dry and sterile dressing are then placed over the mediastinal incision and the chest tubes incision, and the driveline exit site.

Orthotopic implantation of right ventricular assist device is a little different from that of left ventricular assist device. The right ventricle has no well-defined apex where a VAD could be connected. There are still some controversies about the site for the inflow cannula. At present time two options exist for the inflow cannula site:

(1) free wall of the right ventricle, (2) right atrium. The optimal position for the inflow cannula of assist device is on the free wall of the right ventricle (at the point of maximum distance from the ventricular septum). With the guidance of transesophageal echocardiography, the inflow is placed in the right ventricle and secured as described for LVAD, with two additional silicone rings (total 5 mm thickness) to prevent the inflow cannula from entering too long into the right ventricle [49]. The inflow cannula can also be placed into the right atrium at the upper lateral wall with a purse-string suture [51]. The outflow graft is anastomosed end-to-end to a smaller vascular prosthesis in order to reduce the diameter of the outflow graft from 14 to 10 mm. The 10 mm graft is then anastomosed end-to-side to the main pulmonary artery [50, 51].

5.5 Discussion

The pulsatile blood pumps can provide the physiological blood flow, which may benefit the perfusion for the cardiovascular system because the pulse pressure is related to endothelial production of nitric oxide and vasodilation. However, these volume displacement pulsatile pumps are no longer in use for implantation mainly due to its large size, and the need for abdominal implantation [4].

Since pneumatic drive pulsatile pumps are extracorporeal, they are usually used as a short-term mechanical system, providing left, right, or biventricular support for patients whose hearts have the potential for recovery. Furthermore, this pneumatic drive pulsatile pumps could constantly optimize the pump performance to adapt to changing patient conditions through continuously monitoring air flow and the computer control [52].

The implanted pulsatile pumps are usually used for long-term circulatory support and driven by electromagnetic motors. If a blood chamber is actuated by a cam and a torque motor, and a pair biological valves are used to ensure unidirectional flow, rare thrombus formation can be observed inside the pump, achieving low anticoagulation regimens [13]. Furthermore, the plasma-free hemoglobin was less than 10 mg/dl at all measured time points for each test animal during 30 days in a valveless counterpulsation blood pump published by Giridharan et al. [53]. These results suggest that the pulsatile pumps have the capability to minimize the blood trauma. Considering severe adverse complications in the continuous blood pump therapy, the volume displacement pulsatile pumps merit the further investigations due to the potential minimal blood trauma.

The implanted pulsatile pumps could be actuated either by a low-speed torque motor or by a linear motor. When pulsatile pumps are driven by a torque motor, a movement converter such as a cam is required to obtain pulsation. The cam can provide a precision control on the blood ejection process, but it increases the complexity of the movement converter, reducing the reliability and increasing the pump size [28]; when a linear motor is used to actuate the blood chamber, the pulsatile pump has a simple structure with a long duration and fast response for

synchronization, but the linear motor under electromagnetic principle is hard to control the blood pumping process, resulting in the blood trauma [14, 34]. These results suggest that the actuating technology difference may be partially responsible for the neurologic complications occurring significantly more often among the Novacor group, and the higher prevalence of infections and technical problems among HeartMate group. Hence the pulsatile pumps under electromagnetic principle will be difficult to achieve the small size and high reliability and low blood trauma simultaneously. This electromagnetic principle may explain why the VAD landscape has rapidly evolved away from volume displacement pulsatile technology and toward continuous rotary pumps, which also suggests that a novel actuating technology may be needed to develop a pulsatile pump with small size and high reliability and low blood trauma simultaneously.

For the volume displacement pump, the lifetime of flexible diaphragm and biological valves is initially a major concern for the long-term circulatory support because the pusher plate acting on the blood is through the polyurethane membrane, which is a polymer material between rubber and plastics. However, as the related technology continually evolves, the polyurethane membrane has achieved high elasticity of rubber and high strength of plastics, large elongation, wide hardness range, good wear resistance, good biocompatibility, and outstanding anticoagulation performance. According to the fatigue test data in the practical rubber manual [54], polyurethane membranes can flex more than 300 million times, equivalent to 8 years of normal heartbeat. Hence the flexible diaphragm made from polyurethane membrane has an enough lifetime for the long-term support. Biological valves are valves of animals, like pigs, which undergo several chemical procedures in order to make them suitable for implantation in the human heart. Since the use of biological valves in the blood chamber is expected to significantly reduce the incidence of bleeding and thromboembolism, a biological valve does not require anticoagulation. Because biological valves are subject to structural valve degeneration after 10 years [55], their lifetimes could achieve the long-term support of the volume displacement pump. Hence the volume displacement pulsatile pump has potential to regain the attention for the development of VADs.

5.6 Conclusion

The Berlin Heart EXCOR is the only VAD for babies and children with severe heart failure, which is awarded approval from the U.S. Food and Drug Administration (FDA) in 2011. And pneumatic pulsatile VADs are mainly used for short-term assistance. Currently, electromagnetic pulsatile pumps are seldom used in clinic. However, the rare blood trauma of pulsatile HeartMate XVE and the high thrombosis in pulsatile Novacor indicate that precise blood flow control and biomaterials are both important factors to reduce blood trauma. The long-term duration of pulsatile Novacor shows that simple and reliable mechanism is the key to the long lifetime of the VADs. The existing problems of pulsatile pumps such as large size and related

adverse complications are mainly associated with the principle of electromagnetic driving, rather than the pulsatile or continuous blood flow itself. Therefore, the actuator technology is also a key to artificial heart developments besides the biocompatibility of material and flow field.

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Chapter 6
Total Artificial Heart

Lu Han and Wei Wang

Abstract Total artificial heart (TAH)is an artificial organ which can be used as a bridge or destination therapy for severe biventricular dysfunction. The research attempt of TAH device has a long time. Although several TAH devices have been developed, only a few products are used in clinical. Early total artificial hearts mimicked the pumping action of the native heart. Superior biomaterials, biologic tissue valves, and coatings with drug-eluting properties could be incorporated into blood-contacting surfaces to lower risks of hemorrhagic stroke and thromboembolic events, but large size and limited durability adversely affected recipients' quality of life. Inspiring ventricular assist device, a new research orientation is rotary TAH device with continuous flow, but it is ambiguous whether humans can tolerate the long-term absence of pulsatile blood flow. In this chapter, we will give a brief description about the total artificial heart, where they are needed, how they are designed, performance, limitations and introduce some famous TAH devices. It is decided that the TAH devices can improve the survival of patients with biventricular dysfunction. And new technique and innovation will extend its application.

Keywords Total artificial heart · Heart failure · Destination therapy

6.1 Introduction

Total artificial heart (TAH) is an artificial organ to replace the function of heart. TAH can be used as a bridge to transplant or occasionally as destination therapy (DT) for patients with severe biventricular dysfunction. We supposed heart replacement device could provide a needed choice as a destination therapy for patients with end-stage heart failure.

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Heart failure is a progressive and often fatal pathology among the main causes of death in the world. Cardiac transplantation is an effective treatment, but shortage of donor organ has limited the result of its widespread implementation. For the past 20 years, only less than 5000 hearts have been transplanted annually, a small part of patients have got help from this technology [1]. Patients who are not suitable for transplantation and who have suffered only the left ventricle can be treated with a permanent left ventricular assist device (LVAD), and a few patients have had implanted LVAD for more than one decade. Nevertheless, many patients have severe HF with two ventricles involved or other pathological states that would not benefit from only LVAD implantation, such as intractable HF and large recent infarctions, refractory arrhythmias, post-infarction ventricular septal defects, and valve problems. These patients would be helped with the implantation of self-contained, energy-efficient, durable TAHs.

6.2 Origin

The need for a practical mechanical replacement for the failing human heart has motivated scientists and clinicians for more than 70–80 years. However, it was not until 1957 that a TAH was completely implanted by Akutsu and Kolff. This is a milestone in the research of TAHs [2].

The first TAH device which was applied to clinical is Liotta–Cooley TAH (Akutsu III). In 1960, Liotta had developed several different types of blood pumps. Three types of them were applied for animal experiments. The third type pump was named Akutsu III. It was successfully implanted into a calf, which is supported for 90 min and died of pneumonia and sepsis [3]. In 1969, it was reported by Cooley a biventricular support device was used as a heart substitute to bridge a 47-year-old male to transplantation. The patients survived 39 h post-transplantation. The compressed air and inflatable air sacs were used to displace and push the blood. A smooth, multisegmented polyurethane was made of the blood-contacting surfaces, and four carbon-pyrolytic tilting disc valves were integrated in the two sacs to control the blood direction. In 1981, the Akutsu III TAH was used as a bridge to transplantation in a patient aged 36 years who had developed refractory ventricular fibrillation after undergoing coronary artery bypass grafting surgery. The TAH provided adequate hemodynamic support, but unfortunately, 24 h later, the patient developed profound hypoxia and supported with venovenous extracorporeal membrane oxygenation. It was supposed that the pulmonary venous was obstructed by the device. The patient was supported for 55 h until transplantation. The patient passed away 1 week later because of multiorgan dysfunction. Because of improved materials, hemolysis was not observed during the period of implantation.

6.3 Classification

According to the operating principle, total artificial heart devices can be divided into two types: positive-displacement and rotary hydraulic. Early total artificial hearts mimicked the pumping action of the native heart. These positive-displacement pumps with diaphragm could provide adequate hemodynamic support and maintain the human circulation for short periods (such as SynCardia TAH, AbioCor TAH, CARMAT, 3M TAH, and Nimbus TAH), but large size and limited durability adversely affected recipients' quality of life. Hydraulic pump which has a rotary part can be divided into indirect hydraulic and direct hydraulic. Indirect hydraulic pump is still large for its complex transmission. Subsequent research into left ventricular assist devices led to the use of direct hydraulic pumps with rotating impellers. The rotary TAH device is continuous-flow blood pumps (CFTAH, such as BiVACOR and SmartHeart). According to power mode, there are also two types: pneumatic and electric. The electric pump, which uses power from a transcutaneous energy transfer (TET) system, can reduce the chance of infection. Although several TAH devices have been developed, only a few products are used in clinical. Researchers have attempted to integrate this technology into modern total artificial hearts with moderate clinical success.

6.3.1 Positive-Displacement Pumps

6.3.1.1 SynCardia TAH

6.3.1.1.1 Design

The SynCardia TAH (SynCardia Systems Inc., Tucson, AZ, USA) is a pneumatic-driven, pulsatile, partially implantable system. Its predecessor was the famous Jarvik-7 TAHs [4]. Renamed CardioWest in 1993, it is the famous TAH which is applied to clinical. The Jarvik-5 and Jarvik-7 TAHs were developed by Kolff and Jarvik of the University of Utah. As with the Akutsu III TAH, the Jarvik 7 was constructed from multisegmented polyurethane and had four Björk–Shiley tilting valves. SynCardia TAH is a pneumatically driven TAH that replaces the failing native ventricles. The prosthetic ventricles are made. At the beginning, SynCardia TAH volume is 70 ml and 100 ml. It can be selected according to the patient's body surface area. The prosthetic ventricles are made of polyurethane and are attached to the left and right atria. Four monodisc mechanical prostheses (Medtronic-Hall, Medtronic Inc) were used to provide a unidirectional blood flow. The volume of one ventricle is 70 ml and each ventricle comprises a silicone diaphragm to separate blood from the pneumatic chamber. The pulsed injection of compressed air allows the movement of the diaphragm, thus filling and evacuating both ventricles, which are connected to an external console via two drivelines (Fig. 6.1), [5].

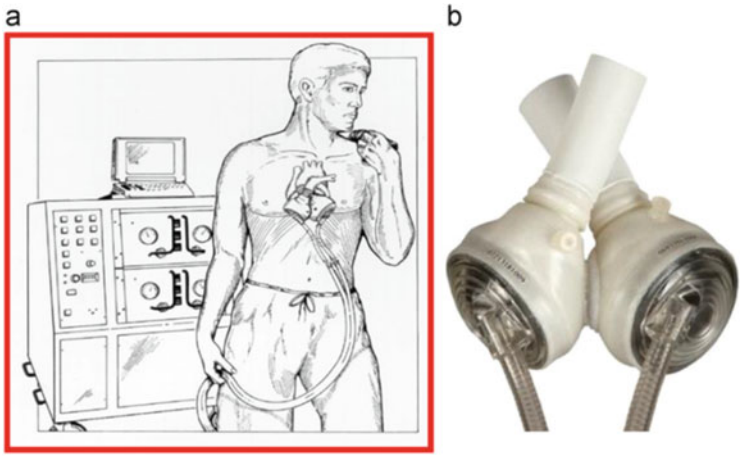

Fig. 6.1 Syncardia TAH system. Reprinted from Journal of Biomechanics, 46, Marvin J. S. et al. The Syncardia™ total artificial heart: in vivo, in vitro, and computational modeling studies, 266–275., Copyright (2013), with permission from Elsevier

6.3.1.1.2 Clinical Application

The Jarvik-7 TAH achieved the U.S. Food and Drug Administration (FDA) approval for a clinical trial as a device for destination therapy. Thus, Dr. William Devries implanted the third TAH in human at the University of Utah in 1982. A Jarvik-7 was implanted into Dr. Barney Clark; he lived for 112 days after the procedure. Another recipient of the Jarvik-7 was William J. Schroeder in 1984. He lived for more than 20 months. In August 1985, this TAH achieved a successful BTT in the University of Arizona Medical Center (UAMC).

After installed for 198 people, the Jarvik-7 was no longer available for clinical implantation in the USA. Totally, it was successfully bridged 143 people to transplant. In 1993, it was re-approved by FDA as the name of CardioWest. Subsequently, it renamed as SynCardia TAH.

Various iterations of the SynCardia temporary TAH have subsequently been implanted in over 1300 patients worldwide, around 80% of whom have been successfully bridged to heart transplantation (1-year survival is 70%). In North America, 373 total artificial heart implants are recorded in the INTERMACS database [6]. With improvements in implant technique and device characteristics, quite a few number of patients receive TAHs and viable length of durable support has increased. Till now, the longest worldwide record of pre-transplant patient survival duration with TAH support is 1374 days. More widely patients with heart failure from different countries have been benefit from this product.

6.3.1.1.3 New Development

As a therapeutic alternative for smaller patients, such as women and children, Symbion developing a smaller version, called the SynCardia 50 recently [7]. A 6.1 kg portable miniature compressor can work continuously for 3 h on fully charged batteries. This technique has improved quality of patient's life by enabling them to join certain kinds of activities, such as ambulation or bike riding, that would not be realized with compressors of previous version [8].

The reduced volume (50 ml) version has achieved approval from FDA in 2013 for bridge to transplant and permanent substitute for patients, having a body surface area of 1.2–1.79 m^2, at high risk of imminent death. In June 2014, SynCardia's newly designed freedom portable driver for TAH recipients received the FDA approval for the clinical use. According to the case report, an 11-year-old child had survival of 4 years after implanting the SynCardia 50 TAH.

6.3.1.2 AbioCor TAH

6.3.1.2.1 Design

The design of AbioCor TAH (ABIOMED, Inc., Danvers, MA, USA) was a pulsatile one with a fully implantable configuration with no protrusions through the skin. The AbioCor device and system components were shown in Fig. 6.2 [9]. This TAH, which weighs about 1 kg, is made of biocompatible titanium and polyurethane materials. A miniature centrifugal pump was integrated within the TAH. In this pump, the polyurethane chamber was forced by a pressurized, low viscosity, hydraulic fluid to eject blood from these chambers. A two-position switch valve controls the release of the hydraulic fluid and modulates the sac filling pressure, thus generating two ventricular pressures. The valve and hydraulic pumping system alternates at rates of 75–150 positions per minute resulting in a pulse rate of 75–150/min. With the robust drive system, the device is able to have the cardiac outputs of 4–8 L/min. A transcutaneous energy transfer (TET) system would provide the energy to the AbioCor. The TET drive system reduces the risk of postoperative infections and other complications that often result from a tether or drive line exiting the thorax.

6.3.1.2.2 Clinical Application

More than a 12-year period, AbioCor® devices were implanted into 120 calves; the latest version of these devices were constructed with the electrohydraulic converter and autonomous pressure equalization system. In the study, several of the animals survived more than 90-day period and could have some kind of work on a motorized treadmill. Formal design readiness testing was begun in 1999, and more than 200 devices were manufactured [10].

Fig. 6.2 AbioCor. Reprinted from The Journal of Thoracic and Cardiovascular Surgery, 127, Robert D D. et al., Initial experience with the AbioCor implantable replacement heart system, 131–141., Copyright (2004), with permission from Elsevier

The 14 patients who were implanted with the AbioCor between 2001 and 2004 lived for an average of only 5 months. All the patients were men who weighed 84–120 kg and, therefore, could accommodate the large size of the device. Of these patients, two died from hemorrhage and one from air embolism perioperatively. And other six cases died from multiorgan failure in 9 months after the implantations. The remaining five patients survived for 9–15 months, but died from various complications such as stroke, infection, or organ failure, except the longest-survivor, in whom the device failed because of ruptured membrane.

In 2006, the U.S. FDA approved use of the AbioCor TAH under the Humanitarian Use Device (HUD) provision for DT. No serious complications related to the transcutaneous energy transfer system were reported. Then, AbioCor was developed to decrease the overall size. However, it was deemed commercially unviable and prohibitively difficult. AbioCor study enrolment was suspended.

6.3.1.3 CARMAT

6.3.1.3.1 Design

The CARMAT® TAH (CARMAT, France; Fig. 6.3), which is under development by Carpentier and colleagues, comprises a prosthetic design that is part bovine and part machine [11]. It is similar in principle to the AbioCor® TAH. Distinguished from the AbioCor, the CARMAT® TAH has four pericardial biomembranes [12]. In

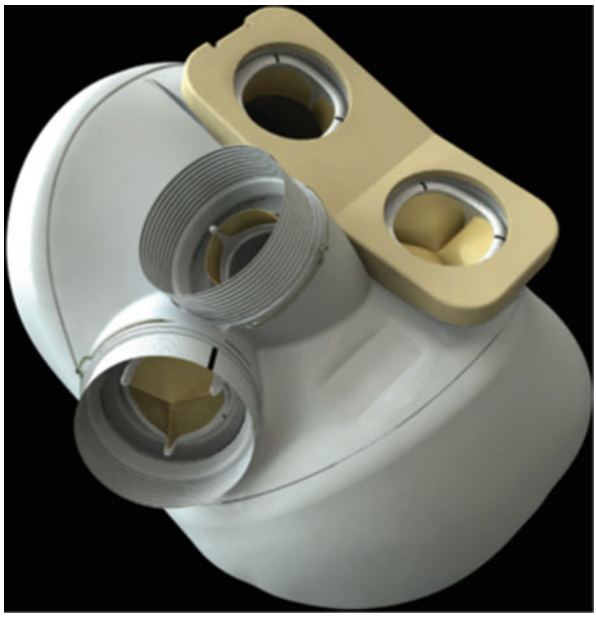

Fig. 6.3 CARMAT. Reprinted from JACC: Heart Failure, 5(12), Brittany N. Weber et al., Evolving Areas in Heart Transplantation, 869–878., Copyright (2017), with permission from Elsevier

every chambers, the flexible membrane acts as a divider and keeps hydraulic fluid and blood on each side. The fluid is driven into and out of the chambers, making the membrane to deflect and displace the blood. To improve biocompatibility, the blood-contacting surface of the flexible membrane is lined with the pericardial tissue of a bovine heart. Incorporation of cardiac tissue into the bioprosthetic valves, a set of sensors that enables to measure flow and pressure in the device, and a specially designed control system can detect the patient's level of physical activity and make necessary adjustments of the TAH to change the pressure and cardiac output. This TAH is able to deliver a pulsatile flow of about 2–9 L/min with flow adjustment capabilities on the pulmonary side related to the bronchial shunt [13]. It is reported that the device is approximate heart size and has an external power supply and driver unit. It is shown in the benchtop experiments that the device had a low platelet adhesion and minute blood cell deposition in the blood-contacting surface of membrane in comparison to other membrane. However, because the device is incorporated with biological tissue, the mechanical durability is not so long. This disadvantage limits the long-term use of this device. The pump rate and output can be autonomously regulated in response to activity level and physiological factors of the patients because of multiple sensors integrated in the TAH. The microprocessor, cooled by silicone oil hydraulic fluid, that controls the device is also integrated into the pump housing. The device is quite large and heavy (1 kg), but computer-aided design helped it to have an anatomical fitting shape. The studies have predicted that it will fit 85% of men and 65% of all patients.

6.3.1.3.2 Clinical Application

In December 2013, the Carmat TAH began clinical trials in Europe; the first patient to be supported by this TAH survived for approximately 75 days. After other clinical data were reported, the device has been certified by the U.S. FAD by 2016. The C-TAH was implanted in two male patients, aged 76 years and 68 years.

6.3.1.4 ReinHeart

ReinHeart TAH are developed in ReinHeart (Bad Oeynhausen, Germany) and the Helmholtz Institute, RWTH-Aachen University (Aachen, Germany). A reciprocating piston is a major generator to alternately compress two polyurethane sacs as the substitute of left and right ventricles. In order to improve durability, the device has a voice-coil and linear actuator combination as the substitute of a screw and roller bearings. The stroke volume of the device is 50 ml, a little smaller than a normal heart, and, therefore, the TAH had the size of 84 × 90 mm and the weight 923 g. An implantable compliance chamber allows passive filling of the sacs, which provides a degree of inherent passive flow balancing. In animal experiments, the researchers achieved a maximum output of 7 l/min and the longest working duration was 50 h.

6.3.1.5 Other TAH Systems Currently under Development

6.3.1.5.1 Sarns-3 M TAH

Sarns-3M TAH (3M Health Care, USA, and Pennsylvania State University, University Park, PA, USA) that was designed by pioneering innovator Dick Sarns is a type of positive-displacement total artificial heart. It is an electric pump, in which a reciprocating brushless direct-current motor and translating roller screw were used to alternately actuate both sides pusher plates. The systemic and pulmonary blood sacs made from seamless polyether polyurethane urea were alternately compressed to provide stroke volumes of up to 90 ml. However, this type of TAH has not reported for clinical use.

6.3.1.5.2 Nimbus TAH

The Nimbus TAH is a positive-displacement total artificial heart (Nimbus, USA, and Cleveland Clinic, Cleveland, OH, USA). A brushless direct-current motor and gear pump were used to generate hydraulic pressure, which actuated a hydraulic piston. A spool valve redirected hydraulic fluid to reverse the piston direction. On both ends of the reciprocating piston were flat plates that alternately compressed systemic and pulmonary blood sacs, but the plates and sacs were not attached in order to allow passive filling, as in the Sarns-3M TAH. The hydraulic mechanism was positioned in

the 21 mm space between the blood sacs, which was vented to an intrathoracic compliance chamber filled with air. The blood-contacting layer of the pumps was covered with a seamless coating of glutaraldehyde cross-linked gelatin with effective biocompatibility. The coating was designed to eliminate the need for systemic anticoagulation. Four bovine pericardial tissue valves (or, in some iterations, human dura mater valves) were integrated into the two blood sacs as left and right ventricles. The outer shell of the device was made from epoxy reinforced with carbon fiber.

The hydraulic cylinder stroke length was 13.2 mm, and the stroke volume was up to 64 cm^3, but the routine operating stroke volume was 53 cm^3. Maximum output was 9.6 L/min at 150 bpm. As with the Sarns-3M device, in mock circulation loop testing the Nimbus TAH could maintain the balance between systemic and pulmonary circulation, and it would autonomously increase pump output when left atrial pressure rose (0.5 l/min/mmHg). The device was implanted in 12 calves, which survived for an average of 32 days (the longest 120 days). Several animals could exercise on a motorized treadmill for an average of 22 min. Despite these encouraging results in lab, many experiments had to be terminated prematurely because of mechanical failures of this device and, ultimately, the device could not get the approval of clinical utility.

6.3.2 Continuous-Flow Design

6.3.2.1 BiVACOR

The BiVACOR (BiVACOR, Inc., Houston, TX, USA) is a TAH that utilizes third-generation magnetic suspension technology. The device, which has both the axial length and the diameter of 60 mm, can be implanted into smaller patients with a BSA less than 1.5 m^2. In vivo, it can provide above 20 L/min to full support the systemic and pulmonary circulatory systems under different cardiac condition, even in the absence of the heart. The BiVACOR has only a disc-like, single rotational component with a set of specially designed blades on two sides of it. Basically, this configuration is a double-sided centrifugal impeller having only one motor to drive both impellers rotating at the same speed. The rotor is levitated within the device housing by an active magnetic suspension system [14]. An electromagnetically coupled motor controls the rotation of the impeller. Movement of the impeller within the pump domain inversely alters LVAD and RVAD outflow. In in vivo studies, the outflow alterations match flow requirements for pulmonary and systemic circulations, while adequate atrial filling pressures were maintained. The controller of the BiVACOR utilizes the Frank–Starling law to balance flow with the change of inlet and outlet pressures. The axial positioning of the impeller would be automatically adjusted to accommodate the changes in order to balance physiological two sides' pressures and flow conditions. This device showed low thrombus formation in experimental testing of calf implantation [15].

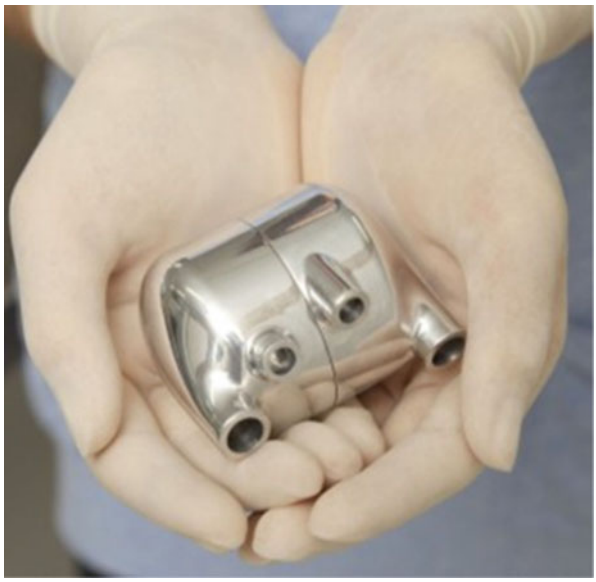

Fig. 6.4 BiVACOR TAH. Reprinted from JACC: Heart Failure, 5(12), Brittany N. Weber et al., Evolving Areas in Heart Transplantation, 869–878., Copyright (2017), with permission from Elsevier

Unlike other TAH devices, the BiVACOR can be accommodated in both adults and children because of its small size, as opposed to having two separately sized models. The device is still being developed in the preclinical phase (Fig. 6.4).

6.3.2.2 SmartHeart

SmartHeart, a valveless, sensorless, pulsatile, continuous-flow total artificial heart, was developed by Cleveland Heart. The most difference between the CFTAH and the assisted device is the number of the impellers [16, 17]. CFTAH almost is designed with two reversed impellers. This total artificial heart (CFTAH) supplying continuous-flow support incorporates second-generation drive technology having only one hydrodynamic bearing. It is constructed of durable, biocompatible titanium and plastic materials and has a diameter of 6 cm and length of 10 cm. This TAH, having a single drive motor and power cable, combines the capability of a left ventricular assist device (LVAD) and a right ventricular assist device (RVAD) into one unit. The impellers that support the systemic and pulmonary circulation are mounted to the opposite ends of the rotor, which can move axially. In order to generate pulsatile flow conditions, it was designed an algorithm to apply oscillating rotational speed impulses. And the CFTAH can provide self-regulation of the relative performance of the left and right side to balance pump inlet pressures. The common causes of its failure rates are durability and batteries of the rotary pump [18–21].

The heart supported by continuous-flow pulsatile blood pump has experimented in calf. Human fitting studies with a mock pump at heart transplantation showed that

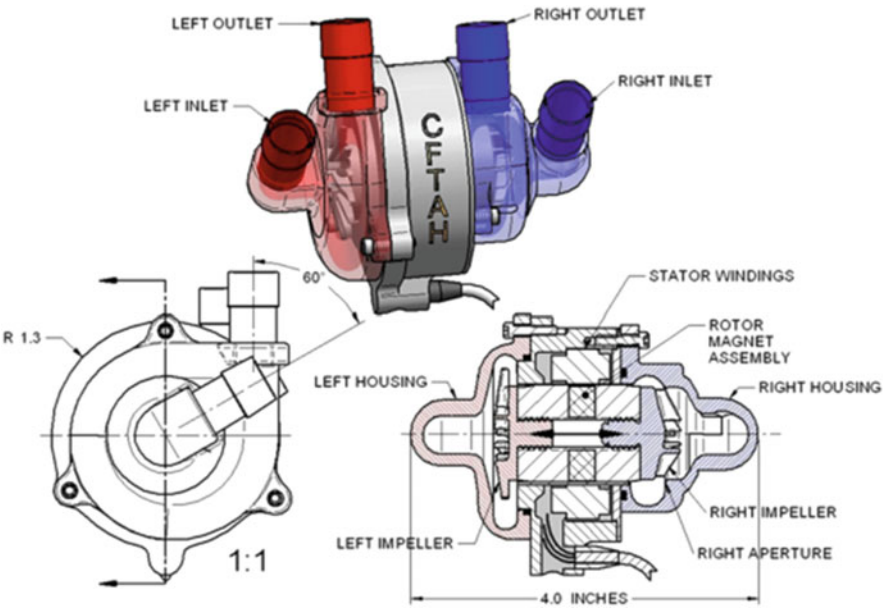

Fig. 6.5 Continuous-flow total artificial heart (CFTAH) pump configuration. Reprinted from The Journal of Heart and Lung Transplantation, Vol(29), Kiyotaka Fukamachi et al., An innovative, sensorless, pulsatile, continuous-flow total artificial heart: Device design and initial in vitro study, 13–20., Copyright (2010), with permission from Elsevier

it has the proper orientation for human great vessels in the current configuration used in in vivo calf studies. Both in vitro and in vivo studies have demonstrated the ability to self-regulate in response to different physiologic conditions. Producing physiological pulsatile blood flow via electromagnetic control is subsequent to focus on [22, 23] (Fig. 6.5).

6.4 Future Prospective

The TAH devices can improve the survival of patients who suffer biventricular dysfunction. Current TAH designs still need much room to be improved to meet the physiologic challenges and ameliorate the complications, such as hemorrhagic stroke, thromboembolic events, neurologic injury, and infection due to the bulkiness of the device and bacteria entering the tissue through the percutaneous line, which may lead to local or systemic immune response. Some TAH designs could also limit activities such as ambulation by having a large drive console or a heavy portable unit; it is well known that patient ambulation could improve the outcomes and overall survival rates. Whether TAH technology advances to the point, where it

becomes a viable alternative to transplantation, remains to be seen. There are several challenges to overcome [24–28].

1. The general chanllenges are as follows: to achieve an adequate durability (>5 years), to minimize thromboemboli and hemolysis, to be more efficiency, to maintain pulmonary-systemic circulatory balance and, to reduce size to accommodate in women, small adolescents and children.
2. Greater autonomous balance between pulmonary and systemic flow intrinsic to rotary pumps might lead to rotary TAHs succeeding there, where the previous attempts have failed.
3. The future step is the development of bioartificial engineered hearts; however, a number of technological barriers remain before a bioartificial heart can move towards preclinical testing and eventually to clinical application [29].

It is still not clear whether humans can tolerate the long-term non-pulsatile blood flow. Several studies indicate that long-term absence of pulsatile support is a viable option based on clinical experience from the implantation of left VADs that support the circulation in parallel with the native systemic ventricle. However, in most patients with LVADs, total assistance of the systemic ventricle is rarely seen, and the ventricular contraction forces a portion of the pulse wave, even much less than normal, through the VAD during each beat. Further study regarding the viability and feasibility of long-term complete continuous-flow conditions would be helpful when new type TAHs and BiVAD configurations are developed and implemented, respectively. In addition, mechanical and technological limitations of the latest version of TAH include a risk of membrane rupture and valve failure in pulsatile devices, higher power consumption than that of VADs, and patient size constraints due to device bulkiness [30, 31]. New technology will advance the state-of-the-art in TAH and VAD development and address design limitations for a wider population of patients. Refined anticoagulation schemes could be devised for those devices to decrease the risk of hemolysis and thrombosis. The smaller size, longer durability, and less power consumption inherent to rotary blood pumps might result in rotary TAHs succeeding where earlier experiments were failure in providing a practical replacement for the human failing heart [32, 33].

The utilization of new materials and design of construction will ensure that the drive consoles and wearable adjunctive components are safer, lighter, more reliable, more portable, and suitable for a wider range of patients—from infants to adults, males to females. Wireless technology has been adopted to develop new TET power systems. It is possible to use a coplanar inductive coupling energy system, or high efficiency resonant coupling unit using magnetic fields so as to address driveline issue and decrease power consumption. Other solutions include new designs that acquire the same function in a smaller size and more compact construction, and thus could be employed to achieve circulatory support for a wider patient population [34]. As compared to the pulsatile configuration, the unique coupling of continuous-flow blood pumps with only one or two moving parts avoids to use mechanical valves and membrane that could fail or rupture. In addition, superior biomaterials, biologic tissue valves, and biocompatible coatings with drug-eluting properties

could be integrated into blood-contacting layer to ameliorate risks of hemorrhagic stroke and thromboembolic events.

Last but not least, the real-time monitoring of TAH devices will be significantly improved through telemedicine with implanted sensors by WiFi or 5G technology to report motor currents, flow rates, magnetic bearing currents, and impeller positions. Incorporation of such innovative features in the next generation of TAHs will have better clinical patient outcomes and improve the overall clinical management of patients with biventricular failure.

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Chapter 7
Evaluation of Artificial Hearts

B. Y. Su and L. P. Chua

Abstract Due to the shortage of heart donors, ventricular assist device (VAD) has been developed as a temporal or permanent cardiac support. Essentially, a continuous flow VAD is a rotary pump to maintain blood supply. In addition to hydraulic efficiency and output power, the blood damage induced by a VAD must be minimized to mitigate potential complications. It has been found in the literature that the blood damage is closely related to detailed flow field, which could only be visualized by experimental measurements and computational fluid dynamic (CFD) simulations. During the development of a VAD, CFD is widely used for optimization, and several numerical models have been proposed to estimate blood damage level. In this chapter, we demonstrated a typical study of an axial flow VAD. The physical model included a straightener, an impeller, and a diffuser, and several designs of diffuser were numerically modeled for optimization in terms of hydraulic and hemodynamic performances. To validate numerical results, experimental measurements at different regions were conducted using particle image velocimetry (PIV). It is worth noting that similar procedure would be applied to a centrifugal blood pump. Before clinical application, animal and clinical trials must be conducted to examine its actual blood damage level and other potential issues, which are valuable for next iteration of design if needed.

Keywords Computational fluid dynamics · Artificial hearts · Hemodynamics

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7.1 Introduction

Due to the modern hectic and unhealthy life style, such as obesity and lack of exercise, there are more people engaging heart disease than before. Some of them may lead to even heart failure and required heart transplant as a last mean to keep them alive. However, the available heart donors are always lacking far behind the demand of the healthy hearts over the world. Luckily with the advance of technology, artificial heart pumps are invented and improved over the time as an alternate mean to help these heart failure patients. Mechanical circulatory support devices can be categorized into total artificial heart (TAH) and ventricular assist device (VAD), and the latter is more widely implanted than the former, especially at the left ventricle (i.e., LVAD). The VAD has been considered as a useful therapeutic modality for bridge-to-transplantation, bridge-to-recover, or even long-term cardiac support [1, 2]. Nevertheless, either one of these two devices (LVAD and RVAD) can be used to bridge across the semilunar valve by connecting the inlet to the ventricular device directly so as to provide energy to eject the blood. On the other hand, the inlet cannulation of left VAD can be placed at the apex with the outlet connected back to aorta, and the inlet of right VAD is located at the superior vena cava with blood ejected to the left pulmonary arteries through outlet. In general, the continuous flow VADs are based on the spinning of a rotor to provide the required energy, that is why they are being named as rotary pumps, with the two most used types are centrifugal and axial pumps. The centrifugal pump has a much bigger size than the axial pump. Centrifugal flow pumps are suitable to generate higher pressure and lower flow rates, whereas axial flow pumps are usually used to generate lower pressure and higher flow rates [3]. The axial pump has also much higher rotating speed than the centrifugal pump, in the long run, the blood may prefer much lower speed of centrifugal pump, which is closer to the nature of the blood flow, but more data is required to prove it. Besides the conventional hydraulic design, the hematologic design has to be considered due to the blood is the fluid being used. Although up to now, the real physiological mechanism of hemolysis and thrombosis processes is not fully known, the scientists are interpreting them from the physics point of view. The hemolysis is due to the shearing effects, it is then connected to the shear stress and the duration of exposure time using the power law, while the formation of thrombus is fluid mechanics related e.g., the stagnation flow, recirculation, and flow separation. Therefore, these phenomena should be minimized or even eliminated if possible, besides the more complicated physiological and biological factors. During optimization phase, computational fluid dynamics (CFD) is a popular tool to numerically estimate both hydraulic and hemodynamic performances before the much expensive prototype fabrication and testing. After the CFD simulation, the experimental validation is necessary, and there are many techniques available such as flow visualization (FV), Laser Doppler anemometer (LDA), and particle image velocimetry (PIV). Each technique has its advantages and limitations. A standard hemolysis test is now used to measure the damage of blood caused by the artificial heart pumps such as the axial and centrifugal pumps for the animal trial, and the

Normalized Index of Hemolysis (NIH) for example is one of the few parameters to indicate the level of blood damage.

7.2 Pulsatile or Non-pulsatile Circulation

In nature the human heart can be treated as a pulsatile pump, and the blood being ejected will flow in both pressure and volumetric waveforms. It is then created a fundamental question to the scientists to answer whether it is a must to keep the arterial pulsation in order to maintain enough blood flow and aerobic metabolism for all the essential organs. Since most artificial hearts are basically miniature rotary pumps, pulsatile circulation indicates the necessity of varying rotating speed during cardiac cycle. In contrast, constant rotating speed can only produce non-pulsatile circulation.

A relatively large amount of study has been carried out in connection with the hemodynamic effects on the pulsatile versus non-pulsatile circulation in animals including human being. The pulsatile perfusion creates advantage on peripheral organs, which is very likely mediated by its effect on systemic vascular resistance and the microcirculation. The pulsation improves splanchnic perfusion and plays an essential role in the movement of lymph in and out of the intestine, the prevention of edema, and the maintenance of capillary patency through the prevention of sludging. The brain microcirculation and cerebrospinal fluid movement are shown to be improved with pulsation, which was also found to improve aerobic tissue metabolism.

Wesolowski et al. [4] have challenged the necessity of maintaining pulsatile circulation in 1953 and successfully kept the circulation and normal organ function for a brief period using non-pulsatile blood flow. The continuous flow implantable DeBakey VAD device has been adopted by Potapov et al. [5] to detect the flow in peripheral vessels and measured transactional Doppler signals in patients after implantation. They [5] have shown that patients with severe heart failure can maintain their lives with the continuous flow VAD. The use of DeBakey VAD resulted in normal organ function and provides unloading of the left ventricle, which can lead to partially restore myocardial function. It has been shown that despite the non-pulsatile flow produced by DeBakey VAD, the pressure changed due to contractions of unloaded left ventricle and the partially recovered right ventricle provided a nearby physiological pulsatile flow. The first clinical experience with the DeBakey VAD is positive and leads to its continuous use. Statistical data indicates that DeBakey VAD has supported over 200 patients at 14 different heart centers and in 7 countries around the world [5]. The mean flow rate for these trials ranged from 3.6 to 5.0 L/min, and cerebral blood flow and, furthermore, organ function were maintained with few signs of hemolysis and thrombosis [6]. Garatti et al. [7] compared the pre- and post-transplant outcomes between pulsatile and non-pulsatile flow VADs and they concluded that the continuous flow pumps were as effective on bridging to transplantation rates, mortalities, and post-transplant

incidences of treated rejections when compared to pulsatile pumps. Although there is no clear conclusion, non-pulsatile circulation has been widely employed in the clinical setting of cardiopulmonary bypass or circulatory support [8]. In terms of design of artificial heart, it is acceptable to set certain constant rotating speed that can generate enough pressure head and flow rate.

7.3 Blood Trauma

7.3.1 Hemolysis

Hemolysis is defined as the breakdown or destruction of red blood cells (RBCs), and the released hemoglobin (Hb) may activate platelet activation and coagulation cascade. Therefore, the continuous lysing or destruction of RBC can weaken its ability to transport oxygen. An obvious pinkish color can be found in the serum due to hemoglobin, when only a small amount of 0.5% of RBCs are being destroyed. This has enhanced the chance to cause renal failure since an excess of plasma-free hemoglobin is toxic [9]. The use of artificial heart pump on patients has inevitably enhanced the chances of physical contact between the blood and solid pump surfaces of the device, which will cause mechanically RBCs rupture, even the applications of artificial heart valves and the hemodialysis treatment as well as the usage of the heart-lung support machine during, for example, bypass operation will have the similar effects and results [10]. Minimal blood damage is therefore an important pre-requisite and demand of artificial heart and even valve devices. Hemolysis is an essential and sensitive indicator of blood trauma, and in vitro assessment provides valuable parameters and feedback for optimization of VAD design features such as blood contact surface finish, pump blade shape, and blood flowing clearance during prototype development. It is therefore very important to be able to predict the mechanical hemolysis which can be concluded to be a very critical parameter and issue for the design and application of VADs.

7.3.2 Thrombus

The final product of the blood coagulation step is blood clot and is named as a thrombus, which is very essential and important to predict thrombus formation for designing and finally production of any medical devices with blood flow. Compared with hemolysis, the mechanism of thrombus formation is much more complicated and there are many complicated processes to induce thrombus in blood flow [11]. Whenever there is a damage of blood vessel, platelets and von Willebrand Factor (vWF) will stick to the wall. After platelets react with collagen, fibrinogens react with them under the proper shear rate and clots are generated by platelet, vWF,

and fibrinogen. These aggregations are called thrombus in vivo. In artificial organs, especially rotary VADs, these aggregations can be found at wall and other parts.

It was observed in animal studies that the shear rates of 1300–1700 (1/s) and 300 (1/s) might be corresponding to the white and red thrombus formation thresholds, respectively, and Yamane et al. [13] have proposed the following two mechanisms: (1) In the case of white thrombus or platelet aggregation, platelets are thought to be activated by high shear rate flow and to deposit on surfaces with low shear rate; (2) In the case of red thrombus or fibrin gel capturing RBCs, it can be argued that low shear rate simply induces coagulation of RBCs. In the development of various types of cardiac prostheses, Nose [12] had experienced that (1) during the first 2 weeks of postoperative period, the white thrombus likely forms inside the implanted prosthesis, and (2) after 2 weeks, all the blood contacting surfaces are pacified by proper protein so that white thrombus is more likely not to form inside for a long period of time. Kihara et al. [15] found that the usage of the anticoagulation coating, for example, 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer, can slow down the platelet adhesion, complement activation, and protein absorption, and consequently they have concluded that it is very efficient in reducing the thrombus formation.

It is found that the conditions of local blood flow can greatly affect the shape, structure, and size of thrombus. The endothelial damage may be caused by the higher shear flows, and further triggers pathological platelet clumping to the vessel wall. On the other hand, platelet aggregates with low levels of granule released from platelets or RBC response can be activated by low shear stress levels. Additionally, interactions between platelets and RBCs, platelets and platelets, or even RBCs and RBCs with a regional stagnant flow can also induce thrombus formation. Further, Ramstack et al. [16] showed that the integrity of the fibrin clot is affected by the local shear flow. It is also found by Hashimoto et al. [13] that thrombus formed easily when blood was subjected to low shear rate of less than 500 (1/s). Furthermore, Wurzinger et al. [18] showed that a low shear flow results from recirculation and vortices, which trap the cells leading to an increase in the local wall shear stress [14]. Moreover, abrupt cross-sectional widening of flow regions may produce flow separation and potentially secondary flow, creating circumstances favorable for thrombus formation.

7.4 Evaluation

7.4.1 In Vitro Measurement of Hemolysis

Hemolysis test has now been taken as a routine and standard method in the evaluation of hemolysis parameters in vitro study of rotary VADs. A schematic view of a hemolysis test arrangement conducted by Arvand et al. [15] is shown in Fig. 7.1. A reservoir bag is connected to an artificial heart pump using silicone tubes with pressure indicator and flowmeter mounted to monitor pressure heads and flow

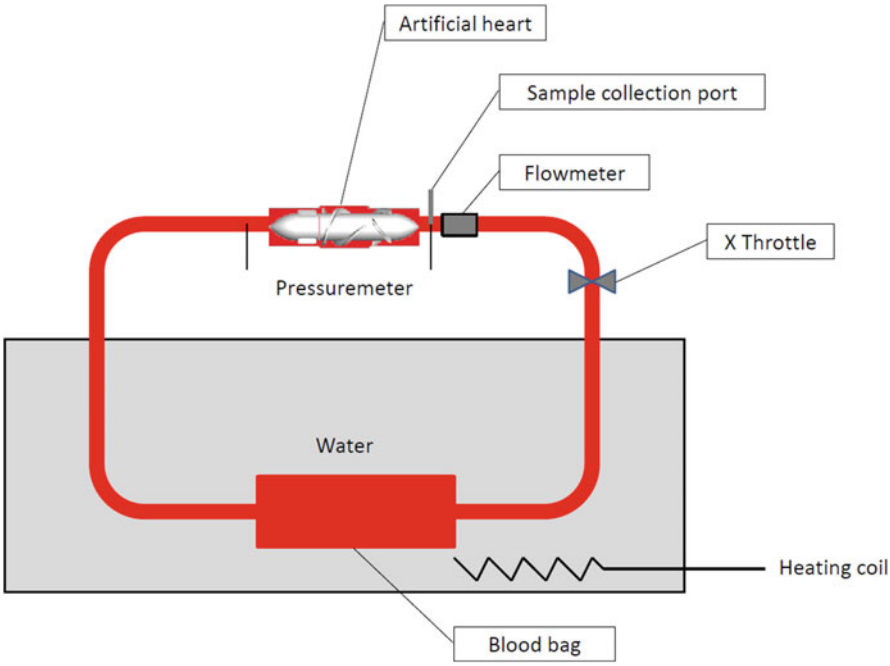

Fig. 7.1 Experimental arrangements for hemolysis tests [15]

rates of the pump, respectively. Fresh bovine blood, goat blood, or even human blood can be tested, and the reservoir bag is submerged in a warmed water bath with temperature kept constant at about 37 °C. Pressure across the pump can be adjusted using resistance throttle applied over a 10 cm length tube to minimize potential for hemolysis due to local narrowing of the tube. After the circuit is filled with the blood suspension, all visible air bubbles should be vented from the blood sampling port and no air interface remained in the reservoir. During the hemolysis test, blood aliquots are sampled from the circulating blood at a regular time interval, and the plasma concentration of hemoglobin is measured thereafter for each sample.

To evaluate blood damage from medical devices such as VADs with continuous blood flow, ASTM F1841-97 Standard [16] proposes three relations for the laboratory measurement of the damage to erythrocytes: NIH, the Normalized milligram Index of Hemolysis (mgNIH), and the Modified Index of Hemolysis (MIH). The NIH and mgNIH measure the increase in plasma-free hemoglobin in grams and milligrams per 100 L of pumped blood, respectively. The MIH, normalized by the total quantity of the hemoglobin in the volume within the closed circuit of the pump device, in a closed circuit, is used to measure the increase in plasma-free hemoglobin. The MIH is the chosen engineer measurement presentation due to it is dimensionless [9].

$$\mathrm{NIH}(\mathrm{g}/100\mathrm{L}) = \Delta\mathrm{freeHb} \times V \times \frac{100 - \mathrm{Ht}}{100} \times \frac{10^2}{Q \times T} \tag{7.1}$$

$$\mathrm{MIH} = \frac{\Delta\mathrm{freeHb}}{\mathrm{Hb}} \times V \times \frac{100 - \mathrm{Ht}}{100} \times \frac{10^6}{Q \times T} \tag{7.2}$$

where ΔfreeHb (L/min) is the increase in plasma-free hemoglobin concentration (g/L) over the time interval, V is the circuit volume (L), Ht is the hematocrit (%), Q is the flow rate (L/min), and T is the sampling time interval (min).

There are quite a number of different and controversial criteria for the cell rupture in the literatures. The mechanism of hemolysis is not fully understood; however, the following three factors listed below are generally believed that the threshold for cell lysis could be affected;

1. Measurement method. Grigioni et al. [17] commented that the orientation of the measurement system affects the shear stress being obtained, when using three-dimensional Laser Doppler Anemometer (LDA) as a measuring tool.
2. Nature of either laminar or turbulent flow. Wurzinger et al. [18] used viscometer to measure hemolysis at laminar shear stress up to 255 Pa and exposure times of 700 ms, while Sallam and Hwang [19] find out that under turbulent flow, the Reynolds shear stress can be as high as 400 Pa under the corresponding estimated exposure time of 1 ms.
3. Material used in experiment. Paul et al. [11] found that the application of the carbon ring seals has strong effect on the measured hemolysis level, as compared with the result obtained by Wurzinger et al. [18] under comparable conditions.

7.4.2 Animal and Clinical Trials

Various artificial hearts have been developed during last few decades and some have undergone animal and/or clinical trials. Due to the complexity of blood, the assumptions related to blood damage are not able to accurately estimate its responses to artificial heart pump, and thus it is compulsory to conduct such trials over certain period of time. Impella CardioSystems (Aachen, Germany) has developed a micro-axial VAD with minimal invasive treatment for the purpose of a temporary support of the left ventricle in acute situations [20]. A maximum blood flow of 2.4 L/min with pressure head of 50 mmHg when the integrated motor drives the impeller at the speed of 50,000 rpm is being designed for this pump. Due to its small size, this percutaneous pump is inserted across the aortic valve with the aid of guidewire through the femoral artery and aorta. This pump has applied to ten patients in 2006 during the high-risk percutaneous coronary interventions [21]. It was found that the free hemoglobin level increased above 1, 5, and 10 times the upper limit of the normal one in some patients. It was therefore concluded that the routine use of this device was not encouraged. The MicroMed-DeBakey VAD has been designed in cooperation with NASA/Johnson Space Center, Baylor College of Medicine, and

MicroMed Technology Incorporated. It could provide a flow rate of 5–6 L/min and a pressure of100 mmHg with the inducer-impeller running at about 10,000 rpm and requires input power less than 10 W. Calves were being operated as animal test in order to estimate the overall performance and hemodynamic effects before the clinical trial in 1999 [22]. Based on the review in 2011, this device is redesigned to reduce high incidence of thromboembolic complications [23]. HeartMate II (Thoratec Inc., Pleasanton, CA) has only one moving part and textured blood contacting surface, and it is 40 mm in diameter with a weight of 176 g. It was FDA approved in 2010 for use as destination therapy for end-stage heart failure and is the most widely implanted VAD with more than 10,000 implants globally [24].

7.4.3 Numerical Evaluation of Artificial Heart

CFD technique as a design tool has been widely adopted to simulate and analyze fluid flows within and around objects of interest, and it significantly influences the development of artificial hearts [25–27]. CFD has the ability to evaluate design promptly at early stage before the commitment being made on the very expensive prototype manufacturing and testing. At the detailed design stage, CFD can also quickly find out the effects of design changes on blood flow to totally avoid or at least reduce the risk of unexpected knock-on effects that would otherwise become obvious only at a later stage. CFD technique has been widely adopted in the development stage of any blood contacting medical device including heart valves, VADs, stents, grafts, blood access, purification devices, etc. The critical challenge for a VAD design is to combine both the hematologic and hydraulic designs optimally [28]. In particular, designers using traditional methods often do not realize that local high shear stress levels and/or flow stasis have the potential to invalidate a design due to adverse hematologic consequences. The application of CFD technique is the most promising avenue for achieving these optimization tasks [29]. When a final design has been reached, CFD analysis can be used to confirm that design goals have been achieved. Detailed CFD results of flow field can often be used to support and explain experimental results, potentially strengthening regulatory submissions and providing a scientific base for clinical application. Due to the limitations of some measuring techniques which results in some blind spots or region of the flow field cannot be obtained, however, CFD is able to overcome these weaknesses with a much lower cost. The basic architecture and flowchart of a CFD-based design process is demonstrated in Fig. 7.2 [30]. The overall goal of the design process is to systematically evolve from some inferior initial designs to an optimized design. The main modules of the design process include: (1) CFD analysis, (2) design evaluation, (3) design modification, and (4) geometry modification.

In order to reduce the costs of design and development of artificial organs, various numerical approaches have been conducted to quantify the shear-induced hemolysis [31]. From the comparative stress theory of fluids that is analogous to the Mises yield criterion for solid materials, Bludszuweit [36] has developed the scalar shear stress,

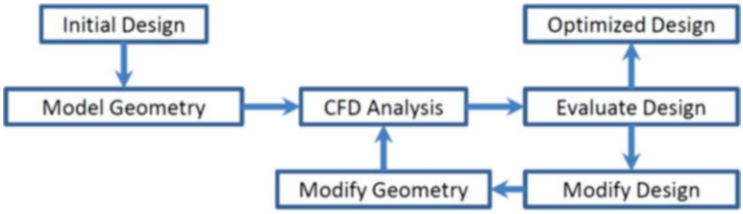

Fig. 7.2 Flowchart of a CFD-based design

which consists of six components of the stress tensor and represents the level of shear experienced by the blood. The scalar shear stress estimation provides information about regions of high stress levels (possible hemolysis) and extremely low levels (like stasis risking thrombosis). In the present investigation, this approach was adopted to account for the three-dimensional shear field and obtained the scalar shear stress according to the stress formula of Bludszuweit [32] as listed below as Eq. (7.3):

$$\tau = \left[\frac{1}{3}\left(\tau_{ii}^2 + \tau_{jj}^2 + \tau_{kk}^2\right) - \frac{1}{3}\left(\tau_{ii}\tau_{jj} + \tau_{jj}\tau_{kk} + \tau_{kk}\tau_{ii}\right) + \left(\tau_{ij}^2 + \tau_{jk}^2 + \tau_{ki}^2\right)\right]^{1/2} \tag{7.3}$$

$$\tau_{ij} = \sigma_{ij} + \rho\overline{u_i' u_j'}$$

$$\sigma_{ij} = \mu\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}\right)$$

$$\rho\overline{u_i' u_j'} = -\frac{2}{3}\rho k\delta_{ij} + \mu_t\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}\right)$$

where δ_{ij} is the Kronecker Delta which equals to 1 for $i = j$ and 0 for $i \neq j$; k signifies the turbulent energy term; ρ is the fluid density; u_i is the velocity component in x_i direction; u_i' is the fluctuating part of the velocity; and μ and μ_t are the molecular and turbulent viscosities, respectively.

A simple but effective correlation between shear stress, exposure time, and the extent of damage to erythrocytes by the power law is developed by Giersiepen et al. [33] under the condition of uniform shear stress. The effectiveness of a power-law formulation as a mathematical model of blood trauma is considered to be suitable only in the presence of the predominance of simple laminar flow. However, the power-law equation provides an acceptable prediction for comparison purposes [34].

$$\mathrm{dHb/Hb} = 3.62 \times 10^{-7} \times t^{0.785} \times \tau^{2.416} \tag{7.4}$$

where dHb/Hb is the ratio of plasma-free hemoglobin to total hemoglobin, τ is the characteristic scalar shear stress (Pa), and t is the stress exposure time (s).

There are generally two approaches to apply Eq. (7.4). The most widely used model is based on accumulated blood damage along a particle track or a streamline. A number of particles are released from the inlet of the numerical domain, and the accumulated blood damages along these tracks are averaged at outlet as the estimated hemolysis. The detailed equations and procedure are described in the following paragraphs.

Trace data of particles along a streamline can be collected, and the shear stress induced in each particle can be calculated. It is assumed that the damage index (D) associated with each particle has a value of 0 initially when the particle enters into a VAD, and increases monotonically due to accumulation of blood damage along the particle trace. When D reaches a value of 1, this particle breaks. The equations are described as follows:

$$d_{p,i} = 3.62 \times 10^{-7} \times \tau_i^{2.416} \Delta t_i^{0.785} \tag{7.5}$$

where $d_{p,i}$ is the blood damage of ith particle, p, during time interval, Δt_i, between t_i and t_{i+1}.

The damage accumulation from time 0 to t_i is given by the following:

$$D_{p,i} = D_{p,i-1} + \left(1 - D_{p,i-1}\right) d_{p,i} \tag{7.6}$$

Hemolysis index (E) is defined as the mean damage:

$$E = \frac{1}{N} \sum D_p \tag{7.7}$$

where N is the total number of particles.

7.4.3.1 Physical Model

Su et al. [29, 35] have done a baseline analysis by means of classic pump design formulas and empirical diagrams to obtain initial pump geometry. As demonstrated in Fig. 7.3, the original design consisted of a three-blade straightener, a two-blade impeller, and a three-blade diffuser. The impeller was shrouded by a cylinder, where the magnet was embedded, and thus both components rotated simultaneously. A 0.2 mm clearance gap was specifically designed for the gap between suspended shroud and pump casing for the present blood pump. The impeller was designed to transfer energy to blood, while the diffuser converted the kinetic energy of the blood from the spinning impeller in circumferential direction to pressure head. For the ease of comparison, the three-blade diffuser (B3) of axial flow blood pump (See Fig. 7.3a) is shown in Fig. 7.3b. The five-blade diffuser (B5) and a three-blade diffuser with a clearance gap of 0.2 mm between the diffuser blades and hub (B3C2) are shown in Fig. 7.3c, d, respectively.

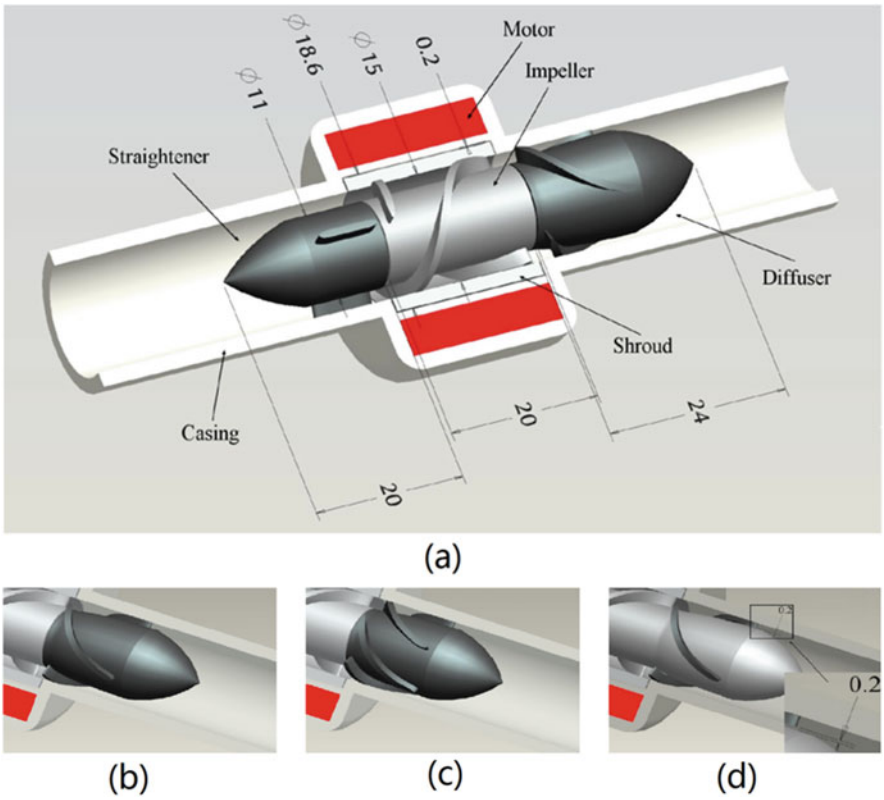

Fig. 7.3 (**a**) An axial flow blood pump assembly; (**b**) the three-blade diffuser (B3); (**c**) the five-blade diffuser (B5); and (**d**) the three-blade diffuser with 0.2 mm clearance gap (B3C2). All dimensions in mm. Note that in (**b**–**d**) the stationary and rotating hub are indicated by dark and light gray, respectively [29]

7.4.3.2 Numerical Model

The blood was assumed as a Newtonian fluid with constant dynamics viscosity of 3.5×10^{-3} Pa s and density of 1050 kg/m^3. The designed operating speed was around 10,000 rpm, and the corresponding Reynolds number was more than 3×10^4. Therefore, the internal flow was turbulent, and shear stress transport k–ω turbulence model was selected for numerical simulation [29, 36]. Since the structure of the axial flow pump was complex, it was divided into three regions connected with interfaces and meshed separately. Approximately, 1.5 million hexahedral grids were generated after grid dependency test. Simulations were conducted using ANSYS FLUENT as finite-volume method based CFD solver.

7.4.3.3 Hydraulic Performance

Pressure-flow curves and hydraulic efficiencies of the three diffuser designs at rotating speed of 10,000 rpm that are based on numerical simulations are shown in Fig. 7.4. Normally, the flow rates of a rotary blood pump for an adult range from 4 to 6 L/min, so all these designs are able to provide adequate static pressure head. The static pressure head drops more steeply in B3C2 model, and the B3 model has the highest static pressure head followed by B5 and B3C2 models at the designed flow rate of 5 L/min. The flow rates at the highest efficiency points are 5–6 L/min, and the hydraulic efficiencies vary between 20% and 26%. The lowest hydraulic efficiency of B3C2 is due to the extra torque required to rotate the diffuser hub.

The velocity vector distributions on the circular sectional slice in the middle between the diffuser hub and tip in different designs are shown in Fig. 7.5. Flow at the diffuser entrance is in the tangential direction following the blade profile smoothly until the region near the trailing edge of side A, where flow separation was observed in Fig. 7.5a, b. It is because of the curvature of the diffuser blade and adverse static pressure gradient along flow direction. Increment of blade number reduced the flow separation region (Fig. 7.5a vs. Fig. 7.5b), which vanished (Fig. 7.5c) due to the rotation of diffuser hub.

7.4.3.4 Hemodynamic Performance

The numerical estimation of hemolysis mentioned earlier has been applied to different diffuser designs. Approximately, 1000 path-lines were collected from inlet to outlet, and the time interval of 0.1 ms was adopted. It can be observed in Fig. 7.6 that the indices were affected by both rotating speed and flow rate, further, among the three models, B3C2 has the highest estimated hemolysis index followed by B3 and B5.

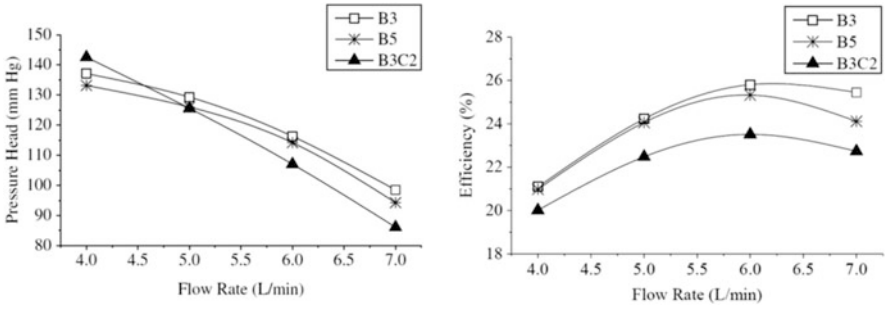

Fig. 7.4 Pressure-flow curve (left) and efficiency-flow curve (right) predicted by CFD at rotating speed of 10,000 rpm

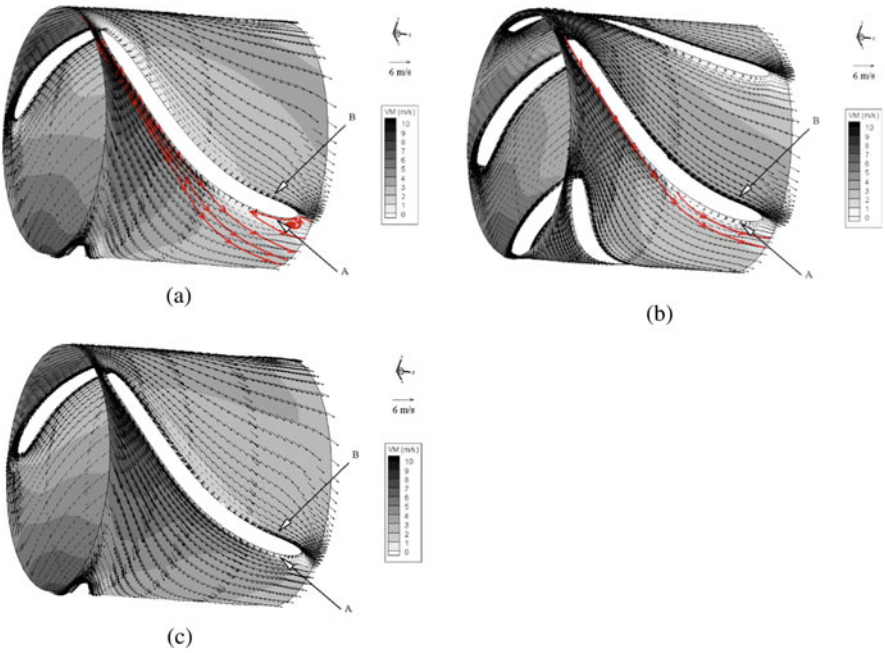

Fig. 7.5 Velocity vector distributions on circular sectional plane at 5 L/min. (**a**) B3, (**b**) B5, and (**c**) B3C2. Streamlines are illustrated near blade trailing edge to indicate reverse flow

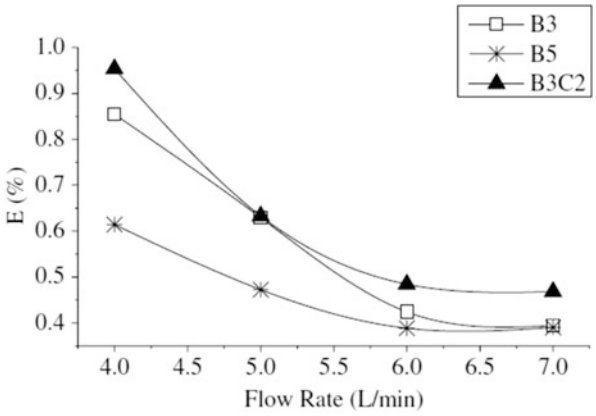

Fig. 7.6 Estimated hemolysis indices at 10,000 rpm

7.4.3.5 Comparisons Based on Numerical Results

Various parameters could be derived from the numerical results, and some are summarized in Table 7.1. For the ease of comparison, linear interpolation was applied to predict these values under the same operating conditions (i.e., 5 L/min and 100 mmHg). As shown in the table, the rotating speeds are 9080, 9130, and

Table 7.1 Comparison of selected parameters in each design

		ω (rpm)	η (%)		FS		E (%)
B3	+	9080	23.90	–	Yes	0	0.34
B5	0	9130	23.70	0	Yes	+	0.30
B3C2	–	9250	22.00	+	No	–	0.43

Best and worst performances are indicated by a plus and a minus sign, respectively, while 0 represents neutral. Note: ω rotating speed, η hydraulic efficiency, FS flow separation, E estimated hemolysis index

9250 rpm for B3, B5, and B3C2, respectively. Both rotating speed and hydraulic efficiency are related to hydraulic performance, and thus were considered under a single group. Based on the table, B5 was superior to the other two. Generally, this example demonstrates a typical approach of numerical evaluation of artificial heart, which includes design of baseline model and its improvements, mesh generations, selections of turbulence model and blood damage model, and the final analyses and comparisons. Owing to the fast advancement of computational speed and parallel computing, the simulation should be completed in a couple of hours. Compared with the optimization using prototypes, the iteration is much more efficient and faster with better cost-effectiveness.

7.4.4 Experimental Measurements for Validation

The pressure-flow curves obtained from in vitro measurements could be used for the validation of the numerical simulation; however, the acquisition of detailed flow field is necessary to examine the competence of selected turbulence model. To visualize flow field, optical access is compulsory, and thus the prototype of artificial heart is transparent. To minimize refraction, the refraction index of blood analog should be close to that of the prototype of artificial heart, which is mostly made of acrylic. The more traditional point-based LDA technique is considered to be the "gold standard" due to its high accuracy and resolution. Since it is able to capture the original fluid fluctuating velocity signal and can be easily used to find the average and root mean square velocities, furthermore these capture turbulence signals can be further processed to obtain for example turbulent kinetic energy, turbulent production rates, and Reynolds stresses. The LDA does not have to calibrate for every measurement, since its signal depends on the specific immutable frequency of laser radiation for direct measurements of velocity. The only disadvantage may be time consuming to acquire the whole flow field using LDA since it is a point-based measurement. This can be overcome by the PIV technique which is able to capture information of the whole flow field in a relatively short time. Beside using seeding particles as the LDA, the PIV measurements make use of high-speed digital camera to capture a successive image pair within a laser-illuminated plane [36]. With the usage of a pulsed laser, each image pair is obtained during a relatively short time interval compared with the transit time of the particle through the measurement

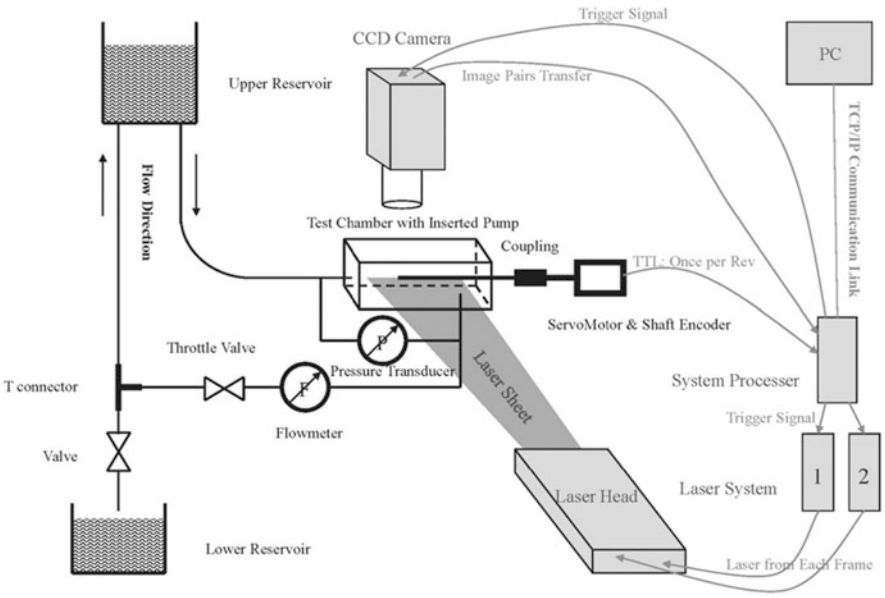

Fig. 7.7 Schematic view of the experimental test rig

region. With the known time interval, the local velocity in any subregion of these acquired images can be found by comparing the particle displacement between a pair of images. This approach completely maps the instantaneous velocity field within the planar illuminated region. Generally, the frequency that PIV system can achieve is in the order of 10–15 Hz, and it is insufficient to capture the turbulent flow structures that have typical frequencies in the order of 10, 100 Hz, and even higher. In contrast, the sampling frequency of LDA can reach as high as 20 MHz. The other weakness of PIV is that the experimental results are only sufficient to capture the mean velocity but not for higher moment turbulence quantities.

Since the primary purpose of experimental measurement is to validate simulation results, it would be desirable if the optical accessible prototype has the same scale of the numerical model [35, 36]. However, prototypes could be scaled up in some studies by obeying similarity laws [26]. Figure 7.7 shows a typical arrangement of experimental measurement of an axial flow pump using PIV, which was designed by Su et al. [36]. The blood analog was firstly injected into the upper reservoir, and then the test chamber was fully filled through the flexible tubes. When the experiment begins, the flow rate of VAD is controlled by the throttle valve located at the downstream of the flow meter. The flow rate and pressure head across the pump model could be found from the flowmeter and pressure transducer, respectively. For illumination of the laser sheets and image acquisition, the VAD model was made of acrylic, and the impeller was driven by a metal shaft, which was further connected to the servomotor mounted with 3-channel optical shaft encoder.

The Dantec FlowMap PIV system from the Dantec Dynamics A/S, Skovlunde, Denmark, was used in the present study. While the Gemini PIV 200-15 from the New Wave Research, Fremont, CA, USA, a double cavity pulsed neodymium aluminum garnet (Nd:YAG) laser system generated two pulsing beams to form pulsing light sheets, and it was further synchronized to shaft encoder through FlowManager software. During the measurement, the servomotor precisely controlled the impeller, and the "once-per-revolution" signal from the shaft encoder triggered the laser and image acquisition. Therefore, the images were taken at designed angular position of the impeller over 100 revolutions. In order to adjust the angular position, a delay was set between shaft encoder and trigger signal. The captured images were sent to system processor and stored in PC through communication link eventually. The charge-coupled device (CCD) camera used was HiSense MkII camera (Hamamatsu C8484-05 digital CCD chip: 1280 × 1024). The measurement area was 10.76 × 8.26 mm^2 with the scale factor of 1.25, and the aperture was *f*/5.6~8. The interrogation area of 32 × 32 pixels was applied with 50% overlap. The final velocity map was obtained by averaging 100 pairs of images.

A qualitative agreement between the numerical and experimental results could be observed in Fig. 7.8 for flow distributions at (a) straightener, (b) impeller, and (c) diffuser, respectively. Note that the solid line and dotted line denote PIV and CFD results respectively in these figures for quantitative comparison. The discrepancies between the experiment and PIV results, which are relatively obvious, can be found at the regions close to the blades, hub, and inner casing surfaces in the figure, due to a few reasons. The fluid close to the interfaces usually has higher velocity gradient in radial direction, owing to the inhomogeneity of fluid field. According to the principle of PIV, the movements of seeding particles in an interrogation area should be homogeneous to estimate velocity accurately. Secondly, the trapped seeding particles on surface could induce relatively strong reflection, leading to an error in PIV measurements. Generally, the CFD results agree fairly well with the PIV results, especially in the straightener region. The L2 relative error norm of the differences in axial velocity between CFD and PIV with respect to the PIV in the straightener, impeller, and diffuser are 11%, 19%, and 27%, respectively. Note that the L2 relative error norm is defined as $\sqrt{\sum_{i=1}^{N}\left(f_i^E - f_i^N\right)^2 / \sum_{i=1}^{N}\left(f_i^E\right)^2}$, where f_i^E and f_i^N represent the values from node $i = 1$ to $i = N$ for PIV experiment and numerical simulation, respectively.

7.5 Summary

Due to the shortage of heart donors, artificial heart becomes a feasible approach to support patients with end-stage heart failure. Alternatively, it is used as a temporal solution to maintain blood circulation. Mostly, the essential part of artificial heart is a blood pump to generate adequate pressure head and flow rate. However, the blood damage must be carefully managed and minimized to avoid medical complications.

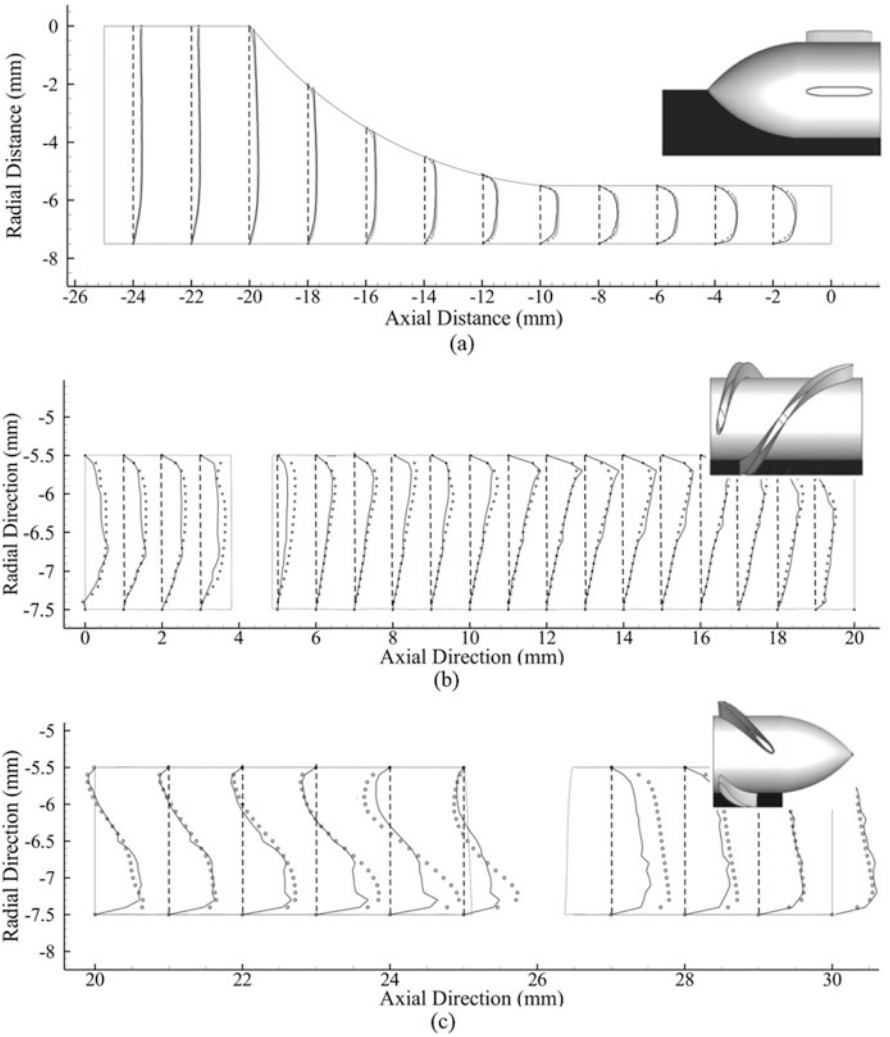

Fig. 7.8 Comparison of the velocity profile obtained from PIV (solid line) and CFD (dotted line) results in (**a**) straightener, (**b**) impeller, and (**c**) diffuser. The position of plane is demonstrated by black color

CFD is a powerful tool to predict detailed flow field, which has been widely validated using PIV, and various blood damage models can be easily implemented so that it facilitates the design of artificial heart by shortening the iteration. Before clinical application, animal and clinical trials are needed to examine its blood damage level and other potential issues, which are valuable for next iteration of design if needed.

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Chapter 8
Selection of Artificial Heart Devices

Yan Zhang

Abstract The number of patients with advanced heart failure that has become unresponsive to conventional medical therapy is increasing rapidly. One of the most promising new alternatives to heart transplantation is use of artificial heart devices. The field of mechanical circulatory support has advanced significantly over the past 20 years, resulting in rapid expansion of patients with advanced heart failure who can benefit from implantable devices. With progress of technology, limitations associated with age, body size, and comorbidities gradually become less prohibitive. The aim of this chapter is to provide a current review of the recent literature relating to artificial heart devices.

Keywords Artificial heart device · Ventricular assist device · Recommendations

8.1 Background

Heart failure is the end-stage manifestation of cardiovascular disease and the main cause of death, which is a major challenge in the field of cardiovascular in the twenty-first century. Although for example pacemaker therapy can significantly improve the prognosis of heart failure, 0.5–5% of patients respond poorly to standard therapy and develop chronic advanced HF [1]. Data from the USA suggest that 250,000–300,000 patients younger than 75 years suffer from advanced systolic HF (defined as NYHA class IIIb–IV). In 2003, China's epidemiological survey found that the prevalence of heart failure in Chinese adults was 0.9%. China's cardiovascular disease report 2013 put forward that the prevalence of cardiovascular disease in China was in a continuous rising stage. The trend of aging also makes the future population of heart failure even larger. Prognosis in advanced HF is grave, with a

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1-year mortality in ambulatory class III–IV patients >25% and exceeding 50% in class IV patients [2].

At present, the main treatment methods of heart failure are: drugs, surgery, mechanical assisted circulation, heart transplantation, cell transplantation. The effect of heart transplantation is the best, but it cannot be widely used because of the shortage of donor heart. Implantable LVADs have been used for decades in very advanced HF or cardiogenic shock primarily as a bridge to heart transplantation.

Mechanical circulatory support (MCS) therapy includes intra-aortic balloon pump (IABP), ventricular assist device (VAD), total artificial heart (TAH), cardiopulmonary support (CPS), extracorporeal membrane lung support therapy (ECMO), and other circulatory support systems. This chapter will introduce criteria about selection of MCS according to the characteristics of each device and the status of patients.

8.2 Classification According to the Technology

8.2.1 First-Generation, Pulsatile-Flow LVAD

8.2.1.1 HeartMate XVE

The HeartMate XVE was a successful first-generation, pulsatile-flow LVAD; however, limitations included its relatively large size, a large line required for de-airing, and the risk of allosensitization, potentially interfering with subsequent transplantation [3]. In 2002, HeartMate XVE was approved for use in pre-transplant support. In 2003, HeartMate XVE was approved for permanent support treatment. The large driveline made this device vulnerable to infection, and the numerous moving parts predisposed to pump failure, with redo surgeries carrying a high morbidity [4]. The REMATCH trial was an RCT in which the outcomes of HeartMate XVE LVAD implantation in patients with severe heart failure who were not candidates for heart transplantation were studied [5]. Compared with the drug treatment group, the risk of death in the left heart assist group decreased by 48%, which was statistically significant. The 1-year survival rate was 52% in the left heart assist group and 25% in the drug group ($P = 0.002$). The 2-year survival rate was 23% and 8% ($P = 0.09$). The incidence of complications in the left ventricular assist group was 2.35 times as high as that in the drug treatment group. The common complications were infection, bleeding, and device failure. In the first year, the quality of life of patients in the left heart assist group was significantly higher than that in the drug treatment group. The nonrandomized INTrEPID (Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent) trial compared outcomes of patients with severe inotrope-dependent heart failure who were not eligible for transplantation and who received a HeartMate XVE LVAD with control patients who received optimal medical therapy only due to patient choice or device unavailability

[6]. Six-month and 1-year survival rates were greater in LVAD-treated patients, with a reduction in symptoms of heart failure and complications.

8.2.2 Second-Generation, Axial-Flow LVAD

8.2.2.1 HeartMate II

Clinical trials show the HMII continuous-flow LVAD is better than heartbeat XVE in clinical treatment. The HMII continuous-flow LVAD is a continuous-flow device, with a portable battery pack lasting 6–8 h on a single charge. The HeartMate II is implanted inside the chest with its entrance attached to the left ventricle and its exit connected to the aorta (the main blood vessel carrying blood from the heart to the body). A small electric motor in the pump drives a "propeller" type rotor inside the pump that pushes the blood into the aorta and out to the body. An electrical cord, also known as a driveline, passes from the patient's abdomen to a controller and battery pack allowing the patient to move about freely. Over 26,600 heart failure patients have received the HeartMate II LVAD. Many have passed the 5-year milestone on therapy, with some still on therapy after 10-plus years.

Table 8.1 summarizes the key research on HeartMate II. The HeartMate II clinical trial is an RCT that compares continuous blood flow HeartMate II LVAD and pulsatile blood flow HeartMate XVE in non-heart transplant candidates [8]. Compared with the pulsatile-flow device group, the survival rate and mechanical failure rate of LVAD group without disabling stroke in 2 years were significantly improved [9].

Table 8.1 HeartMate II Studies

Miller (2007) [7]	Prospective observational study ($n = 133$). HMII provided up to 6 months of effective hemodynamic support to improve functional status and quality of life.
HMII trial (2009) [8, 9]	RCT of HMII versus HM XVE. Compared with HM XVE group, HMII group had a higher survival rate of non-disabled stroke and a lower 2-year mechanical failure rate.
REVIVE-IT (2014) [10]	In patients with NYHA III, HMII was compared with conventional drug therapy. There were more than average pump thrombosis in HMII patients, and the study was suspended and terminated.
ROADMAP (2015) [11, 12]	Prospective, multicenter, nonrandomized trial of HMII versus optimal medical management in NYHA IIIb/IV patients. More HMII patients survived to 2 years compared with medical management
PREVENT (2017) [13]	Prospective, multicenter, nonrandomized trial. Adherence to recommendations including INR 2–3, heparin bridging therapy, early aspirin, minimum pump speed 9000 rpm, and surgical implant technique.

HMII HeartMate II, *HM XVE* HeartMate XVE, *INR* international normalized ratio, *NYHA* New York Heart Association, *rpm* revolutions per minute

The ROADMAP study was a prospective, multicenter, nonrandomized trial in 41 centers to compare HMII LVAD treatment with optimal medical management (OMM) in patients with NYHA IIIB/IV grade heart failure who met LVAD destination treatment criteria [11, 12]. The composite primary end point was the survival rate of the original treatment and the improvement of the 6-min walking distance of 475 m. At 12 months (LVAD 39% v OMM 21%; odds ratio 2.4; 95% confidence interval 1.2–4.8; $P = 0.012$) and 24 months (LVAD 30% v OMM 12%; odds ratio 3.2), more patients with LVAD obtained the main results (95% confidence interval 1.3–7.7; $P = 0.012$) [9, 14].

The REVIVE-IT study was designed to compare the results of NYHA class III heart failure patients treated with HMII LVAD or conventional medical management [15]. The aim was to study LVAD as an alternative therapy for heart failure patients with obvious impairment of exercise ability, functional state, and quality of life. However, the severity of these damages is not enough to meet the conventional indications of LVAD implantation. However, due to the higher than average incidence of PT observed in the HMII group, especially in three treatment centers, the study was suspended, reviewed, and subsequently terminated early [15, 16]. The PREVENT trial was conducted in response to the observation of increased rates of PT in some centers but not in others [17].

Clinical results after implantation of the HeartMate II improved steadily to 85% 1-year survival. Patients with this continuous-flow device demonstrated dramatically improved survival compared with patients on first-generation pulsatile-flow devices. The FDA approved the HeartMate II as a BTT in 2008. In January 2010, the HeartMate II was approved for permanent support in patients not suitable for heart transplantation.

8.2.3 Third-Generation Devices: HeartMate 3 and HeartWare Ventricular Assist Device

The third-generation blood pump is characterized by magnetic suspension design which includes a fully suspended impeller that rotates in a magnetic field without mechanical contact or bearing, such as the HeartMate III and HeartWare HVAD. The HeartMate III is a centrifugal continuous-flow LVAD with a fully magnetically levitated impeller. Advances in miniaturization allow for a minimally invasive surgical approach for intrapericardial device placement without the need for CPB or the creation of a pocket [13]. The small device size also allows for the implantation of two devices for both LVADs and RVADs for long-term biventricular support if required [18, 19]. The key studies on the HM3 and HVAD devices are summarized in Table 8.2 [19]. The FDA approved the HeartMate III as a BTT in 2012.

The MOMENTUM 3 (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3) study

Table 8.2 Third-generation centrifugal continuous-flow LVAD studies

Study	Comments
Momentum 3 (2017) [20]	RCT HM3 versus HMII for BTT and DT
	HM3 had fewer redo surgeries for pump malfunction than did HMII
	No difference in rates of mortality or disabling stroke
HM3 CE Mark Trial (2017) [21]	Prospective nonrandomized study of HM3
	1-Year outcomes similar to other devices, with no pump thrombosis or pump failure
ENDURANCE (2017) [22]	RCT HVAD versus HMII
	HVAD noninferior for 2-year survival without disabling stroke or device malfunction requiring removal
	HMII demonstrated a higher mechanical failure rate
ADVANCE BTT trial (2012) [23]	Multileft trial of HVAD implantation compared with outcomes from INTERMACS registry of other LVAD
ADVANCE BTT (2013) [24]	Additional enrollment to trial (n ¼ 332)
	Significant improvement in quality of life

compared the HeartMate III with the axial-flow pump HeartMate II [20]. The important finding was that none of the patients with HeartMate III experienced a pump thrombosis. The HM3 CE mark trial was a prospective, nonrandomized trial in patients with severe heart failure receiving the HM3 device as a bridge to transplantation or destination therapy [21]. At 1 year, mortality was 18%, stroke 18%, gastrointestinal bleeding 12%, driveline infection 16%, and outflow graft thrombosis 2%.

The ENDURANCE trial randomly assigned patients to receive the HeartWare HVAD versus the HMII. Noninferiority was demonstrated for HeartWare compared with HMII with respect to the primary composite outcome, 2-year survival without disabling stroke, or device malfunction requiring removal [22]. The mechanical failure rate of HeartMate II is high, and about 8.8% of patients need to change the blood pump. Compared with HeartMate II, HeartWare is smaller and more suitable for implantation without cardiopulmonary bypass [22, 25].

The HeartWare ADVANCE bridge to transplantation trial was a multicenter trial in 30 centers that enrolled 140 patients who required MCS with the HeartWare HVAD while awaiting heart transplantation [23]. Eighty six percent 1-year survival was reported after HVAD implantation, with significant improvement in functional capacity and quality of life. Based on this BTT evaluation, the HVAD received FDA approval in 2012. An additional 192 patients were enrolled in the Food and Drug Administration-approved continued access protocol, with the same criteria for enrollment as the original ADVANCE bridge to transplantation trial [23]. According to the analysis of the comprehensive results of two advance trials, with a 180-day survival of 91% and a 360-day survival of 84%. The quality of life score improved significantly, and the incidence of adverse events was low.

The HeartWare HVAD is approved for BTT with the DT trial ongoing.

8.3 Classification According to the Assistant Time

According to the expected duration of support, ventricular assist devices can be divided into short-term application, intermediate- to longer-term devices, and long-term application (see in Table 8.3).

8.3.1 Short-Term Devices

Patients with cardiogenic shock need to reconstruct normal hemodynamics and restore perfusion of important organs. Cardiogenic shock can be caused by myocardial ischemia, valvular heart disease, myocardial disease (myocarditis), or myocardial infarction. In general, left ventricular support should be easy to establish and allow sufficient support time to resolve organ disorders and assess nervous system status. The treatment of patients is a gradual process, that is, the application of vasoactive drugs, followed by intra-aortic balloon pump, and then consider VAD treatment. Percutaneous devices include Impella 2.5 and 5.0 (ABIOMED, Denver, MA), TandemHeart (Pittsburgh, PA), and extracorporeal membrane oxygenation (ECMO). Impella 2.5 has been successfully used in patients with left ventricular support, myocardial infarction, and cardiogenic shock during high-risk coronary intervention [26]. Impella 5.0 can be placed through skin or entered through femoral artery incision; the device was approved by FDA in 2009. The two impeller devices (2.5 and 5.0) provide a flow rate of 2.5 or 5.0 L/min to unload the left ventricle

Table 8.3 Types of the assist device

Assist Term	Type	Company
Short-term use	Thoratec PVAD and IVAD	Thoratec, Inc.
	Impella Recover LP 2.5, 5.0	Abiomed, Inc.
	TandemHeart (pVAD)	Cardiac Assist, Inc.
Intermediate- to longer-term devices	The Bio-Medicus bio-pump	Medtronic, Inc.
	Abiomed BVS5000 and AB5000	Abiomed Inc.
	CentriMag	Levitronix, Inc.
Long-term implantable devices	Novacor	WorldHeart Inc.
	HeartMate II	Thoratec, Inc.
	Jarvik 2000	Jarvik Heart, Inc.
	DuraHeart LVAS	Terumo Heart, Inc
	INCOR	Berlin heart, Inc.
	VentrAssist	Ventracor, Ltd.
	HeartMate III	Thoratec, Inc.
	HeartWare HVAD	HeartWare, Inc.
	Cardiowest TAH	SynCardia Systems, Inc.

directly. However, Impella equipment has its own disadvantages, including relatively short support time, frequent casing displacement, lower extremity ischemia, and difficulties in transportation to the tertiary care center [26, 27].

TandemHeart is another percutaneous ventricular assist device. Under the guidance of transatrial septal fluoroscopy, the inflow cannula (17F) was inserted into the femoral vein and into the left atrium. Insert the outflow tube into the femoral artery. The pump has been successfully used in high-risk coronary intervention, heart failure after open heart surgery, bridge to bridge (BTB), and bridge to transplant (BTT) [1–3]. One of the main disadvantages of the pump is that the cannula is dislodged into the right atrium, which leads to a serious decrease in arterial oxygen saturation. In the process of transporting patients, this equipment is easier to manage. ECMO has considerable experience in the treatment of cardiogenic shock. The main additional equipment of ECMO circuit is oxygenator. It is the first choice for patients with both heart and respiratory failure. Catheterization depends on the clinical situation; percutaneous catheterization of femoral, subclavian, or cervical vessels is often used in cardiogenic shock. ECMO can provide sufficient cardiopulmonary support, but the disadvantages of the device strategy include strict anticoagulation requirements leading to bleeding, limb ischemia when using peripheral catheterization, and incomplete decompression of the left ventricle. This type of device can be used as a recovery bridge (BTR), BTB, or BTT.

8.3.2 Intermediate- to Longer-Term Devices

Since 1980s, the Bio-Medicus bio-pump (Medtronic, Inc., Eden Prairie, MN, USA) has been widely used in clinic. It is a centrifugal pump. One of the main advantages of the pump is simplicity. It is widely used in most cardiac surgery centers. Because the equipment is simple, it is easy to implant and transport patients. However, this kind of pump is easy to form fibrin and thrombus in the circuit, which promotes the development of other types of circulatory devices.

ABIOMED BVS5000 is a pneumatic auxiliary device, which consists of a filling chamber (passive filling), through which blood flows back to the patient. Pulsatile blood flow is usually inconsistent with natural heart contraction, and the maximum flow can reach 6 L/min. The pump head needs to be changed every week, even if there is enough anticoagulant. Similarly, the device can be used as a support for the heart before recovery, or as a bridge to long-term implanted VAD or BTT. The new external VAD based on improved centrifugation technology is CentriMag (Levitronix, Waltham, MA, USA). CentriMag's patients can support until weaning as a bridge to a long-term implantable VAD or transplant [26]. Anticoagulation is required and the pump can be replaced if fibrin is deposited in the circuit or pump head. Each of these devices can be used for single or biventricular support. Centrifugal pumps can be combined with membrane oxygenators to provide effective cardiopulmonary support as an ECMO, although the duration is limited.

8.3.3 Long-Term Implantable Devices

As previously discussed, LVAD selection mainly depends on the indication for mechanical circulatory support. In the United States, long-term, implantable ventricular assist devices have been approved for clinical use on two indications, either as BTT or DT. This section focuses on long-term ventricular assist devices that have been approved by FDA. The main treatment of BTT with implantable ventricular assist device is to reduce the waiting period mortality. Various VADs based on pulse pump technology have been approved for BTT; these VADs include Thoratec PVAD (Thoratec Inc., Pleasanton, CA, USA) and Berlin Heart EXCOR (Berlin Heart AG, Berlin, Germany), as well as implantable devices such as HeartMate XVE and Novacor VAD (WorldHeart Inc., Oakland, CA, USA). Recently, HeartMate II, an axial-flow pump, has been shown to be effective in improving functional status, quality of life, and survival in patients waiting for clinical deterioration of transplantation. At present, the third-generation centrifugal pump technology is used in clinical practice. The third generation of blood pumps are mainly HeartWare LVAD, HeartMate III, which is FDA-approved for BTT and is under study protocol for DT.

On the other hand, due to the limited number of suitable heart donors, most patients with advanced heart failure are not eligible for heart transplantation at all. HeartMate XVE is the first FDA-approved device based on the results of a REMATCH trial in which patients who failed to transplant were randomly assigned to optimal medical management or LVAD treatment [5]. At 1 and 2 years, patients who received LVAD had significant survival benefits compared with the best medical management. At the same time, the quality of life of patients supported by LVADs was also significantly improved. Although it has been approved by FDA, it has not been widely implanted because of its large size, special patient care requirements, and many technical problems. Sepsis and failure of LVAD device are the main causes of death. The high failure rate of LVAD still has problems within 2 years [8]. Generally accepted indications (Medicare and Medicaid service standards) include ejection fraction $<25\%$, functional IIIB or IV grade maximum oxygen consumption, or reliance on intra-aortic balloon or inositol therapy. Most patients were evaluated for heart transplantation at the same time before LVAD implantation, and they were labeled BTT or DT according to preoperative examination. In some cases, transplant candidates are unclear, and these patients informally receive LVAD as a "bridge to decision." LVAD technology has developed from large pulsating pump to small continuous-flow pump. HeartMate II has been shown to be more durable than HeartMate XVE and significantly improved survival and quality of life in people supported by the new axial-flow pump [6]. At present, HeartMate II is the only device approved by FDA for BTT and DTT, while HeartWare HVAD is approved for BTT, and the clinical trial of DTT is in progress. The long-term consequences of using these continuous-flow pumps to support patients are not fully understood. However, the incidence of bleeding appears to be increased, possibly due to anticoagulation, acquired vascular pseudohemophilia

defects, and/or decreased pulse pressure. A unique device, also approved by FDA for BTT, is the pneumatic all artificial heart West TAH (SynCardia Systems Inc., Tucson, TX, USA). The indication of TAH implantation is different from that of most VADs. The pump is mainly used in patients with severe cardiogenic shock leading to severe multiple organ disorder, extensive myocardial infarction leading to biventricular failure, left ventricular failure with extensive intraventricular thrombus or primary graft failure or rejection after transplantation.

8.4 Mechanical Circulatory Support Recommendations Fig. 8.1

8.4.1 CLASS IIa [28]

1. Mechanical Circulatory Support (MCS) is beneficial in carefully selected patients with stage D HF with reduced EF (HFrEF) in whom definitive management (e.g., cardiac transplantation) or cardiac recovery is anticipated or planned [29–32].
2. Nondurable MCS, including the use of percutaneous and extracorporeal ventricular assist devices (VADs), is reasonable as a "bridge to recovery" or "bridge to decision" for carefully selected patients with HFrEF with acute, profound hemodynamic compromise [33–36]. (Level of Evidence: B).
3. Durable MCS is reasonable to prolong survival for carefully selected patients with stage D HFrEF [5, 6, 8, 37]. (Level of Evidence: B).

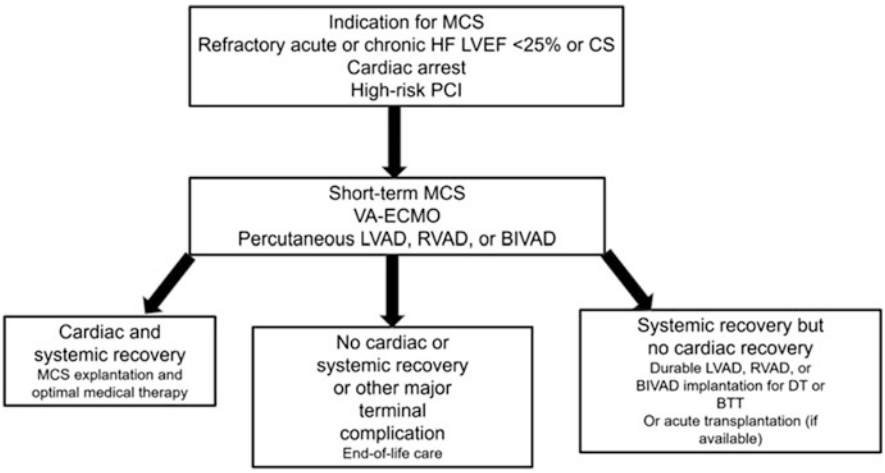

Fig. 8.1 A decision tree for mechanical circulatory support. *BIVAD* biventricular assist device, *BTT* bridge to transplantation, *CS* cardiogenic shock, *DT* destination therapy, *HF* heart failure, *LVAD* left ventricular assist device, *LVEF* left ventricular ejection fraction, *MCS* mechanical circulatory support, *PCI* percutaneous coronary intervention, *RVAD* right ventricular assist device, *VA-ECMO* venoarterial extracorporeal membrane oxygenation

Nondurable or temporary MCS provides an opportunity for decisions about the appropriateness of transition to definitive management such as cardiac surgery or durable, that is, permanent, MCS or, in the case of improvement and recovery, suitability for device removal. Nondurable MCS thereby may be helpful as either a bridge to decision or a bridge to recovery.

More common scenarios for MCS, however, are long-term strategies, including: (1) bridge to transplantation, (2) bridge to candidacy, and (3) destination therapy. Bridge to transplant and destination therapy have the strongest evidence base with respect to survival and functional capacity.

The data from INTERCS provide valuable information for the evaluation of risk factors and prognosis of MCS patients. Among the patients receiving bridging transplantation, the greatest risk factors for death included the severity of the clinical condition and the condition of right ventricular failure [38]. MCS can also serve as a bridge for candidates. Retrospective studies have shown that MCS treatment can reduce pulmonary artery pressure in patients with heart failure who are considered to have "fixed" pulmonary hypertension [30, 32, 39]. Therefore, patients who cannot be transplanted due to irreversible severe pulmonary hypertension can get MCS support over time. Other candidates may include obesity and smoking in heart transplant candidates (chart 2).

There is no accepted standard for LVAD implantation. Commonly accepted indications include ejection fraction <25%, peak oxygen consumption <14 mL/kg/min, New York Heart function class IIIB or IV, or reliance on intra-aortic balloon or inotrope therapy. Most patients were evaluated for heart transplantation at the same time before LVAD implantation, and they were labeled BTT or DT according to preoperative examination. In some cases, transplant candidates are unclear, and these patients informally receive LVAD as a "bridge to decision."

Criteria for HeartMate II destination therapy (HM2-DT) trial (list blow Fig. 8.2).

Absolute contraindications include systemic illness with a life expectancy of less than 2 years or malignancy within 5 years, irreversible renal or hepatic dysfunction, severe obstructive pulmonary disease, or other systemic disease with multiorgan involvement [40].

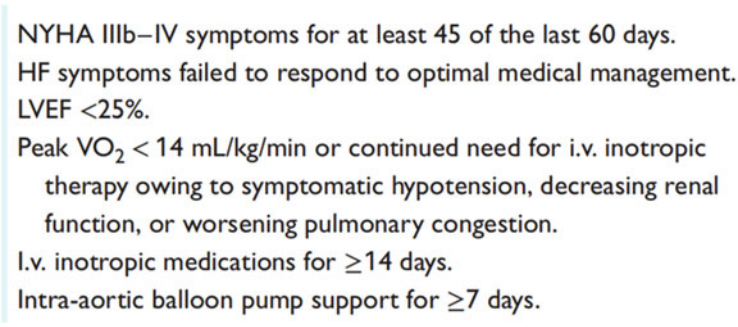

Fig. 8.2 Main inclusion criteria for HeartMate II destination therapy (HM2-DT) trial

8.5 Specific Considerations Relating to Left Ventricular Assist Device Candidacy

8.5.1 Patient Size Considerations

The previous pulsatile pump was limited to patients with a body surface area greater than 1.5 m^2, but the continuous flow of LVADs is one seventh of the size of pulsatile device, which has been proved to be safe for patients with a body surface area as low as 1.3 m^2 [8], which makes these nonpulsatile VADs available to women and younger adults and adolescents. LVAD implanted in the pericardium has no physical limitation. Jarvik 2000® VAS is suitable for patients with advanced heart failure, who may be a bridge for transplant candidates or lifetime recipients. If the body surface area (BSA) is at least 1.2 m^2, the patient is considered suitable for implantation.

8.5.2 Age

Advanced age is not a contraindication to LVAD therapy, but many elderly patients have multiorgan dysfunction, frailty, or other significant co-morbidity that may compromise outcomes.

Indeed, age is a potent risk factor for mortality or prolonged hospitalization after LVAD implantation. However, several centers have experience in treating elderly patients. In a study including 30 patients >70 years (and 6 >80 years), a 70% 3-year survival, which was not different from that observed in patients <70 years, was found [41]. Hence, carefully selected elderly patients can undergo LVAD implantation and experience excellent survival. Social support is crucial in LVAD patients, especially elderly or fragile patients.

8.5.3 Infection

Active systemic bacterial or fungal infection is a contraindication of LVAD implantation, while localized and controlled infection (such as urinary tract infection after treatment) should not delay the operation. Infection is also an important factor affecting the quality of life and long-term survival. It is reported that with the help of a HeartMate, about 45% of patients have infections, 40% of which are related to equipment and 32% come from wires. In the rematch test, the infection rate was 41% and 28%, respectively [42].

8.5.4 Aortic Valve Regurgitation

Untreated significant aortic regurgitation (AR) is a contraindication to LVAD implantation as it prevents pump flow from contributing to organ perfusion. AR may be corrected at the time of LVAD implantation either by valve replacement using a bioprosthesis or by oversewing the valve. Results regarding outcome after LVAD implantation requiring aortic valve intervention are conflicting, and some centers consider significant AR a relative contraindication to LVAD implantation or at least a factor which must be weighed in the overall operative risk [43, 44].

8.5.5 Right Ventricular Function

Right heart failure is an important factor affecting postoperative survival. After the left heart assist implantation, the right ventricle should have enough ejection fraction to ensure that the pulmonary circulation has enough blood supply to supply the output of the assist pump. Low right heart ejection fraction not only cannot meet the needs of the body, but also cause venous congestion, liver function damage, multiple organ failure, and other serious consequences. Many predictors of LVAD-RV failure have been identified [45–47], but there is no agreement on the measurement of RV function, which will constitute an absolute contraindication of LVAD implantation. It is important to evaluate (or re-evaluate) the RV function after the liquid overload has been adequately corrected. Preoperative assessment of RV function with inotropic drugs or temporary mechanical circulatory support may lead to an underestimation of RV dysfunction. In a larger study, it was found that the risk factors of severe right ventricular failure before operation were increased central venous pressure (CVP) or CVP/PCWP ratio, severe renal insufficiency, and ventilator dependence. Specific echocardiographic measures of RV function have exhibited poor reproducibility across studies and should probably not per se exclude patients from LVAD implantation. Late RV failure after LVAD implantation clearly occurs, probably due to progressive cardiomyopathy or an increase in RV afterload, but is not yet well described. It manifests as recurrence of HF symptoms and fluid overload [45–47].

8.5.6 Bleeding Disorders

Implantable LVADs need anticoagulation to avoid pump thrombosis, usually vitamin K antagonists, targeting international normalized ratio (INR) between 2 and 2.5, [16, 48]. In addition, CF-LVADs are associated with acquired von Willebrand disease because device-related shear stress affects the macromolecular form of von Willebrand factor [49]. This will lead to a significant risk of bleeding after implantation; therefore, other sources of bleeding (hereditary bleeding disorders, severe liver dysfunction, etc.) will constitute an unacceptable high risk of LVAD

implantation. In addition, continuous blood flow may lead to the formation of arteriovenous malformations, especially in the gastrointestinal tract. Arteriovenous malformations predispose to bleeding, may be difficult to diagnose and treat, and hence are a cause of morbidity in LVAD recipients [50].

8.6 Future Directions

Patient presentation and acuity of illness dictate the appropriateness of which device is selected for support. Temporary devices can serve as a bridge in order to stabilize patients and facilitate a work-up for candidacy for long-term implantable devices. This field continues to evolve as do the indications for their use.

Accumulation of clinical experience will allow consensus guidelines to be developed. However, at the current rapid pace of technologic progress, such guidelines may be outdated at the time of their publication, somewhat similar to the experience with coronary stents. Therefore, cardiac surgeons performing MCSD surgery should remain updated. MCS is still a relatively new technology in the treatment of HF, and much research remains to be done to elucidate its role in clinical medicine and also to better understand HF itself. Both basic and clinical investigations are warranted with support from nonprofit organizations and industry.

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Chapter 9
Therapy Management of VADs

Yueh-Ting Chou

Abstract Cardiovascular disease is the leading cause of global morbidity. Chronic ischemic heart disease, acute heart failure, and myocardial infarction are among the primary causes of mortality in Europe (45% of all deaths), the United States of America (34.3%), and worldwide (45% of noncommunicable diseases). Different strategies can be planned for the treatment of heart disease according to the severity, cause, and course of heart failure. It includes adjusting patients' lifestyle, medication, and surgical treatment. But for patients with end-stage heart failure waiting for heart transplantation, the number of donated hearts is usually insufficient. Therefore, the auxiliary equipment of ventricular implantation becomes very important. Because it can provide different treatment options for patients with heart failure from excessive to recovery, decision, transplantation, or ultimate treatment. According to the seventh INTERMACS data showed that more than 13,000 patients received left ventricular support from the United States in 2014, of which 955 received pulsatile flow LVADs and 12,030 continuous flow LVADs. This chapter provides an overview of the current implantable rotating left ventricular assist device (LVAD), patient selection, surgical overview, and postoperative management strategies.

Keywords Ventricular assist device (VADs) · Patient assessment · Adverse events · Management

9.1 Introduction

One in 5 Americans over 40 suffers from heart failure; nearly 50% die 5 years after diagnosis [1, 2]. Nearly 70% of patients with end-stage or advanced heart failure will die or be hospitalized within 1 year [3]. Heart transplantation is the ultimate long-term treatment for end-stage heart failure [4]. However, due to insufficient heart

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donors, the demand for ventricular assist devices (LVADs) is slowly increasing. In the past decade, the use of LVADs has increased significantly. In the United States alone, nearly 2400 non-pulsating LVADs are implanted every year, compared with 459 in 2008 [5]. Currently, more than 16,000 patients in the United States have received LVAD treatment [6]. These devices are lifesaving devices for patients with advanced heart failure (HF) who are not eligible for heart transplantation or who are too ill to wait safely for medication alone. Left ventricular assist device implantation can effectively improve the survival rate of patients, it is estimated that the 1-month survival rate is 95%, and the 1-year and 2-year survival rates are about 80% and 70%, respectively [5].

In 1994, the Food and Drug Administration (FDA) approved the first-generation pulsatile left ventricular assist device (LVAD) as a bridge for patient transplantation (BTT) on the waiting list, and later approved patients who did not qualify for heart transplantation as destination therapy (DT). The new generation of continuous flow LVADs is designed to reduce mechanical wear, double the 2-year survival rate of pulsating LVADs, and improve the quality of life of patients with BTT and DT [7–9]. At present, the 2-year survival rate of the new generation of continuous flow LVADS patients is over 80%, which is comparable to that of heart transplantation [10, 11].

Since 2006, more than 4000 mechanical circulatory support devices have been implanted and re-admitted after index hospitalization. Intensive care physicians will definitely encounter these patients in the future [11, 12]. The management of these patients requires an understanding of the principles, indications, and limitations of this unique technology. This chapter focuses on the physiology of LVAD patients, perioperative period, and the management of common complications related to ICU. In addition, with the increasing number of LVAD patients, it is very important to provide care for LVAD patients. We need to use limited data and guidelines to obtain general medical and cardiovascular care to help heart failure specialists and non-LVAD specialists provide care for these patients. The following will be divided into patient assessment, ventilator settings during respiratory failure, adverse events, and complications management.

9.2 Patient Assessment

9.2.1 Preparation

Preparations for LVAD implantation began before surgery. In the best case, patients are undergoing an outpatient evaluation, and once their examination is completed, eventually they will discuss it at a multidisciplinary meeting. In many cases, this will be considered for a variety of advanced treatments, including heart transplantation, left ventricular counterpulsation, or other mechanical circulatory support. Members of the multidisciplinary meeting include heart failure specialists and advanced practice providers (APPs), cardiac surgeons and residents, critically ill physicians, pharmacists, social workers, finance, administration, and consultation whose input

may be valuable in decision-making. Including neurological diseases, gastrointestinal diseases, liver diseases, kidney diseases, infectious diseases, and psychiatric diseases consultants, depending on the individual patient's pathology. Once we agree that advanced therapies are medically appropriate, we will review patient support structures to ensure that medical staff are identified to help patients transition and stay at home once they are ready to leave the hospital. Our heart failure applications and social workers are helpful in reviewing these details and their input is seriously considered. For surgeons, a review of existing imaging is particularly valuable at this time. We are most interested in identifying any assistive procedures that will be necessary and evaluating the right ventricle for LVAD implantation. In particular, we evaluated the aortic valve and developed a plan to correct any degree of aortic insufficiency greater than mild aortic valve insufficiency. This is particularly important in DT (Destination Therapy). If aortic valve insufficiency worsens, then transplantation cannot be used as a lifesaving measure for this group of people after LVAD implantation [13]. For tricuspid valve, it needs to adopt repair strategy, if the regurgitation is severe or moderate and the tricuspid annulus is larger than 40 mm [14]. For mitral valves, it tends to be conservative and only repairs severe mitral regurgitation (MR) if there is a prolapse component, although VAD fully unloads the left ventricle, which is expected to lead to severe and residual MR. At this point, if the patient needs to undergo sternotomy again, it will also review CT scan imaging. This will help medical team plan to intubation strategy and enable to assess the degree of right ventricular injury during reoperation. If the patient has had a previous coronary artery bypass, we request and review the preoperative coronary angiography. In particular, we wanted to determine the process of limbal transplantation to see if there were other transplants that might be injured during the anatomical process. A new area of interest to us and others is the ongoing LVAD implantation for patients with atrial fibrillation (AF). Our current strategy is to perform LVAD implantation in patients with atrial fibrillation clipped to the left atrial appendage. There is evidence that this can reduce the risk of stroke in many LVAD patients [15]. Whether it can be inferred that the current recommendations for invasive surgery are useful for adult cardiac surgery for atrial fibrillation in LVAD patients remains to be seen. However, considering that stroke is still one of the most common complications of LVAD implantation, it seems appropriate to explore all options to reduce this risk.

In evaluating a patient as a surgical candidate for left ventricular diastolic dysfunction, nothing is more important than the status of RV and the prediction of severe RVF. Because, the function of the right ventricle will affect the patient's complex postoperative course. The reported incidence of early RVF after LVAD implantation ranged from 6% to 44%, mainly due to different definitions of RVF. The most comprehensive definition of RVF is the revised definition provided by INTERMACS. It defines RVF as the right ventricular insufficiency symptoms and signs displayed by the central vein persistently exist in the absence of an increase in the left atrium, with central venous pressure (CVP) > 18 mmHg and cardiac index <2.0 L/min/m^2. RVAD placement, or intravenous inositol or nitric oxide injection for more than 14 days after LVAD implantation also conforms to this definition. The

pathophysiological mechanism leading to RVF manifestations is multifactorial. Devices are brought about by pre-existing conditions and other related hemodynamic changes. First, in patients with common dilated cardiomyopathy (whether genetic predisposition, chemotherapy-induced, or other mechanisms), it is expected that the same cardiomyopathy process will affect the left ventricle as well as the right ventricle. To a large extent, the decline of right ventricular systolic function and the decline of right ventricular diastolic function are determined by this process, and chronic pulmonary hypertension can be further aggravated by afterload. Similarly, in patients with ischemic cardiomyopathy, coronary artery perfusion may be impaired by atherosclerotic disease, which may be further exacerbated by lower perfusion pressure associated with high CVP and low systemic blood pressure, which is common in patients under consideration for LVAD treatment. Cardiopulmonary bypass can lead to an acute increase in pulmonary vascular resistance (PVR), thus aggravating RVF, which may be caused by inflammatory mediators. Blood transfusion and protamine management have been shown to cause pulmonary vasoconstriction and exacerbate right ventricular dysfunction. LVAD implantation itself may aggravate RVF through several mechanisms. The interdependence of ventricular effects is most prominent in the settings of load changes after LVAD implantation. This interventricular septum has an important effect on right ventricular systolic pressure and cardiac stroke volume, and is used as a support structure for RV free wall contact. Excessive left ventricular decompression leads to left displacement of ventricular septum, which endangered the effectiveness of right ventricular systolic function and output. In addition, LVAD increases cardiac output and systemic blood flow, further leading to increased venous return to the failed right ventricle. RVF may be aggravated without significant and immediate reductions in RV afterload. Over the years, many risk prediction models for RV failure have been developed, all of which are based on retrospective analysis of patients with AVF and those without AVF. The main limitations of some of these models are that they largely ignore changes caused by physiological anesthesia, changes in intrathoracic pressure, positive pressure ventilation, and volume changes. In addition, they seldom considered the effects of pump on ventricular volume, pressure, and interventricular septal function. In assessing RV, we used hemodynamic values (PAPi, CVP: PCWP) and echocardiographic data (RV: LV diameter, TR severity, objective assessment of RV free wall contraction function, TAPSE) to assess RVF. In the absence of any standardized approach, this is largely based on subjective and empirical considerations. Therefore, in selecting patients, the most important factor is the need for RVADs to optimize preventive measures. These methods include active preoperative diuresis to reduce CVP, ideally <10 mmHg, without increasing creatinine, and free use of creatinine support (to optimize peripheral perfusion while dredging the liver). Other considerations include minimizing intraoperative blood transfusion, using inhaled pulmonary vasodilator procedures, and maintaining an average system blood pressure of more than 70 mmHg to optimize RV performance.

9.2.2 Patient Selection

Selection is the key factor in determining the ultimate outcome of patients receiving left ventricular assist devices. In general, patients receiving left ventricular assist devices are selected as end-stage heart disease and there is no irreversible end-organ failure. Short-term extracorporeal left ventricular assist devices are the first-line treatment for patients who are too ill to undergo heart transplantation and cannot be removed from cardiopulmonary bypass. Left ventricular assist devices are effective bridges for patients who must wait a long time for heart transplantation [16].

9.2.2.1 First: Cardiac Factors Affecting Selection

(a) ***Valvular heart disease.***
Patients with existing mitral stenosis or aortic regurgitation may need to correct valve lesions before implantation.

(b) ***Coronary artery disease.***
Patients with inoperable coronary artery disease, supported by left ventricular assist devices, sometimes continue to suffer from angina without adverse effects on hemodynamics. However, right ventricular ischemia and myocardial damage shortly after implantation can lead to right heart failure, resulting in reduced left ventricular assist device blood flow. In order to reduce the risk of perioperative right ischemia and arrhythmia in patients undergoing coronary artery bypass surgery, the right coronary artery must be treated and protected. Sometimes, right coronary artery bypass surgery is performed during implantation to optimize perioperative right ventricular function.

(c) ***Arrhythmia.***
Atrial and ventricular arrhythmias, common in heart disease patients, continue to occur after implantation of devices [17]. Atrial fibrillation hinders right ventricular filling, but is reasonably tolerated in patients receiving left ventricular assist devices. Severe ventricular arrhythmias were previously considered contraindications to single ventricular support. However, recent experience has shown that hemodynamics is not severely impaired in patients with late-stage arrhythmias. In a 1994 study, 9 out of 21 patients receiving left ventricular assist devices had severe ventricular arrhythmias.Zero to 186 days after implantation. Mean arterial and central venous pressures were not altered by arrhythmia. At the beginning of arrhythmia, the flow through the device decreased by an average of 1.4 L/min, but returned to normal after cardioversion. No syncope, thromboembolism, or major end-organ dysfunction occurred. In the absence of ventricular fibrillation and pulmonary hypertension, patients receiving left ventricular assist devices can tolerate the equivalent of Fontan (systemic vein to pulmonary artery) circulation. Nevertheless, early electro-cardioversion or drug cardioversion is guaranteed to avoid thrombosis and improve exercise endurance [18].

(d) ***Congenital heart disease.***
It is important to pay attention to the key problem that the intracardiac septal defect should be repaired at the time of implantation to avoid right-to-left shunt and subsequent decrease in oxygen saturation due to sudden decrease of left filling pressure.

9.2.2.2 Second: Extracardiac Factors Affecting Selection

Patients receiving device implantation as a bridge for heart transplantation often have terminal organ dysfunction associated with long-term cardiac insufficiency. They are usually chronically debilitated and must withstand the rigorous test of two kinds of surgery (instrument implantation and heart transplantation), and the re-do operation of immunosuppressive therapy will bring risks. When selecting candidates for implantation of left ventricular assist devices, functional impairment of the terminal organs must be carefully considered.

Irreversible major neurological deficits are contraindications for implantation of left ventricular assist devices and heart transplantation. Severe obstructive or restrictive pulmonary disease is also contraindication, because these patients often have lower oxygen saturation during the perioperative period, leading to hypoxic pulmonary vasoconstriction and right heart failure. On the other hand, decreased lung diffusivity, which is common in [19] patients with heart failure (especially amiodarone [20]), is not considered a contraindication. Moderately elevated pulmonary vascular resistance is also common in [21] patients, which does not hinder the successful implantation of the device, especially in the case of low central venous pressure. Although dependence on hemodialysis is a contraindication for implantation devices, moderate renal insufficiency due to low cardiac output does not rule out this possibility. In patients with renal insufficiency, renal function improves with the improvement of hemodynamics and the decrease of demand for vasoconstrictor drugs. Continuous veno-venous hemofiltration (CVVH) is often necessary to facilitate fluid management during the postoperative period of these patients. Preoperative liver insufficiency was mainly manifested by prolonged prothrombin time, which was more common in patients with right heart failure. Perioperative bleeding, which is easy for these patients, will further exacerbate right heart failure and lead to increased liver congestion and coagulation. Any coagulation disorder before operation should be corrected actively. The duration of prothrombin time exceeding 16 s is usually prohibited. Lower extremity artery and aortic diseases complicate the external circulation through the femoral artery, which is sometimes required when removing the cardiopulmonary bypass device. Other factors that may complicate device placement and endanger survival include long-term glucocorticoid therapy and smaller body surface area (less than 1.5 m^2). Complications due to small body surface area are due to the need to implant a pump chamber under the abdominal wall without causing excessive damage to the wound. Finally, the development of long-term implantable devices allows patients to leave the hospital and return home, which requires assessing patient management capabilities before implantation.

(a) ***Interaction between patients and LVAD devices.***
Left ventricular assist device was used as a bridge to restore resting hemodynamics and exercise endurance after transplantation. In the latest sub-maximum exercise capacity assessment, 14 patients using left ventricular assist devices (LVADs) performed significantly better on a 6-min walk test than those 14 patients with dobutamine dependence and were similar to those 20 patients with mild heart failure. Distance walked was significantly greater for LVAD patients than dobutamine patients and was similar to that for patients with mild heart failure (LVADs, 1562 ± 404; dobutamine, 948 ± 241; and mild heart failure, 1358 ± 278 ft; $P < 0.01$) [22, 23]. Similarly, the oxygen consumption of the LVAD group was higher than that of the other two groups (16.3 ± 6.5 mL/kg/min in the left ventricular assist device group, 9.8 ± 4.8 mL/kg/min in the dobutamine group, and 11.2 ± 2.0 mL/kg/min in patients with heart failure, $P < 0.05$). Peak oxygen consumption was significantly better in patients who were supported by left ventricular assist devices for 5 months than in patients with New York Heart Association Class III heart failure. Peak oxygen consumption was higher than the predicted maximum pump flow, suggesting recovery of cardiac function. The mechanical load provided by left ventricular assist devices can lead to the reduction of myocardial histological abnormalities caused by chronic heart failure [24], including normalization of fiber orientation, regression of hypertrophy cardiac myocytes [25], reduction of wavy fiber cardiac myocytes [26], and necrosis of contractile bands [27]. Long-term left ventricular unloading reverses ventricular dilation, as evidenced by an improved end-diastolic pressure-volume relationship. Long-term support with left ventricular assist devices can improve the efficiency of myocardial mitochondria [28] and reduce neuroendocrine disorders associated with congestive heart failure (including abnormal renin activity in plasma and plasma levels of angiotensin II, adrenaline, norepinephrine, and arginine vasopressin [29, 30]). Some centers reported patients with left ventricular assist devices whose myocardial function has improved sufficiently. In order to remove the heart transplantation device, rather than the necessary heart transplantation, it is now called the "bridge to myocardial recovery." Another valuable lesson learned from the experience of [31, 32] as a left ventricular assist device for transplantation bridges is that the use of porcine inflow and outflow valves and wandering eddy flow patterns can reduce the risk of thromboembolism. More and more evidence suggests that the interaction between the host (patient) and the graft (left ventricular assist device surface) activates the balance between coagulation-promoting and fibrinolytic cascades [33]. A recent study documented persistent thrombin production and fibrinolysis in patients with left ventricular assist devices, despite their normal values in routine coagulation tests [34]. The incidence of thromboembolic events was lower in patients receiving textured surface left ventricular assist devices. Equipment has shown that this low-grade disseminated intravascular coagulation reduces the risk of clinically important thromboembolism. Tissue macrophages expressing tissue factors absorbed on the surface of the device may be the trigger for this systemic procoagulation state [35].

(b) ***Patient's adaptation to LVAD devices.***
Surgical treatment can not only restore normal resting hemodynamics, but also substantially improve the quality of life of patients. Weak recipients of left ventricular assist devices need several weeks of active nutritional support and rehabilitation to restore muscle quality and strength. Early after surgery, patients begin a rehabilitation program that encourages progressive exercise from walking to treadmill exercise to cycling. These programs promote optimal physical recovery before heart transplantation [36]. In most cases, they help patients return home from hospital. In addition, there is no doubt that the autonomy gained increases the emotional well-being of patients. After implants of left ventricular assist devices, patients can usually return to work and engage in other activities, including gardening, dancing, and driving. Only activities (such as swimming) that lead to immersion of percutaneous puncture lines are prohibited, although showers are possible and special precautions are taken against vents [37, 38].

9.2.3 Hemodynamic Monitoring

The measurement of blood pressure after operation is very important. But because LVADs belong to non-pulsating blood flow, the pulse is usually not touched, so it is usually difficult to measure blood pressure. Therefore, it is better to measure blood pressure with invasive pulmonary artery catheter during acute attack. The occlusive pressure measured by Doppler at the brachial artery can be used to assist the diagnosis, because the pressure measured by Doppler has a good correlation with the measurement of invasive artery. High blood pressure can lead to nervous system events, bleeding, and lower left ventricular outflow tract.

Pulse oximetry is unreliable when there are few or no pulses. Low values need to be confirmed by arterial blood gas analysis [39].

Invasive monitoring of pulmonary artery catheter is helpful in the diagnosis of shock state and equipment function [40, 41].

Echocardiography provides other valuable information to determine preload, ventricular function, device location, and performance [42]. Diaphragm location and chamber size provide assessment of cardiac function and guide pump speed adjustment. Assessing aortic valve opening preload may be an early sign of sepsis.

Hypotension in low LVAD OWS requires assessment of cardiac function and blood pressure, as this may be a sign of hypovolemia, RV failure, arrhythmia, or other causes (such as tamponade or device-related complications) [7].

9.2.4 *Left Heart Failure and Pulmonary Hypertension*

After implantation, the left ventricular septum moves to the left with the unloading of the left ventricle. Because of the geometric changes of RV, RV compliance increases, but contractility decreases. Then left ventricular stroke volume increased and venous return increased. However, due to pulmonary hypertension caused by chronic heart failure, right ventricular afterload was still very high. Although unpredictable, some patients developed acute right ventricular failure after left ventricular assist device implantation [43–45]. Usually clinical manifestations are characterized by increased central venous pressure, increased pulmonary vascular resistance, decreased pulmonary artery pressure, and decreased left ventricular diastolic pressure and cardiac output [40]. In very severe RV failure, pulmonary arterial pressure may be very low or normal. Within 1 month after implantation, if left and right ventricular pressure decreased, right ventricular stroke index decreased and cardiac output increased [45, 46]. The lung function will improve accordingly.

The emphasis of clinical observation is to understand the contribution of natural cardiac function to global output and valve function [47].

Immediately after surgery, hemodynamic management needs to be adjusted according to the measurement of MAP, cardiac index, and ventricular function. In addition to regulating the volume and speed of blood vessels, it is necessary to use a combination of positive inotropic drugs, vasodilators, and vasopressives. Milrinone can reduce pulmonary artery pressure and pulmonary vascular resistance (PVR) without causing excessive hypotension or arrhythmia [47, 48]. Selective pulmonary vasodilators, such as inhaled nitric oxide or epoxy prostaglandin, can also be used. Because RV systolic force is affected by systemic hypotension [49], MAP should be maintained between 70 and 90 mmHg [50, 51]. Phosphodiesterase 5A inhibitors, such as sildenafil, are used to reduce pulmonary vascular resistance [51].

9.3 Ventilator Settings During Respiratory Failure

There is no in vivo study on the effect of mechanical ventilation on LVAD performance or cardiac output in patients with LVAD. Moreover, the optimal ventilator settings for LVAD patients are uncertain. Pulmonary vasoconstriction in hypoventilated alveolar area may increase pulmonary venous pressure and further deteriorate RV dysfunction [52]. In addition, the computer model of LVAD shows that the left ventricular efficiency decreases and the right ventricular efficiency increases with the increase of intrathoracic pressure. This counteracts the increase in RV stroke power generated by continuous low flow pumps [53]. Therefore, RV failure may deteriorate after extubating. Therefore, the effects of airway pressure, ventilation, and perfusion on RV performance should be considered in the treatment of patients with left ventricular failure with respiratory failure [44, 54–65].

9.4 Adverse Events and Complications

The most common complications in patients with LVAD include bleeding, heart failure, nervous system events, arrhythmia, infection, thrombosis, or hemolysis [66–72].

9.4.1 Bleeding and Thrombus

The major thromboembolic events in patients with LVAD include pump thrombosis and arterial thromboembolism. Thrombosis occurs in impellers or low-pressure areas, such as aortic valves, atrial appendage, or a dilated left ventricle. About 8–10% of LVAD patients suffer from ischemic stroke [66, 68]. Active infection increases the risk of stroke because of increased activity of the coagulation-promoting pathway [73, 74]. About 4% of patients with pulmonary hypertension or sustained low load left ventricular outflow tract [66, 68] developed hemolysis.

Symptoms of pump thrombosis include hemolysis, thromboembolism, heart failure and end-organ insufficiency, and increased power and low flow rate readings on LVAD [75]. Pump thrombosis has been treated by thrombolysis [76], heparin [77], or clopidogrel [78]. Patients who did not undergo medication or needed emergency treatment provided equipment exchange [75, 79] or emergency transplantation [78].

Hemorrhage was the most common adverse event [80]. Twenty six percent of patients (70%) had early bleeding that required surgery. The most common site of early hemorrhage was mediastinum, followed by pleural cavity, lower gastrointestinal tract, chest wall, and upper gastrointestinal tract [81]. Patients considering transplantation should only receive irradiated blood products with leukopenia.

The common bleeding events over 30 days after implantation included epistaxis, gastrointestinal bleeding, mediastinal and thoracic bleeding, and intracranial bleeding (see [82]) [66, 83, 84]. The average INR of gastrointestinal bleeding patients was not higher than that of non-bleeding patients [85]. The causes of gastrointestinal bleeding include the most common arteriovenous malformations, as well as mucosal erosion caused by polyps, gastric tube bleeding, and gastroesophageal re-bleeding.

9.4.2 Central Nervous System Events

Cerebral hemorrhage can be caused by ischemic stroke, traumatic subdural and subarachnoid hemorrhage, and spontaneous intracranial hemorrhage. Intracranial hemorrhage is a common neurological complication of LVADS. Many patients did not have excessive anticoagulation during bleeding [86, 87]. Postoperative INR or anticoagulation regimens were not associated with neurological

complications [88]. We and others have observed that high LVAD OWS and hypertension (MAP >90 mmHg) predispose patients to spontaneous intracranial hemorrhage. The prognosis of intraparenchymal hemorrhage was particularly poor. The 30-day mortality rate was 59% [86].

9.4.3 Gastrointestinal Bleeding

The treatment of gastrointestinal bleeding in many projects includes temporary maintenance of anticoagulation therapy. If the bleeding stops, the target INR can increase slowly, while continuing to discontinue aspirin. There was no anticoagulation therapy and no thrombotic complications [77, 89–91] in the patients for more than a year. After the occurrence of intracerebral hemorrhage events, the retrospective analysis showed that aspirin could recover after 1 week, warfarin could recover after 10 days, and there was no enlargement of hemorrhage or thrombotic events [85].

Recombinant activating factor VIIa can be used in non-surgical life-threatening hemorrhage patients who do not respond to standard measures. High dose thrombin inhibitor VIIa [92] can significantly increase the incidence of thromboembolism.

Treatment of LVAD patients requires balancing the risk of thrombosis and bleeding. In patients receiving LVAD support, both procoagulant and anticoagulant pathways were activated [77]. Platelet contact activation may not be as good as people think. In fact, platelet activity may be significantly impaired, independent of aspirin use [78, 89, 93]. The absence of large von Willebrand factor monomer is characterized by acquired type 2 von Willebrand syndrome due to the shear stress of the rotor, but it returns to normal after removal of the device [78].

The anticoagulant regimen varies from institution, equipment [89] to individual patient. Antiplatelet drugs and warfarin anticoagulation are normal phenomena. However, recent data suggest that hemorrhagic complications are far greater than thrombotic complications [82, 94, 95]. In addition, anticoagulation may not be required early after surgery [95]. Warfarin usually begins drainage on the third day after surgery. The target international standardized ratio (INR) for outpatients ranges from 1.5 to 2.5 [77, 94]. The dose of aspirin is usually 50–325 mg. Some institutions give patients doses based on platelet function tests (evidence of acquired von Willebrand syndrome) [78], clinical conditions [93], or special device schemes.

9.4.4 Infection Control

Infection is the second most common cause of death after heart failure [92]. The International Society for Cardiopulmonary Transplantation (ISHLT) classifies it as an infectious complex [50] according to its relationship with equipment. However, any type of infection is associated with increased length of stay and increased

mortality [96]. Equipment-related infections usually occur after discharge [97]. Post-operative infection was also associated with neurological complications [74, 87, 88].

Specific infection of LVAD is the infection of power system or pump chamber. These symptoms are characterized by local fever and erythema, cellulitis, fever, and leukocytosis. These feeds can rise to or fall from the pump chamber. Pump bag infections may also show water discharged from the outlet of the power system and abdominal tenderness. CT, white blood cell labeled plane scintillation scan, or mixed single photon emission CT have limited application in diagnosis [97, 98]. Ultrasound can identify effusion and guide needle aspiration. Where feasible and appropriate, deep tissue swabs or biopsies should be obtained from the device.

Most LVAD-specific infections are caused by Gram-positive bacteria. *Staphylococcus aureus* is the most common, but Enterococcus and other staphylococci are often isolated. *Pseudomonas aeruginosa* [99] is the most common Gram-negative pathogen in *Pseudomonas aeruginosa* infection.

Because of the risk of implantation equipment, all types of infections require active treatment. Local infections in the power system or surgical site can be empirically treated with anti-Gram-positive coverings alone. The coverage of drug-resistant bacteria is determined by institutional prevalence and drug resistance, as well as the history of infection and previous antibiotic treatment. Deep wound infections or pump bag infections are often empirically treated with Gram-negative and anti-Gram-positive coverage. Although the power system itself cannot be replaced without replacing the pump, sometimes surgery is needed to remove the power system from the infected pipe. Deep tissue infections are usually treated with surgical debridement [100], and pump bag infections are sometimes treated with antibiotic impregnated beads [101], omentum or muscle AP or vacuum-assisted closure devices [102–104]. In severe or refractory cases, the device is transplanted and the patient is subsequently transplanted [104] or given additional physical support until the transplantation occurs. Before surgery/dental surgery, there were no trials to address the need for supplementary prevention. The ISHLT guidelines recommend that secondary prevention is appropriate, but it is still up to the therapist to decide [50, 105–107].

9.4.5 Arrhythmia

Although not necessary for left ventricular assist function, loss of atrial kick may still lead to decompensation due to reduced right ventricular output and function, so patients may need heart rate or rhythm control. In the absence of contraindications, the target INR increased to 2–2.5.

Ventricular arrhythmias are common after LVAD [108]. The reentrant circuit can be formed by placing LVAD intubation [47, 109]. In hemorrhagic events caused by hypovolemia, RV failure or venule size, contact between intubation and interventricular septum can also trigger arrhythmias. Intubation dislocation may

occur several months after implantation, as the device moves from significant changes in weight or scar tissue [110] and leads to recurrent ventricular arrhythmias.

Ventricular arrhythmias are often treated step by step. First, the left ventricular ejection velocity decreases to increase ventricular tremor, thus keeping the cannula away from the next wall. Hypovolemia was treated with fluid boluses. Beta-blockers and amiodarone are first-line antiarrhythmic drugs combined with mexiletine in the treatment of refractory ventricular tachycardia. Other antiarrhythmic drugs (sotalol, lidocaine) can be used as needed. The INR target remained unchanged [110]. In many cases, antiarrhythmic therapy can decrease over time, because the incidence is highest in the first month after implantation [110, 111]. Those with intractable ventricular tachycardia may be eligible for catheter ablation, cannula reduction, or equipment replacement [66, 112–115].

9.4.6 Aortic Valve Insufficiency

With the prolongation of LVAD support time, the prevalence and severity of aortic obstruction increased [116]. At high LVAD speed, the local heart works in series with the LVAD pump, and the aortic valve does not open. At lower speeds, the left ventricle works in parallel with the LVAD, and left ventricular contraction sprays blood into the aortic valve. However, the maximum open area and time are greatly reduced, resulting in functional aortic stenosis. Higher transvalvular pressure and increased leaf tension can lead to closure or insufficiency [42, 117], leading to reflux [111]. Aortic valve regurgitation forms a continuous oxygenated blood circulation from aorta to left ventricle, which cannot achieve systemic circulation and reduce pump effectiveness and oxygen supply, resulting in pulmonary edema and increased erythrocyte shear stress [117]. When the aortic valve does not open properly, the patient is at risk of aortic valve thrombosis [118], which poses a threat to the brain or other organs. Continuous echocardiography is used to determine the degree of aortic valve opening and to adjust the velocity to balance the optimal valve function during left ventricular unloading.

9.4.7 Non-cardiac Surgery

Non-cardiac surgery can be performed, but the risk of bleeding leading to disease is small. VAD coordinators or nurses familiar with equipment management should accompany patients in the operating room management console, monitor LVAD flow and handle any alarms. If emergency surgery is required in a center without VAD support, the care provider should call the manufacturer or the nearest hospital through the VAD program to obtain recommendations on equipment management. General anesthesia can be used safely. Arterial intubation was used to monitor MAP. Intra-abdominal surgery must be performed with extreme caution to avoid

encountering a subcutaneous tunnel drive line. Ultrasound can be used to mark the position of transmission system. It is safe to use LVAD electric knife, but the implanted defibrillator should be discontinued before operation.

There was no anticoagulant therapy during the perioperative period, and a variety of methods [119] were used. Given the low long-term risk of anticoagulant therapy and the high risk of perioperative bleeding [104, 110], it seems advisable to discontinue warfarin 5 days before elective surgery [119]. Antiplatelet therapy with low-dose aspirin can continue. Patients with other anticoagulant causes (atrial fibrillation, acute thromboembolism) can be bridged with intravenous heparin [119–121].

9.4.8 Equipment Failure and Cardiac Arrest

LVAD patients with cardiac arrest should be managed by advanced cardiac life support (ACLS) with some precautions. Severe cardiogenic shock or complete cardiac arrest may occur in patients who have stopped equipment. Appropriate management should be carried out when looking for the causes of dysfunction. Once restarted, a major problem is thromboembolism from the device. If necessary and feasible, the equipment can be replaced urgently. Pulse is not a reliable indicator of recovery. Electrical activity without cardiac contractility should prompt the search for potential causes, such as tension pneumothorax and electrolyte disorders. If cardiac arrest is not due to equipment failure, patients may or may not have enough flow through their equipment. When patients with end-stage rhythms have power output indicating the flow through the device, according to ACLS guidelines, the use of only electro-cardioversion/defibrillation, epinephrine, and atropine drugs may be sufficient to terminate arrhythmias and restart the heart. When the power output is very low, chest compression may be required to maintain perfusion. The main risk factor for chest compression during CPR is the displacement of the device or its outlet cannula located just below the sternum. This is mainly related to larger preperitoneal devices, such as HMII. Another possible option is abdominal compression, 1–2 in. to the left of the midline. Abdominal compression in LVAD patients maintains coronary perfusion pressure at 15 mmHg [122], which is the minimum pressure required for spontaneous circulation recovery and is better than the perfusion pressure normally achieved by chest compression [123]. In spontaneous circulation recovery, attention should be paid to supporting ischemic RV [115, 120, 121, 124].

9.5 Conclusion

With the increasing demand for treatment of advanced heart failure and technological progress, intensive care physicians are facing more and more opportunities for patients requiring LVADs support, which is a challenge in medical care. Management of these unique patients in intensive care units is best accomplished by a multidisciplinary team of specialists in advanced heart failure, left ventricular outflow tract care coordinators, and critical care physicians.

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Chapter 10
Challenges of Artificial Heart Devices

Po-Lin Hsu and Tingting Wu

Abstract The adverse events (AEs) associated with AHD implantation and its interaction with the patient circulation system still profoundly impair the short- to mid-term prognosis, patient's quality of life (QoL) and, in the worst-case scenario, survival rate. As a result, the associated risks significantly limit the use of AHDs to less than 0.5% of the target population. Addressing the AEs is thus the greatest challenge currently faced by device designers.

The various AEs are categorized into four groups: (1) hemocompatibility; (2) biocompatibility or interface; (3) physiology; (4) the device itself. The underlying mechanisms of each AE group are also illustrated. Despite being complex and mutual restraining, individual mechanism (definition, consequences, and currently available solutions) is introduced and discussed.

After reading this chapter, the readers may understand that optimization of AHDs to eliminate AEs is multidisciplinary and requires simultaneously balancing multiple variables. The readers are encouraged to deepen their understanding and research each mechanism or the interactions of the mechanisms further, in order to overcome the challenges and create revolutionary innovations in the future.

Keywords Artificial heart devices · Mechanisms · Adverse events · Challenges

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10.1 Introduction

Artificial heart devices (AHDs), particularly ventricular assist devices (VADs), have become effective alternative to heart transplant for end-stage heart failure (HF). Artificial heart with a comparable 1-year survival rate (>80%) is inserted when a donor heart is not available [10]. Advances in engineering, manufacturing, and materials have led to astonishing development in devices, such as device miniaturization that permits less invasive surgery, increased reliability, and zero in-pump thrombosis [2–8]. Additionally, better patient monitoring and improved clinical management have been achieved over the past decades [9]. In the first 2 years, 80% of VAD patients responded a favorable impression [10]. The improved outcomes have encouraged the application of VADs to earlier stage HF (Table 10.1).

The adverse events (AEs) associated with device implantation and its interaction with the patient circulation system still profoundly impair the short- to mid-term prognosis, patient's quality of life (QoL) and, in the worst-case scenario, survival rate. According to the eighth INTERMACS report, early causes of death are multiorgan failure (MoF), right heart failure (RHF), and strokes (both ischemic and hemorrhagic), which (in the presence of neurological events) dominates as the major cause of death 6 months post-device implantation [10].

The top two frequent complications, in terms of AEs, 3 months post-device implantation are bleeding (mostly surgical; 16.24 events/100 patient-months) and infection (13.63 events/100 patient-months). Gastrointestinal (GI) bleeding (4.08 events/100 patient-months) and thrombosis/embolism (thrombotic event + stroke; 1.25 events/100 patient-months) follow [10].

This complication rates have remained more or less stable in the INTERMACS reports [10–17]. Engineering was once believed to be the source of these

Table 10.1 Continuous-flow device implantation [10]

Patient profile at time of implant	Implant Data Era						Total	
	2008–2011		2012–2014		2015–2016			
	N	%	*N*	%	*N*	%	*N*	%
1. Critical Cardiogenic Shock	741	15.7%	1073	14.3%	857	15.9%	2671	15.1%
2. Progressive Decline	1924	40.8%	2691	35.8%	1817	33.7%	6432	36.5%
3. Stable but Inotrope Dependent	1192	25.2%	2373	31.6%	2027	37.5%	5592	31.7%
4. Resting Symptoms	609	12.9%	1075	14.3%	607	11.2%	2291	13.0%
5. Exertion Intolerant	141	3.0%	197	2.6%	64	1.2%	402	2.3%
6. Exertion Limited	80	1.7%	58	0.8%	18	0.3%	156	0.9%
7. Advanced NYHZ Class 3	35	0.7%	40	0.5%	5	0.1%	80	0.5%
Not Specified	0	0.0%	3	0.04%	5	0.1%	8	0.05%
Totals	4722	100%	7510	100%	5400	100%	17,632	100%

CF-LVAD/BiVAD Implants: April 2008–December 2016, $n = 17{,}632$

Table 10.2 Categories of the adverse events and the corresponding underlying mechanisms

Category	Adverse events or issues	Underlying mechanisms
Hemocompatibility	Bleeding	Mechanical blood trauma
	Neurological event	Flow morphology
	Pump thrombosis	Clinical management
	Stroke	Patient factor
Biocompatibility (interface related)	Infection	Bio-mechanical interface
		Clinical management
Physiology related	RHF	Physiological interaction
	LV decompression/suction/ backflow	Pulsatility
		Clinical management
Device factor only	Invasiveness due to size	Engineering
	Device malfunction	

complications, but it has become clear that other factors are also involved. Hemocompatibility-associated complications, for example, are weaved by engineering, patient factors, and clinical management [18]. Severe RHF post-left VAD (LVAD) implantation, which has poor prognosis and high (up to 70%) mortality, is another good example [19]. Although the underlying mechanism is still not yet fully understood, LVAD-induced RHF has been associated with the patient profile prior to LVAD implantation (patient factor) and perfusion level (clinical management).

Given these risks, it has been difficult to justify the overall benefit of AHDs and significantly limits the use of this life-saving technology to less than 0.5% of the target population [10, 20, 21]. With the overall survival rate essentially unchanged since Era 2 (2011–2013) in the INTERMACS database [10], modern VAD technology must address the complications.

VAD complications originate from interactions between the human circulatory system and the implanted electro-mechanical device and its accessories. We categorized the AEs into four groups (Table 10.2)—AE(s) related to: (1) hemocompatibility, the Achilles heel of VADs that is attracting more attention and research nowadays [2]; (2) biocompatibility or interface; (3) physiology; (4) the device itself. The table also describes the underlying mechanisms associated to each AE. In the following sections, the definition, consequences, and currently available solutions for each underlying mechanism will be introduced and discussed.

10.2 Underlying Mechanism for the AEs

10.2.1 Mechanical Blood Trauma

Mechanical blood trauma is the damage to blood cells and/or other components induced by mechanical shear stress, such as hemolysis, clot formation, platelet activation, and depletion of the typical multimeric structure of the von Willebrand factor (vWF).

Normally, the average wall shear stress in the human aorta is about 1 Pa, and it can reach 5 Pa in the systole and 15 Pa in smaller arteries [22, 23]. In stenosis vessels, the average wall shear stress ranges from 3.6 to 45 Pa and up to 100 Pa for a short period in severe aortic stenosis [1]. In AHDs, the moving parts and the geometry along the flow path can result in a few tens or hundreds of times of shear stress than those observed in normal physiological or patho-physiological conditions. This is known as non-physiological shear stress (NPSS). Modern AHDs utilizing rotary blood pump technology achieve the pumping function and generate continuous flow through a fast-spinning impeller with a rotational speed ranging from 1500 to 33,000 rpm; this may induce a local peak NPSS of 20–500 Pa (analytical estimation), depending on the impeller design [24–26]. Some simulations even found that the transient local peak NPSS can reach over 1000 and 3060 Pa for centrifugal and axial flow pumps, respectively [24].

Continuous exposure to NPSS is known to cause irreversible blood damage, including hemolysis and impaired coagulation function, which can then cause severe AEs, such as renal failure, anemia, hyper-coagulation, and bleeding [23]. It has been well established that the level of shear stress combined with exposure time can contribute to mechanical blood damage.

Hemolysis, the liberation of hemoglobin into the plasma due to erythrocyte (red blood cells, RBCs) damage, is the most extensively studied mechanical blood damage. A relationship was observed between the hemolysis index (HI), the percentage difference in plasma free hemoglobin, a power-law function of the shear stress acting on the cells, τ, and the time of the exposure to that shear stress, t, using single-pass blood through Couette-flow devices [28, 29]:

$$HI(\%) = \frac{hb}{HB} * 100 = Ct^{\alpha}\tau^{\beta}$$

Table 10.3 HI coefficient

	C	α	β
Giersiepen et al.	3.62×10^{-5}	0.785	2.416
Heuser et al.	1.8×10^{-6}	0.765	1.991
Zhang et al.	1.21×10^{-5}	0.747	2.004
Fraser et al.	1.745×10^{-6}	0.7762	1.963

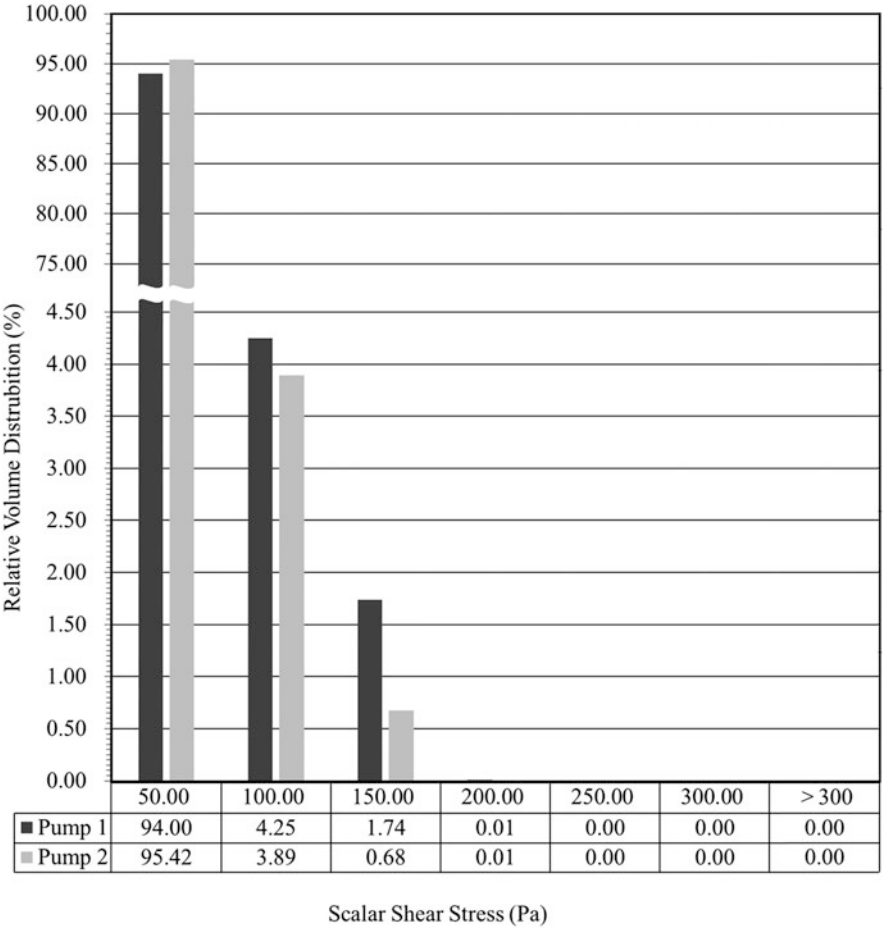
where HB represents total hemoglobin concentration and hb represents the increase in plasma free hemoglobin. The coefficients in the above equation varied significantly in the literature (Table 10.3) [26, 28–30]. The discrepancy is believed to stem from the varying Couette-flow devices used and the high sensitivity of the experiment [31].

NPSS can induce the deformation and even degeneration or degradation of blood cells and other components, particularly the RBCs and the platelets [23, 32]. NPSS is also known to deplete vWF and shields of platelet receptors when activating clotting. This results in a paradoxical effect in the coagulation process of the circulatory system, where thrombosis occurs simultaneously with non-surgical bleeding (mainly in gastrointestinal system) [33]. Recently, much effort has been devoted to understanding the mechanism of the impaired coagulation function, also known as acquired von Willebrand syndrome (AvWS), in AHD recipients [33–38]. Furthermore, the effects of shear stress on leukocytes (white blood cells, WBCs) starts to attract more attentions. They are linked to inflammatory responses and contribute indirectly to the thrombus formation. Much lower shear stress level, compared to that for the RBC, was reported to alter WBC viability, morphology, counts, and enzyme release [39–41].

Minimizing the negative effects of NPSS has been central to designing blood contacting medical devices. Using cutting-edge computational fluid dynamics (CFD), blood pumps can be designed to minimize the global as well as regional shear stress "hot spots" at the concept design stage. The threshold for trauma-inducing NPSS in the flow path has been set to 150–250 Pa by the VAD community; but the threshold does not consider other important factors, such as the exposure time and percentage volume of blood under different NPSS. Sometimes, a high shear rate can be accepted if exposed for only a very short time or if only a very small amount of blood experiences the high shear stress. For example, a blood pump design may still be comfortable when only 1% of the total priming volume undergoes a shear stress >250 Pa and none occurs in the critical path. In another case, a pump design may be comfortable with a significant wash-out passing through the high-shear regions. A useful tool that accounts for these factors is the shear stress histogram (Fig. 10.1) [42], which presents the relative total blood volume (in percentage) at individual shear stress regimes.

Pulsatile flow pumps are known to have much lower shear stress in the pump cavity than the corresponding continuous-flow pumps. However, the critical hot spot in the traditional pulsatile device designs mostly occurs at the artificial valve, employed to keep the unidirectional flow. High NPSS and complicated flow field occur with the sudden open and close of the leaflet. Unless the valve complications are resolved, the benefits of pulsatile devices in mechanical circulatory support technology remain limited.

It is important to note that blood damages induced by flow stagnation, inflow cannula malfunction, aortic insufficiency, and off-operating-point pumping are sometimes also considered to be mechanical trauma. In this section, we only refer to the blood damage induced by the shear stress. Flow-related blood traumas will be described in the following subsection titled Flow Morphology.



	50.00	100.00	150.00	200.00	250.00	300.00	> 300
Pump 1	94.00	4.25	1.74	0.01	0.00	0.00	0.00
Pump 2	95.42	3.89	0.68	0.01	0.00	0.00	0.00

Fig. 10.1 Exemplary shear stress histogram with the scalar shear stress (SSS) distributions of two pumps in a side-by-side comparison

In short, improving AHDs goes beyond optimizing the shear stress distribution. The optimization alone involves multiple factors, as described above. Therefore, a careful blood pump designer must work to balance all variables before reaching a satisfactory design. Current effort is centered on deepening our understanding of the NPSS mechanism(s) that cause(s) blood damage and the subsequent relationship to AE. The knowledge gained will enable us to bring in future innovations on device design and development.

10.2.2 Flow Morphology

During circulation, blood flow is mainly laminar; turbulent flow normally occurs inside the ventricle. A consistent flow pattern has been found inside the left ventricle. A large vortex forms during the diastole, which contributes to a diastole suction and miniaturization of kinetic energy loss and cardiac work [43–48]. The inflow of blood within one diastole is washed out completely after few cardiac cycles; this is attributed to the art of the LV vortex [49]. Given the anatomically complicated structure, this vortex behavior is the key to preventing blood stagnation inside the ventricle [45].The use of AHDs alters the flow morphology inside patients circulation.

It has been demonstrated that flow-induced thrombogenicity is the most severe mechanically induced blood trauma. Thromboembolism has been recognized as a source of patient morbidity and long-term complications in 10–15% LVAD recipients [50, 51]. Thrombosis is frequently observed at the locations where contains non-physiological flow morphology[52].

Non-physiological flow morphology such as high shear stress, turbulence, and flow stagnation or recirculation that are characterized by low shear but longer retention time can cause platelet activation and aggregation, which further form thrombosis [54, 114, 115]. Those high-risk zones include the aortic root prior to the AHD outflow cannulae, the LV apex adjencent to the pump inflow cannulae, and the prothetic valve area for those pulsatile AHDs. Prosthetic valves in the early pulsatile LVADs was the biggest risk of thrombosis in patients (1–2% per year), even with anticoagulation therapy [53]. This is because the valves generated high shear stress with part of the flow becoming turbulent, causing flow-induced thrombogenicity [54].

Thrombosis was also found in continuous-flow assist conditions, though many factors accounted for thrombus formation, the non-physiological flow morphology may be the culprit [117, 118]. Continuous-flow VAD usually contains an inflow cannula inserted at the LV apex [5]. The LV flow morphology was altered with the introduction of LVAD, and the area around the inflow cannula at the LV apex became susceptible to blood stagnation induced thrombosis [52, 116]. Several groups have subsequently studied the influence of the inserted inflow cannula length, which confirmed the importance of the flow morphology on the clotting formation [49, 55, 56]. To reduce pump-induced thrombosis events, efforts have been made to enhance washout by introducing periodic speed modulation in continuous-flow AHDs [119, 120]. Computational fluid dynamics results showed good washout of HeartMate 3 (HM3), which is consistent with clinical outcomes of low thrombus occurrence rate [121, 122]. While the artificial pulse mode of HM3 does not increase pump washout significantly compared with continuous-flow mode, it is believed that the drastic change in flow morphology, wall shear stress to be specific, may enhance the removal of potential blood deposits in the pump cavity [121]. The Lavare Cycle of HeartWare HVAD modulates pump speed every minute, altering flow morphology inside the left ventricle. This patient cohort had a significantly lower rate of

stroke in comparison with the other cohort treated by purely continuous flow [120]. A good hypothesis is that the decreased pump speed allows increase in preload, avoiding constant stagnant regions, while the increased pump speed promotes flow dynamics, enabling better washing. Potentially, the altered flow morphology may bring in additional risk factors, such as an increase in shear stress or temporary turbulence. Nevertheless, clinical practices are still limited, and the quantified impact of flow modulation on flow morphology and thus the thrombosis still requires thorough investigation.

10.2.3 Physiological Interaction

In addition to being biocompatible and hemocompatible, AHDs must also be physiologically compatible (defined as the ability to reduce unwanted impacts to global and local hemodynamics). We herein refer to the term as "physio-compatibility."

The left and right hearts are the main drivers of the systemic and pulmonary systems of the circulation, respectively. However, they are not two independent pumps. Systemic circulation originates from the left ventricle and returns to the right atrium via the vena cava, while the pulmonary circulation originates from the right ventricle and returns to the left atrium. Therefore, the left and right hearts are considered to be connected serially through the blood circulations. Additionally, the two ventricles interact structurally or mechanically through the septum, pericardium, and cardiac muscles. Both mechanisms influence the filling and pumping functions of the heart and contribute to the phenomena called ventricular interdependency [57]. Finally, the circulatory system is dynamically balanced through complicated neural regulations, such as baroreflex for maintaining the arterial pressure and auto-regulation in the brain and kidney for maintaining near constant perfusion over a wide range of blood pressure [58, 59].

When an AHD is implanted or connected to the patient's circulatory system, interaction between the electro-mechanical device and the human physiological system begins. The main goal of an AHD is to revive the malfunctioning circulatory system. Another goal is to help relieve the specific ventricle(s), depending on which side (or both) of the heart that the device is aiming to support [60].

The most frequent AE induced by physiological incompatibility is RHF, reported in up to 40% of LVAD patients [61]. One possible cause is the sudden increase in the return blood flow to the right heart from the systemic circulation, which can result in elevated right ventricular (RV) preload. Another cause is the leftward shift and tension change in the ventricular septum, which can enlarge the RV [62–64]. Ongoing research by the authors revealed that it was the baroreflex mechanism that worsened the RV preload during LVAD support (publication in preparation). It is clinically acknowledged that careful adjustment of LVAD flow rate (perfusion) can reduce the occurrence of RHF, and constant monitoring of the pulmonary arterial

pressure index can improve RHF prognosis. To date, the hypothesis that LVAD can induce RHF lacks sound quantitative evidence.

One main goal of assist devices is to recover the hemodynamics to a healthy level. This is quite straightforward as normally the mean/systolic arterial pressure and averaged cardiac output are used as the tools of quantification measurements. However, even similar average level of support was achieved, the pulsatile devices generate significantly different transient pressure and flow waveforms compared with the continuous devices, which might cause considerable differences in the molecular level and overall physiology in the long run [65–67]. Of course, pulsatility can be considered as part of the physio-compatibility. However, in light of the attention this topic has acquired, there have been significant research done around it. We will discuss pulsatility in an independent subsection.

Another goal of assist devices is to improve ventricular unloading. Continuous-flow pumps can also have different dynamic profiles when ventricular unloading is concerned [68]. Ventricular unloading, and the summed interaction with the coupled circulation are best described by the ventricular pressure-volume (PV) loops [69, 70]. This, unfortunately, is not easy to observe without invasive catheterization. This poses challenges in finding the superior support mode for individual patient or for various severity of the disease.

Many groups use lumped parameter models to simulate the physiology and analyze the hemodynamic effect and ventricular unloading [70–72]. This useful numerical platform provides useful insight into the physiological interaction between the device and the circulatory system during AHDs support. It is commonly used for evaluating extracorporeal life support, where cannulation methods are versatile and can lead to significant changes in the native physiology, such as the competing flow in the upper and lower bodies in the ECMO cases [73]. Nevertheless, the most common models are still overly simplified and can offer only a general overview instead of a patient-specific prediction. Neglecting the neural regulations of most models leaves some clinical phenomena unexplained, such as LVAD-induced RHF described earlier.

Nowadays, AHD technology allows patients to carry the device for extended periods of time and even as a destination therapy. Understanding the physiological interactions with long-term VAD implantations becomes important, especially for the physiological controller-algorithms that prevent ventricular suction or back-flow to the ventricle when the device does overwhelming or insufficient pumping, respectively, or automatically adapt level of support to the patient's need [74–77]. Part of the challenge for these advanced controllers is long-term reliability, as most sensors encounter drifting and can lead to inaccurate readings. The other part is the regulatory process as the risk and patient outcome from controller malfunction are significant and most likely not manageable by outpatients and their caregivers. The potential improvement in the patients' QoL provided by a physiological controller, which can allow the AHDs to "feel" and "react" like natural hearts, becomes difficult to justify when patients' survival is in question.

10.2.4 Pulsatility

Pulsatility is an intrinsic part of cardiovascular circulation. Pulsatile blood flow has been suggested as being a main factor in maintaining the fluid balance and exchange of nutrients at the cellular level [78]. It can also create cyclic strain and shear stress, constantly inducing complex cellular signaling pathways and significantly affecting the endothelium regulation of vasodilation and vascular remodeling [79, 80]. Nakano et al. demonstrated that both amplitude and frequency are related to endothelium-derived nitrous oxide in an acute response *in vivo* study [81]. Thacher et al. also demonstrated that reduced cyclic stretch influences the endothelium functionality, which significantly increases the production of reactive oxygen species and is known to damage cardiovascular tissue and react with nitric oxide [82]. The results from Patibandla et al. demonstrated that arterial endothelial cells subject to diminished pressure and pulsatility experienced significant changes in the transcriptional regulation of genes and the translation of proteins associated with antioxidant response [83]. Pulsatile flow is believed to be important to maintain the microcirculation. An animal experiment showed that despite the comparable mean pump flow and arterial pressure, the continuous-flow device caused collapsed capillary structure, increased shunting, and perfusion reduction [65]. Interestingly, the reduced capillary circulation and altered sympathetic nerve activity under non-pulse flow can be recovered by re-introduction of pulsatility [66, 84].

AvWS was observed in patients with continuous-flow support, associated with an increased risk of nonsurgical bleeding (70% is GI bleeding) in the first 3 months of LVAD support [67, 85–87]. The shear rate and stress are significantly increased by using continuous-flow assistaince, both inside the device and systematically. An increase in fluid shear stress above certain thresholds is known to alter the structure of vWF multimers. Induced vWF cleavage by ADAMTS-13 and vWF binding to platelets may contribute to bleeding and thrombosis, respectively [34]. Vincent et al. demonstrated that the vWF defect reflects the balance between degradation induced by the shear stress and the endothelial release of new vWF triggered by the pulsatility, and the modulation of vWF levels could explain the relationship between pulsatility and bleeding events [88].

Pulsatility has been reported to influence vital organ functions. Diminished pulsatility in calve models induced periarteritis in kidneys and lungs with continuous-flow LVAD and RVAD, respectively [89, 90]. It was suspected that the reduced pulsatility may activate the local renin-angiotensin system and elevate the angiotensin II level, resulting in an inflammatory reaction and vascular proliferation. This could be one possible explanation of the pathological changes seen in the studies.

In general, cardiac reverse remodeling rarely occurs in end-stage HF patients supported by AHDs. However, continuous-flow support has an even lower myocardial recovery rate ($<2\%$) compared to the pulsatile one. This could be related to the more preserved ventricular physiological PV relationship during pulsatile flow support [79, 91].

Continuous-flow assist devices are also associated with higher occurrence of aortic insufficiency (AI), which is known as a result of constant aortic valve closure [92]. Although similar hemodynamic pressures, flows, and ventricular unloading are normally achieved by pulsatile- and continuous-flow devices, the constant and rapid unloading by the continuous-flow devices are more likely to cause constant valve closure [67]. Furthermore, such a rapid unloading provided by continuous-flow AHDs may contribute to volume overloading in the right ventricle (RV), which can result in a left-ward septal shift and, ultimately, RV dysfunction [62]. However, it was mentioned in the previous subsection that the precise underlying mechanism causing LVAD introduced RHF is still not understood. Newest continuous flow AHDs aim to address these issues by bringing in the periodic speed modulation but clinical outcomes are not totally clear. Further study of speed regulation is needed regarding flow pulsatility, flow wave form, the interaction with native circulation, etc. Nevertheless, the published medical data did not control for patient profile and the amount of support, which may have contributed to the difference and arguements in results.

10.2.5 Interfaces with the Biomaterials

Biocompatibility, broadly defined, is the quality of interactions between artificial material surfaces and the tissue. The chemical and morphological characteristics of artificial material (biomaterial) surfaces are crucial for improving biocompatibility.

In AHDs, the main interfaces exist between (1) the blood and pump internal surfaces, (2) the cardiac endothelium or any other contacting tissues and pump housing surfaces (in the pump pocket), (3) the cardiac muscle and the inflow cannula surface and suture ring, (4) the vascular smooth muscle tissue and the outflow graft, and (5) the skin and the tunneled percutaneous driveline materials.

It is apparent that the interface (1) is associated with hemocompatibility-related adverse events. Biomaterial surfaces induce cell activation and adhesion upon their contact with blood, leading to thrombus formation (composition of platelets, fibrinogen, WBCs, and RBCs). Materials commonly used in modern AHDs have different impact level on different cells and enzymes [39, 93]. Since all AHDs utilize materials which do not release micro-particles and are not toxic to the blood, the interaction between the blood and its contacting surface belongs to the field of biomechanics, which was mostly covered in the mechanical blood trauma subsection. The surface morphology design and alternation are covered in this subsection because it traditionally belongs to the field of materials science, although the interaction remains mechanical.

Super-hydrophobicity, as observed on lotus leaves, the phenomenon where surfaces exhibit highly enhanced repelling of water (contact angle $>150^{\circ}$), is known to reduce the shear stress experienced by fluids over surfaces [94]. As a result, super-hydrophobic coatings are potentially useful in blood contacting medical devices—such as the stents, valves, and artificial hearts—to reduce thrombus

formation, hemolysis, and platelet activation [95]. However, application of such coatings is not as straightforward as it may seem. The coating may significantly alter the pumping performance and even the fundamental function because it changes the drag forces on the surfaces. This may lead to a complete re-design of the device. Zhang et al. showed a competing response between the fibrinogen and platelet adhesion to various surfaces at the molecular level, potentially leading to complex behavior at a global scale [96]. More studies are required before these advanced materials can be safely and effectively utilized in AHDs with surfaces that contact the blood.

Alternating the surface morphology is state-of-the-art for interfaces (3) and (4). Presently, titanium particle sintering is applied to the inflow—and in some cases outflow—cannula(e) in all clinically available VADs [97–99]. With very similar purposes as oncological applications, the surfaces have the roughness and microstructure to encourage endogenous tissue ingrowth to provide stability and even prevent thrombosis formation [99].

Interfaces (2) and (5) attract great attention in the field of AHDs as they are located where device-related infections occur. Device-related infection remains one of the most frequent complications—along with GI bleeding and stroke—and can be categorized into driveline infection, pump-pocket infection, and LVAD-associated endocarditis [100–102]. Pump pocket infections and LVAD-associated endocarditis—which can induce sepsis—have been significantly reduced with the introduction of smaller and less invasive devices, advances in surgical technique and clinical management, and better patient selections [100] At present, driveline infections are the most common device-related infections, accounting for 19% of infections 12 months post-LVAD implantation [103, 104]. Leuck et al. stated that "the exit site creates a conduit for entry of bacteria and the prosthetic material of the driveline creates an ideal environment for the formation of bacterial biofilms [105]." The diagnosis and differentiation of the infection type based on clinical signs and symptoms are not always easy; and aggressive treatment is highly recommended to prevent pathogens from moving deeper into the tissues [106, 107].

The transcutaneous power transmission (TET) system was developed to solve the issues caused by the percutaneous driveline [108–110]. However, the long-term efficiency and reliability for tissue/muscle growth remains a concern for such technology to be widely applied [111]. Furthermore, the extra internal components, such as induction coils and additional battery module, may require larger patient body surface area, limiting the use in smaller patients. Extra components could even increase the risk for severe pump pocket infection, requiring surgical intervention [112]. Like other engineering advances that may improve patients' QoL, TET systems or other wireless energy transmission technology will certainly return to the clinical arena after the risks are comprehensively addressed [110] and also rely on breakthroughs in other applied basic research fields, such as energy storage or power management technologies.

10.2.6 Clinical Management/Patient-Specific Factors

Among all the underlying mechanisms of AEs, patient selection is probably the most important for the success of the therapy. Patient-specific factors—including severity of heart failure prior to device implantation, genetic susceptibility to infection or other complications, and hematological status—are known to greatly impact morbidity and mortality. Medications (such as for INR management) and patient monitoring/follow-ups also influence the extent of complications and the QoL for both in- and out-patients [113]. Clinical management and patient selection overview is discussed in detail in Chaps. 8 and 9.

10.3 Summary

State-of-the-art AHDs are considered an essential and effective option for end-stage HF. Although they were initially intended to bridge patients for heart transplants, the longer survival and improved QoL, together with the advances in device reliability and durability, have allowed these devices to be used in destination therapy and in healthier patients. As patients with devices live longer, long-term complications increase and pose significant risk to patients.

Addressing the AEs is the greatest challenge currently faced by device designers. Results from research studies must be applied clinically. In this chapter, we attempted to categorize the various AEs and illustrate their underlying mechanisms. Optimization of AHDs to eliminate AEs is multidisciplinary and requires simultaneously balancing multiple variables. Mechanisms are very much interwoven and may even be mutually restraining, making the overall development as complex as untangling a tangled yarn. Furthermore, each mechanism is complex and often interlinks with other mechanisms. Every individual mechanism probably deserves an entire chapter or even a book to describe. This chapter serves merely as a general introduction to encourage readers to deepen their understanding and research each mechanism or the interactions of the mechanisms further, in order to overcome the challenges and create revolutionary innovations in the future.

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Chapter 11
Innovation Updates for Biocompatible Ventricular Assist Devices

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Abstract To improve the biocompatibility of ventricular assist devices (VADs), the possible approaches are mimicking the blood flow pattern in the left ventricle or assisting the diseased heart without blood contacts. Currently VADs are driven by electromagnetic motors which are suitable working at high rotation speed with maximum efficiency, resulting in compact, fully implantable VADs with continuous blood flow. These VADs provide meaningful increases in survival, functional capacity, and quality of life. Implantation volumes continue to grow, but severe adverse complications remain to be overcome before VADs will be considered as the therapy of choice for all patients with advanced heart failure. Most of severe adverse complications are associated with high shear stresses in the blood flow and asynchronization with the native heart. To reduce these severe adverse complications, this chapter explores the feasibility of VADs to mimic the blood flow pattern in the left ventricle driven by ultrasonic motors, which are characterized light weight, small size, fast response with mechanical time constant less than 1 ms, high torque density, accurate speed and position control, and unaffected by the magnetic field. The VADs actuated by ultrasonic motors have the potential to be small size, and improved biocompatibility with actuate synchronization and favorable blood flow pattern. This chapter also introduces the preogress in the development of direct cardiac compression devices.

Keywords Ventricular assist devices (VADs) · Biocompatibility · Pulsatile pumps · Ultrasonic motors · Direct cardiac compression devices

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11.1 Introduction

Heart failure (HF) is a condition in which the heart is unable to pump enough blood to support the basic needs of the body [1], and affects 4.5 million people in China alone [2]. Although medical management has reduced the overall mortality, a small percentage of the patients progress to end-stage HF [3], for which cardiac transplantation and ventricular assist device (VAD) implantation are the two main treatment options. However, cardiac transplantation is limited due to the number of available organs, and the patients are forced to use VADs as a bridge to transplantations or even as destination therapy [4].

With advancement of device technology, more than 22,000 patients have now received a continuous flow LVAD in the United States with overall survival remaining >80% at 1 year and 70% at 2 years [5]. However, VAD therapy is associated with significant numbers of post-implantation adverse events, such as bleeding, infection, thrombosis, embolism, and hemodynamic alterations. In general, major adverse events can be categorized into those intrinsic to the pump and its constituents such as pump malfunction, and those related to the biocompatibility of VAD [6], which can be further divided into biological reactions and material reactions associated with the materials contacting with blood, blood trauma associated with non-physiological blood flow, and the complications associated with the asynchronization [7–9]. For a durable continuous flow VAD, improving biocompatibility will be a major challenge to reduce adverse events [6].

As for the materials contacting with the blood in VADs, the biological reactions and material reactions have been significantly suppressed due to the progress of material technology. For example, the blood-contacting surfaces of HeartMate XVE (Thoratec, Pleasanton, CA) and its conduits are textured to promote the formation of a biologic neointima lining that markedly reduces the thrombogenicity of the device. As a result of this surface and the use of biological valves, anticoagulation is not required for most patients [10], which suggests that the biocompatibility related to blood trauma caused by the non-physiological flow dynamics and the complications caused by asynchronization therapy are the major sources of adverse complications in current VAD techniques [9].

The flow dynamics and asynchronization are mainly associated with the actuating technology of VAD. For example, implanted pulsatile pump such as Heartmate XVE (Thoratec, Pleasanton, CA) uses a cam to convert the rotation of low-speed torque motor into a reciprocal motion [11]. On one side, this cam could precisely control on the blood ejection process, reducing the potential blood trauma caused by blood dynamics; but on the other side this cam adversely increases the size of VAD with lowering reliability [10]; the pulsatile pumps such as Novacor (WorldHeart, Oakland, CA) uses a solenoid to squeeze a seamless, smooth surfaced polyurethane sac to pump the blood [12]. This simple actuating technology increases the pulsatile pump duration up to 6 years with a synchronization operation mode [13] but the large solenoid is difficult to control the blood pumping process, inducing a higher rate of thromboembolism [14]; the rotary pumps such as HeartMate II (Thoratec,

Pleasanton, CA) have only one moving rotor assembly [15]. This simple actuating technology increases the duration of continuous flow VAD over 6 years [5], but the high-speed rotating impeller causes blood trauma and induces thrombosis or bleeding [16] and restricts the possible synchronization with native heart [9]. Since electromagnetic motors are more suitable working under constant rotation mode with high efficiency and reliability and small size comparing to their linear mode [17], the non-physiological flow and asynchronization of continuous flow VADs are mainly attributed to the characteristics of electromagnetic actuating technology.

To reduce the adverse complications, the first advance is to optimize the electromagnetic actuating technology. The newest HeartMate 3 (HM3) (Abbott) is an optimization example with fully magnetically levitated impeller. The clinical investigations have shown improvement in terms of pump thrombosis. But the complications such as stroke, bleeding, right-sided HF, and functional capacity have no obvious improvements [7].

One promising actuator for VADs is ultrasonic motor because it characterizes light weight, small size, fast response with mechanical time constant less than 1 ms, high torque density, accurate speed and position control, and unaffected by the magnetic field [18]; the VAD actuated by ultrasonic motors has potential to be light weight, small size, actuate synchronization, and compatible with nuclear magnetic resonance imaging. For example, Shiba et al. proposed an ultrasonic motor direct-drive artificial heart powered by a wireless energy transmission system [19]. Although ultrasonic motors look like very attractive to be the actuators of VAD, they are initially considered as unsuitable for being the actuator of VAD due to the limited durability and drooping speed-torque characteristics and intermittent operation mode [20].

However, the performance of the ultrasonic motor is rapidly improved as the time goes on. For example, as the friction material progresses, 100,000 h lifetime of the ultrasonic motor has been reported in the laboratory [21]. Using heat dissipation technology, a high-performance and stable operation of the ultrasonic motor has been realized [22]. With the resonant frequency tracking of the stator, the stable operation of the ultrasonic motor under variable loads has been achieved [23]. Hence ultrasonic motors are becoming the potential actuators of VAD with small size, light weight, long durability, and the possible low rates of complications due to the precise control of the blood flow.

To improve the biocompatibility of VADs, an existing approach is to use a direct mechanical ventricular assist device without blood contacts. For example, Roche et al. proposed soft robotic techniques to develop a tethered implantable sleeve, providing circulatory support for patients with compromised heart function [24]. Yang et al. investigated a self-moving linear ultrasonic motor for a cardiac compression assist device [25]. However, all these investigations are still in their early stage for the clinical applications.

This chapter will introduce innovation updates for improvements of biocompatibility. In one aspect, this chapter introduces the feasibility study of VAD driven by ultrasonic motors for reducing the adverse complications; in another aspect, this chapter also introduces the existing direct mechanical ventricular assist device

without blood contacts to reduce the possible risk of thromboembolic events in VADs. This chapter is organized as follows. Section 11.2 describes the pulsatile pumps based on the ultrasonic motors, including the principle of ultrasonic motors, structure of VAD driven by ultrasonic motors, and in vitro experimental results of flow patterns, synchronization, and hemolysis. Section 11.3 introduces the development of epicardial compression mechanical devices, including design and future considerations.

11.2 Pulsatile Pumps Driven by Ultrasonic Motors

11.2.1 Method

Since ultrasonic motors feature with light weight, small size, fast response with mechanical time constant less than 1 ms, high torque density, accurate speed and position control, and unaffected by the magnetic field, small size and physiological blood flow and synchronization can be achieved in VAD when driven by an ultrasonic motor. However, the shortcomings such as drooping speed-torque characteristics and intermittent operation mode of commercial ultrasonic motors prevent the applications for being the actuators of VADs [22, 23]. Therefore, the techniques to overcome these shortcomings will be mainly introduced as follows.

11.2.1.1 Ultrasonic Motors

As actuators and power sources, traditional electromagnetic motors have been widely used in many fields and have contributed greatly to our societies after being developed more than 100 years. Over many years, the technologies of electromagnetic motor have been developed so successfully that little improvement can be made to them. However, there are situations such as heart assist devices, and precision instrument that electromagnetic motor may impose some limits for the applications. For example, continuous flow VADs driven by an electromagnetic motor may have small size, light weight, and high reliability that is desired, but high rotation speed of the impeller makes blood trauma and asynchronization complications hard to avoid [26]. Therefore, it is necessary to explore various small new motors such as ultrasonic motors.

Ultrasonic motor is a type of electric motor powered by the ultrasonic vibration of a stator, placed against the rotor or slider depending on the scheme of operation, as shown in Fig. 11.1a. When the reverse piezoelectric effect is used to generate elliptical motion on the stator surface as shown in Fig. 11.1b, the mechanical movement and torque are achieved by means of single direction friction driving force between the stator and the rotor or slider. Hence ultrasonic motor features with small size, light weight, fast response, and high precision positioning due to the friction drive. These features are desired to be the actuators of VADs because they

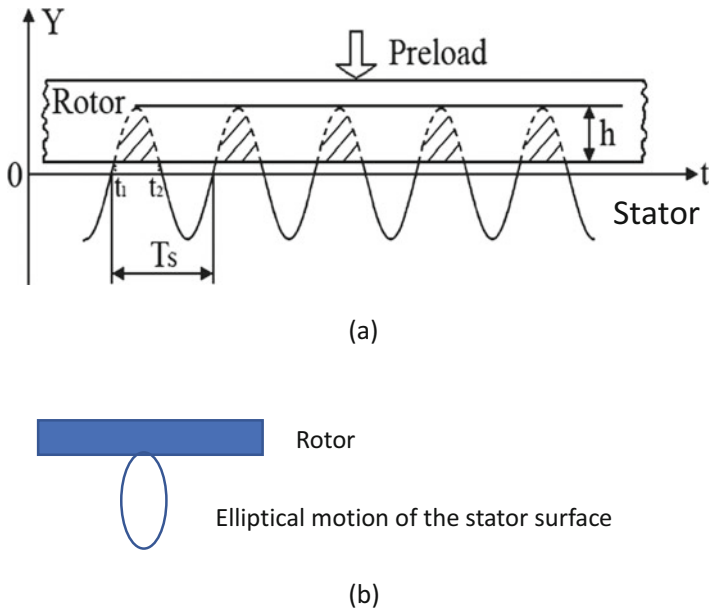

Fig. 11.1 (**a**) The principle of ultrasonic motors; (**b**) elliptical motion of the stator surface

allow the VADs to generate physiological blood flow and coordination with native heart possible due to the super dynamic performance of ultrasonic motors. However, on the other side, these friction drives could also generate heat causing temperature rising, restricting ultrasonic motor at intermittent operation with a relatively short lifetime due to the wear, which make ultrasonic motors impossible being the actuators of VADs. Hence a specially designed ultrasonic motor for the VAD has to be adopted, in which the heat dissipation designs must be incorporated into the structure of the VAD. Furthermore, because the lifetime of ultrasonic motors reaching 100,000 h has been reported in the laboratory [21], it is possible to design and fabricate the frictional material used on the sliding surface of the ultrasonic motor for the long-term VAD support.

Heat generation inside an implanted device is a critical issue, and the surface temperature must remain below 42 °C to prevent burning of the surrounding tissue [27]. Hence it is necessary to design heat dissipation in the implanted VADs. Generally, an auxiliary cooling design appears to make ultrasonic motors complex, requiring a larger space and complicated control. However, output power of heart is usually smaller than 2 W, and the power of ultrasonic motors for the VAD is usually smaller than 8 W [18]. Since the specific heat capacity of blood is large, the heat power taken away by the temperature rise of 0.1 °C is more than 10 W when the flow rate is 3 L/min. Therefore, the blood flow can be used to cool ultrasonic motors in VADs with high thermal conductivity materials connecting the VAD ultrasonic motor and the blood chamber. Therefore, the water-cooling system could be

designed to prevent the temperature rising of ultrasonic motors for being the actuators of VADs.

Apart from the heat dissipation and wear, one more challenge for being the actuator of VAD is the optimum frequency tracking to overcome the variations in rotation speeds of ultrasonic motors due to varying loads. Usually direct current (DC) motor exhibits maximum efficiency approaching to the no-load speed, where the output torque is smaller comparing to the maximum torque of the DC motor. However, the absolute value of this output torque of DC motor is much greater than that of the ultrasonic motor. Hence dynamic process of the arterial system will have significant influence on the load characteristics of the ultrasonic motor because its absolute value of output torque is smaller comparing to the electromagnetic motor. In other words, the arterial pressure will slow down the rotation speeds of the ultrasonic motor when ejecting blood to the arterial system. To control the blood ejection process, the rotation speed of ultrasonic motor has been adjusted to coordinate different aortic pressure. Fortunately, there is a high-efficiency optimum frequency existing in the ultrasonic motor. Through tracking this optimum frequency, the ultrasonic motor could control the velocity for different loads [23].

11.2.1.2 Design of the VAD

Ultrasonic motors have two types, one is linear motor, and the other is rotary motor. Although ultrasonic linear motor could directly drive the blood chamber of VAD with a simple structure and high reliability [17], this chapter selects rotary ultrasonic motor as the actuator of VAD for the feasibility study. The reason is in two aspects. The first aspect is that ultrasonic rotary motor and ultrasonic linear motor share same properties in terms of small size, light weight, fast response, and high precision positioning, which are key to mimic the ventricle blood flow and synchronize with the native heart. The second aspect is associated with the commercial availability. Although a rectangular ultrasonic motor of 62 mm $\times$ 30 mm $\times$ 8 mm with a maximum no-load speed 435 mm/s and a maximum thrust force 100 N has been developed in laboratory [28], making a direct driving blood chamber of VAD possible, there is no similar commercial ultrasonic linear motor available currently. Hence a commercial rotary ultrasonic motor is adopted for the feasibility study.

11.2.1.2.1 Actuating Structure

Since rotary ultrasonic motor usually has a rotation speed of about 100 RPM and a power of 5 W, the VAD is developed as a pulsatile blood pump. When a rotary ultrasonic motor is used as the actuator, a cam is needed to transfer a rotation into a reciprocation of the push plate as shown in Fig. 11.2. When the motor operates, two roller bearings mounted on the rotor follower move along the cam groove and push the cam to move up and down alternately. The motion of the cam is constrained in the vertical direction by the guides fixed on the housing. Being connected with the

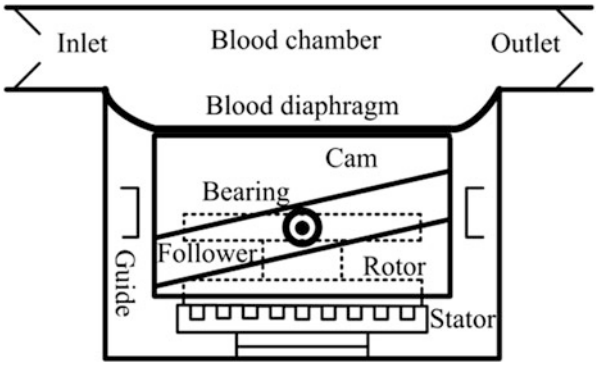

Fig. 11.2 Structure of the VAD driven by a rotary ultrasonic motor

cam through the embedded push plate, the blood diaphragm compresses and relaxes the blood chamber, corresponding to pump ejection and refilling, respectively. A couple of mechanical valves are located inside the inlet and outlet ports to ensure unidirectional flow through the blood chamber.

Theoretically, a cam-type pulsatile pump can obtain a transmission efficiency of about 65% from the rotation of the motor to the reciprocation of the push plate, yielding a pump output power of 3.2 W [29]. Generally, a healthy patient has a ventricular pump flow of 5 L/min against a mean afterload pressure of 100 mmHg, which is corresponding to a pump power of around 1.1 W. Thus, a rotary ultrasonic motor would provide enough power to support systemic circulation [29].

11.2.1.2.2 Design of Blood Chamber

Development of a blood pump faces the challenges to minimize the risk of thrombosis and hemolysis, which are not only associated with the blood contacted material but also related to the flow states within the blood chamber of pulsatile blood pumps. And the flow state in the blood chamber is mainly associated with the inflow and outflow channels arrangement, valves orientation, geometrical shape, and the actuating technology [8]. Since ultrasonic motors can be controlled with precise positions at different time [30], the blood trauma caused by blood flows could be minimized.

The next factor related to the blood trauma is the valves, which are used to prevent blood from flowing backwards. Usually there are two kinds of valves, mechanical valves and biological valves. These mechanical valves contribute to blood hemolysis and thrombogenesis [8], which restricts clinical practice of pulsatile blood pumps. However, as valve technology is continually evolving, a biological valve subject to structural valve degeneration exceeding 10 years is commercially available now [31]. Since biological valves are made with the valves and tissues derived from animals or human donors, they do not cause blood clotting on their surface and also replicate the form and function of the normal human valve.

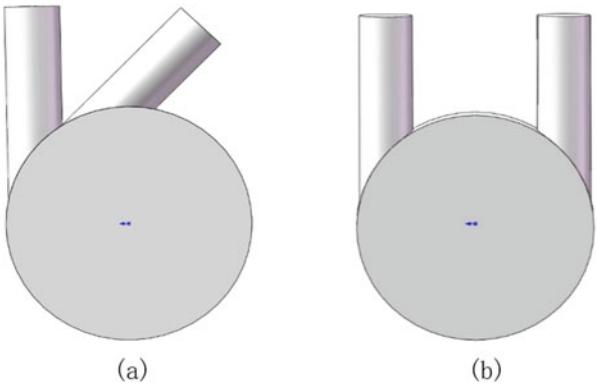

Fig. 11.3 The inflow and outflow channel arrangements of the blood chamber, (**a**) adopted [32]; (**b**) conventional

Therefore, the VAD driven by an ultrasonic motor will use biological valves to prevent blood from flowing backwards.

The geometry of the blood chamber also has important influence on the blood flow. Since the inflow and outflow channel arrangements are associated with the blood flow pattern, an arrangement to mimic anatomic structure of aortic and mitral valves has been designed as shown in Fig. 11.3a because the blood flow pattern in the ventricle has been optimized by long-term evolution [32]. Furthermore, this kind of arrangement also has a smaller dead space between the inflow and outflow channel comparing to the conventional parallel arrangement, as shown in Fig. 11.3b.

11.2.1.2.3 Design of Heat Dissipation

In electronic devices, the main methods for heat dissipation are air cooling, water cooling, and heat pipe cooling. The choice of heat dissipation method depends on the heat output of the device, operating environment, temperature control requirements, processing costs, and so on. Air-cooled heat dissipation takes heat away by air flow around the radiator to cool heating objects. It has the widest utilization, simple structure, and low cost. The performance of air-cooled heat dissipation depends on the flow state of air. However, the air is hard to flow when the VAD is implanted. Hence the air cooling could not be adopted in this design.

Water cooling is to use the convection of water to take away the heat, reducing the temperature. Water-cooling heat dissipation is generally composed of pipeline system. After water takes away heat from the surface of the heater, it circulates through the pipeline and dissipates heat at the cold end of the radiator. Because water has very good heat transfer performance, its heat transfer structure can be miniaturized at the heat transfer end without increasing the bulk volume of the device. The design of pipeline system is flexible. It can easily bring heat from heating end to outside cooling end. Therefore, the heat dissipation application of water cooling is not restricted by device installation environment [29]. Since the blood flow has a large specific heat capacity, the heat power taken away by the temperature rise of

0.1 °C is more than 10 W when the flow rate is 3 L/min. Hence the water cooling could be adopted as heat dissipation for the VAD driven by an ultrasonic motor, in which high thermal conductivity materials are used to connect the VAD motor and blood chamber [29].

Because the stator and rotor of ultrasonic motors are precisely designed and machined, any small variation will cause significant variations in the output performance of the motor. To avoid possible performance degradation, the water-cooling design of the motor is embedded in the base in which the water-cooling structure is composed of pipeline structure embedded in the base. The pipeline structure consists of inlet, outlet, and annular channel.

11.2.2 Experimental Results

An ultrasonic motor driven pump with a dimension of 86 mm in diameter and 47 mm in thickness has been developed, as shown in Fig. 11.4a. Since this book chapter concentrates on the in vitro study, a pair of bi-leaf mechanical valves (GK, Beijing Star Medical Devices Co., Ltd., China) is located inside the inlet and outlet ports to assure unidirectional flow through the pump for hydraulic performance test. For the convenience to investigate the effect of water cooling, a commercial computer water cooler (Seidon GAMING V3, Cooler Master Co., Ltd., China) is used to cool the pump base. To create a scenario as close as possible to the systemic circulation, the pump is connected to a mock circulation loop, in which a mock left ventricle (LV) is driven by a pneumatic driver. As shown in Fig. 11.4b, the mock circulation loop is able to change arterial compliance by adjusting the amount of air sealed in the arterial compliance tank, and peripheral resistance by tuning the ball valve downstream of the arterial compliance tank. Peripheral resistance corresponds to the pump afterload. A pressure transducer is located near the outlet port to record the afterload pressure, and an ultrasonic flowmeter (MA-16PAU, Transonic, Inc., NY, USA) is used to measure the pump output flow. A self-developed controller based on a NI

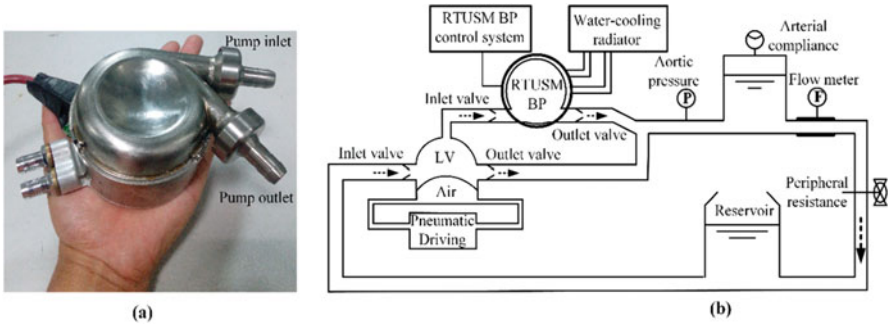

Fig. 11.4 (**a**) Photograph of the RTUSM BP. (**b**) Experimental setup for hydraulic performance test

Crio-9082 controller (NI Corp., USA) is used to control the pump and acquire the pressure and flow data [29].

11.2.2.1 The Flow Pattern

Minimizing risk of thrombosis and hemolysis is crucial in the design of any blood pump. Usually thrombus formation is due to areas of blood stagnation, that is inadequate "washing out," and hemolysis is due to areas of high shear stress. Therefore, it is necessary to investigate the flow pattern in blood chamber of the VAD. Particle image velocimetry (PIV) study and computational fluid dynamics (CFD) model are standard tools of the fluid mechanics recommended for the development and optimization of artificial organs. The PIV study is focused on the flow in the blood chamber, especially during pump ejection and filling in order to identify potential area(s) at risk for persistent blood stagnation that may promote thrombus formation. CFD was used primarily to assess order and regions of high shear stresses, with a primary focus in the chamber where the highest shear stresses were anticipated. Hence both CFD and PIV are performed to validate the blood flow pattern, as shown in Fig. 11.5 [32].

From Fig. 11.5, it is found that the flow patterns of computational results agree with the PIV data. Both of them display similar chamber rotational patterns from the filling phase to the ejection phase. During the initial filling phase of the pump, the tangential placement of the inflow interface generates a jet that pushes the fluid in the blood pump to swirl along the chamber housing at 200 ms. Areas of high flow velocity formed along the inflow of the pump. As the filling phase proceeds, a vortex begins to form at 300 ms. This large fully developed 2D-vortex has remained through the middle to the end of the filling phase at 400 ms. The max velocity is approximately 0.5 m/s. During the ejection phase at 700 ms, the flow pattern

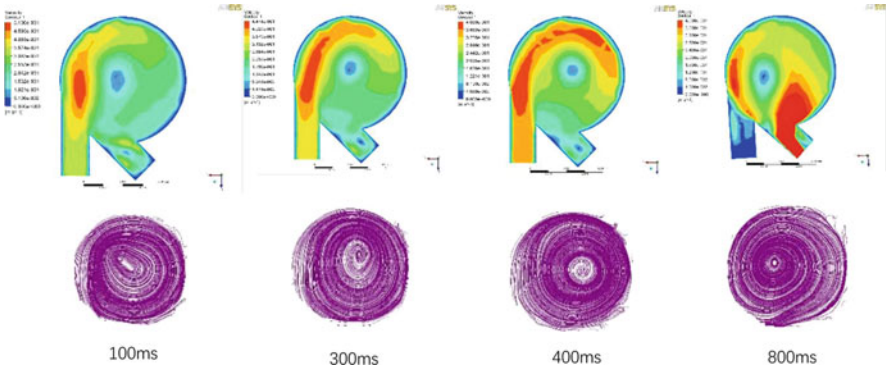

Fig. 11.5 Velocity counters of experimental (bottom) and computational (top) comparison. [Reprinted from Technology and Health Care, 23, Liang Xu, Ming Yang, Lin Ye and Zhaopeng Dong, Computational fluid dynamics analysis and PIV validation of a bionic vortex flow pulsatile LVAD, S443–S451, 2015, with permission from IOS Press]

generated by the ejection phase is consistent with the filling phase. That is, the vortex formed during the filling phase in the chamber keeps on moving. The vortex flow through filling phase and ejection phase has the same rotational direction. No areas of persistent blood stagnation or flow separation were observed. And also contours of wall shear stress in the middle of filling phase and ejection phase are well below the hemolysis threshold of 400 Pa [32]. These results suggest that the flow pattern of the VAD has good washing characteristics and favorable range of shear stresses.

11.2.2.2 Hemolysis

Hemolysis is the breakdown of red blood cells, which is often used to measure the degree of the blood trauma in the VAD. To validate the flow pattern design, an in vitro hemolysis experiment is designed, in which blood is freshly collected from the heart of anesthetized, adult New Zealand white rabbits into a 200 mL disposable blood bag (Nigale Biomedical, Sichuan, China), which contained CPDA-1 (citrate-phosphate-dextrose-adenosine) preservative. The blood is then introduced into the recirculating flow loop, which is composed of the VAD, artificial blood vessel, and blood sac. Blood samples are taken just before operating the VAD and every 10 min during the first hour and every 20 min during the following hour after that; 2 mL blood is sampled each time for analysis. The experiment is carried out over a 3-h period at a room temperature of 25 °C. In order to elevate the measurement accuracy, the experiment is repeated three times under the same operating conditions. The hemolysis induced by VAD is determined by measuring the plasma-free hemoglobin with an Ultrospec 2100pro UV/Visible Spectrophotometer (GE Healthcare, Freiburg, Germany) and subsequently calculating the hemolysis index (IH). The hemolysis rate increases with the running time of the VAD, which exhibits an exponential relation initially. Using mechanical valves will increase the hemolysis rate because it may alter the blood flow pattern and leads to the extra blood trauma in the mechanical valves. Treat the blood chamber of the VAD with such soft coatings as chitosan will decrease the hemolysis rate because the swell of chitosan provides a soft surface to blood red cell that lessens the blood trauma, permiting the hemolysis maintained at a relative low level ($<8\%$) at the experimental conditions without mechanical valves. These results suggest that the hemolysis rate is at a low and stable level, which partially validate the design of the flow pattern [33].

11.2.2.3 Hydraulic Performance

With water cooling, the VAD is able to eject water at >4.1 L/min, corresponding to >75 BPM, against the mean afterload pressures of 110 mmHg. When the afterload pressure is increased to 120 mmHg, the pump output decreases to 2.3 L/min. Generally, a diseased heart runs at a mean arterial pressure lower than 90 mmHg. Apparently, this VAD could provide a fundamental requirement for supporting the systemic circulation [29].

11.2.2.4 Synchronizing with the Native Heart

Shortly after adoption of continuous flow VAD therapy, it is noted that worsening of existing aortic valvular regurgitation is known complications of continuous flow VAD therapy. The underlying mechanisms is absence of synchronization with the native heart, decreasing the aortic valve opening leading to commissural fusion with myxomatous degeneration of the aortic valve leaflets [34]. While there are many associated benefits to pulsatile VAD, it has also been linked to consequences of non-synchronization pulse flow relating to early accelerated flow and late decelerated flow. Early accelerated flow may lead to premature closure of aortic valve and a reduction of stroke volume. In addition, late decelerated flow may increase LV afterload and myocardial oxygen consumption and reduce cardiac output [9]. However, synchronizing with R-wave on the patient's cardiac monitor, enhanced external counterpulsation technique has been proven to alleviate anginal symptoms and improve quality of life in patients with coronary artery disease [35]. Hence these previous clinical practices suggest that synchronizing support with native heart would improve the cardiac function while simultaneously avoiding complications of non-synchronization therapy.

The synchronization of VAD depends on the dynamic response of actuators. Currently pneumatic VAD has a quick response, but because air is compressible, pneumatic VAD may need a relative long time to establish required pressure. Since electromagnetic motor usually has a slow response, the VAD driven by electromagnetic motors is hard to achieve synchronization with native heart. However, the ultrasonic motors characterize with a response time of milliseconds and a positioning accuracy of micrometers. The synchronization of ultrasonic motor driven VAD with the native heart could be varied with a phase shift in increments of 10% cardiac cycle [36]. There immediately a question may arise in which phase difference between the native heart and VAD synchronization will have a better effect on the arterial system.

To investigate the phase shift influence, baseline hemodynamic measurements are acquired by the mock left ventricle, and the VAD is turned off at the beginning. The pneumatically driven mock left ventricular pressure, vascular resistance, and compliance are tuned initially to reproduce mean aortic pressures and cardiac outputs of a failing ventricle. Then hemodynamic waveforms generated by the mock left ventricle and VAD are recorded, respectively. In these experiments, the heart rate (HR) of the native left ventricle is fixed at 60 beats per minute (bpm). Also, the preload is set as approximately 10 mmHg, and the afterload is set as approximately 60–90 mmHg. In addition, the phase shift is designed as the percentage of the cardiac cycle and varied from 0% to 90% in increments of 10% [36]. In particular, it can be observed that the phase shift of 0% and 50% are equivalent to the co-pulsation mode and the counterpulsation mode, respectively. For all experiments, the ejection duration of the VAD is maintained approximately at 25% of the pumping cycle.

11.2.2.4.1 Metrics

To demonstrate the effects of the phase shift influence, the surplus hemodynamic energy (SHE) is used as metric for quantifying vascular pulsatility. To calculate the surplus hemodynamic energy, mean arterial pressure (MAP) and energy equivalent pressure (EEP) have to be obtained first [36].

- The mean arterial pressure (MAP) is calculated according to expression (1), denoting as:

$$\mathrm{MAP(mmHg)} = \frac{1}{T_{\mathrm{HR}}} \int_0^{T_{\mathrm{HR}}} P_{\mathrm{sys}}(t)\mathrm{d}t \tag{1}$$

  in which $P_{\mathrm{sys}}(t)$ represents the arterial pressure.
- In addition, the EEP expressed in mmHg is the ratio of the integrated hemodynamic power curve to the integrated aortic flow during each cardiac cycle and is equivalent to units of pressure. It is calculated as expression (2):

$$\mathrm{EEP(mmHg)} = \left(\int_0^{T_{\mathrm{HR}}} P_{\mathrm{sys}}(t) \times Q_{\mathrm{sys}}(t)\mathrm{d}t \right) / \left(\int_0^{T_{\mathrm{HR}}} Q_{\mathrm{sys}}(t)\mathrm{d}t \right) \tag{2}$$

- The surplus hemodynamic energy (SHE) is usually used as metric for quantifying vascular pulsatility. The SHE, representing the extra energy required for generation of pulsatile flow in terms of energy units, is the difference between the energy equivalent pressure (EEP) and MAP. It is calculated as follows:

$$\mathrm{SHE(erg/cm^3)} = 1.332 \times (\mathrm{EEP} - \mathrm{MAP}) \tag{3}$$

  where the coefficient of 1.332 converts the unit of pressure from millimeters of mercury to dynes per cm^3.

11.2.2.4.2 Results

The VAD is actuated in synchronous trigger mode, and the trigger signal is generated by the controller of mock LV, which is also used to calculate delay. The value of this delay, relative to between the cardiac cycle and the ejection of VAD, represents the phase shift. The VAD is operating at the fill-to-empty mode, so that the state of VAD can be analyzed by the displacement of pusher plate along the cam. A rise is the motion of the pusher plate away from the bottom to top position of the cam, and a return is the motion of the pusher plate toward from the top to bottom position of the cam.

Figure 11.6 demonstrates the variations of SHE with varying phase shift. The trend of SHE is first decreased from the phase shift 0–40%, where the minimum

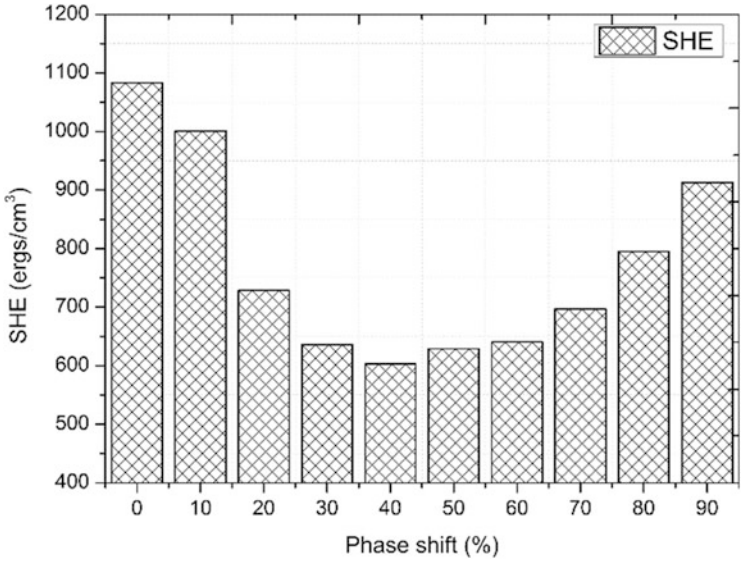

Fig. 11.6 Surplus hemodynamic energy (SHE) with varying phase shift of the VAD

value is achieved, and then increased until the phase shift 90%. It is shown that the varying phase shifts have a significant impact on the SHE. The values of SHE obtained at the phase shift 30%, 40%, 50%, and 60% are significantly smaller than others, especially the minimum value achieved at the phase shift 40%, whereas the values of SHE obtained at the phase shift 0%, 10%, and 90% are significantly greater than others. These results suggest that synchronization with different phase shifts may have a significant influence on the hemodynamics.

11.2.3 Discussion

Usually pulsatile pumps have large size, and need for abdominal implantation, which is the major reason that they are not in clinical use [37]. The size of the pulsatile pumps is highly associated with the actuator. If a commercial ultrasonic motor with a diameter of 40 mm is adopted, a VAD with a diameter of 60 mm and a thickness of 40 mm has been reported [29]. If a specially designed ultrasonic motor for VAD is available, a balance between size and the output flow may be achieved.

Although the friction drives of ultrasonic motors bring the merits of fast response and precision positioning, these friction drives may also cause deterioration of the performance of the ultrasonic motors, which is preventing ultrasonic motors for being the actuators of VADs. Since dynamic properties and life of piezoelectric ultrasonic motors are strongly related to the frictional material used on the sliding surface, numerous studies have been implemented to obtain ideal friction materials

with improvement in lifetime and the energy conversion efficiency [38]. As material technology is continually evolving, the lifetime of ultrasonic motors in the commercial products may reach the laboratory lifetime of 100,000 h in near future [21]. Apart from the material study, a dual traveling wave rotary ultrasonic motor has been proposed [39], in which a gear drive between the stator wave and the rotor wave may have the potential to have a long duration.

The other fundamental issue related to blood pumps is the material, which should enable blood to be pumped smoothly through the blood vessels and ensure that no coagulation takes place. Selected materials must be biocompatible. In this prototype, titanium alloys are used as a part of blood pumps that are contacting with tissue and blood because of their biocompatibility and consistent mechanical properties. A particular type of polyurethane polymer has been used as a diagram. According to the fatigue test data in the practical rubber manual [40], polyurethane membrane can flex more than 300 million times, equivalent to 8 years of normal heartbeat. Hence, it may be reasonable to anticipate that a pulsatile blood pump could reach a long duration accepted for the heart failure therapy in future.

Hemocompatibility is crucial to the development of VADs. CFD and PIV are standard tools used for evaluation of a blood pump design for hemocompatibility. Figure 11.5 shows that a vortex formed during the filling phase in the blood chamber keeps on moving during cardiac cycle, which is like the echocardiographic flow state in left ventricle [32]. Such a blood flow pattern prevents blood from being destroyed by impact force, and results in a relatively low hemolysis rate, suggesting that a significant improvement in hemocompatibility may be anticipated in future.

Synchronization of VADs has significant influence to the native heart [9]. Figure 11.6 shows the variations of SHE with varying phase shift, which suggest that a precise synchronization is important for the optimizable control for VAD assistance.

One more benefit is associated with the immunity of electromagnetic wave. Implantable cardioverter defibrillators (ICDs) have been shown to have a significant benefit in reducing sudden cardiac death (SCD) in patients with advance heart failure. And most patients with a VAD also have an ICD [41]. Therefore, immunity to the electromagnetic interference of ultrasonic motors can make the VAD easy compatible with other electronic devices such as ICD.

11.2.4 Limitation

Although the lifetime of 100,000 h for ultrasonic motors has ever been reported in the laboratory [21], and the commercial ultrasonic linear motors can reach a lifetime of 100 billion cycles [42], the high driving voltage for ultrasonic motors is still a limit. Therefore, the current commercial ultrasonic motors need to take further development for being the actuators of VADs.

11.3 Epicardial Compression Mechanical Devices

Treatment of end-stage heart disease remains a major clinical challenge. Currently ventricular assist devices (VADs) are used as a life-prolonging therapy, either as a bridge to transplant or, in some cases, as a "destination therapy." Using current VADs, blood is removed from the heart and is then pumped into the aorta. In this scenario, the VAD assumes the function of one or both failing ventricles of the heart. The first generation of VADs is based on a pulsatile flow whose direction is controlled by valves. The second generation of VADs uses a continuous, valve less, axial-flow technology, and the third generation is a continuous flow pump with magnetic levitation technology [43]. Although the technical improvements have reduced prothrombotic components, the contact between blood and artificial surfaces remains, which induces the risk of thromboembolic events including stroke. It is the stroke which dominates as the major cause of death after 6-month implantation of VADs [5].

To avoid the risk of thromboembolic events in VADs, a direct mechanical ventricular assist device was first developed by Anstadt et al. in 1965 and later approved for clinical use in 1989 [44, 45]. This early direct mechanical ventricular assist device is called Anstadt cup, which is a mechanical circulatory support modality that uses a direct cardiac compression (DCC) device for helping the failing heart. Since the DCC device wraps on the heart surface without blood contact, it evades the complex complications induced by left ventricular assist device, including thromboembolic events, hemolysis, bleeding, and immune reactions [46]. The results of clinical trials confirm that Anstadt cup can effectively improve heart function in patients with heart failure and is an effective transitional alternative therapy for heart transplantation [45, 47].

Since early DCC devices do not integrate and synchronize with native cardiac contraction mechanics and direction, most of these external devices reduce biomimicry and efficiency [48, 49].

To overcome the shortcoming of existing technologies, Roche et al. developed a soft robotic sleeve to support heart function, in which a biologically inspired design is used to orient individual contracting elements or actuators in a layered helical and circumferential fashion, mimicking the orientation of the outer two muscle layers of the mammalian heart. By implanting this soft robotic sleeve in a pig model with acute heart failure, the device was found to restore cardiac output to approximately 97% of normal baseline levels, improving diastolic function [24]. This soft robotic sleeve is composed of a number of custom-designed soft pneumatic artificial muscles integrated with a soft matrix that approximated and conformed to the outer surface of the heart. It can be controlled by inflation and deflation to reduce contraction and relaxation, and simultaneously undergo twisting and compressive motions. It can separately control the inflation and deflection of the left and right sides and can also adjust the different pressures of the left and right ventricles. The biggest advantage of the soft robotic sleeve is that it can pressure the heart regularly, synchronizing with the normal heart cycle, conforming to the heart's own beating

and rhythm, and simultaneously monitoring heart rate, pulmonary artery pressure, ascending arterial pressure, and blood flow rate. Furthermore, a hydrogel is used as a protective layer at the device-tissue interface to reduce friction and minimize inflammation when the device is moving over the heart surface [24].

These progresses have demonstrated the feasibility of direct cardiac compression for supporting heart function in an acute heart failure with customized to patient-specific needs.

11.3.1 Design and Methods

The physiology of epicardial compression stems from the investigations using isolated canine hearts placed inside compression chambers whose pressures could be controlled to mimic the normal heart function [50, 51]. The experimental results demonstrate that the dynamic cardiac compression augments net ventricular pumping capacity without increasing myocardial oxygen demand or compromising coronary blood flow [50].

The strength of ventricular contraction can also be characterized by ventricular pressure with fixed ventricular volume. In this case, the assisted ventricular pressure can be expressed as the sum of the myocardial contraction pressure and the pressure exerted on the epicardium [51]. Namely:

$$\mathrm{Pic}(V,t) = \mathrm{Ptm}(V,t) + \mathrm{PDCC}(t) \tag{4}$$

Among them, Pic represents intraventricular pressure, Ptm represents ventricular transmural pressure, and PDCC represents pressure exerted by the direct ventricular assist device on the epicardium. Based on this principle, it is obvious that the end-systolic pressure–volume relationship will shift upward by an amount determined by the external compression pressure.

Applying this principle, the design of DCC devices will usually include the design of structure, actuators, materials, and monitoring system.

11.3.1.1 Structure

The structure of the direct ventricular assist device is mainly divided into a cup shape and a cuff shape. In 1965, Anstadt et al. [44] designed a cup-shaped epicardial compression device for cardiopulmonary resuscitation. The outer shell is semi-rigid material, the inner layer is a silicone diaphragm, and the upper end is sleeved at the atrioventricular groove to avoid the device from squeezing the atrium. Since the inner layer is tightly sealed to the epicardial compression, this device could provide both diastolic decompression and epicardial compression. CardioSupport System (Cardio Technologies, Inc., Pine Brook, NJ) has a cuff-like structure [52], in which cuff's compression bladder circumscribes the heart between the apex and the

atrioventricular groove. The negative pressure applied to the apex of the heart is used to fix the device to the heart. In addition, there are two electrodes inside the vacuum seal, which provides ECG synchronization for timing the inflation and deflation of the DCC [51].

11.3.1.2 Material

Non-blood contact ventricular assist devices are directly placed onto the surface of the heart. Therefore, the selected materials must have good biocompatibility to avoid or reduce the inflammatory reaction caused by implantation, and to ensure the safety of the device. Secondly, a flexible and thin material is wrapped around the epicardium. On one side, the outer layer requires a rigid material. When the pressure is regulated, the inner layer can withstand a certain pressure range of contraction and expansion to augment heart function with a better fitment, and the outer layer can maintain the basic structure of the device. In addition, the entire device should be made of lightweight materials to prevent the device from becoming a heart-pulsating load [47]. The fabrication is usually based on silicone-casting or thermoplastic-forming process [24].

11.3.1.3 Actuator

The actuator technology is one of major issues in the development of DCC devices. Usually pneumatic pump and liquid pump are used to implement the inflation and the deflation of the DCC devices. However, hydraulic drive may be heavy due to the weight of the working fluid for the device wrapping around the heart surface, and also possible contamination due to the leaking of the fluid, which is a risk factor for the implantation of devices. In addition, pneumatic pumps are usually bulky, restricting the mobility of patients. Therefore, an optimized design for actuators is necessary for the development of DCC devices.

11.3.1.4 Monitoring

Since DCC devices need to be coordinated with diseased heart, monitoring hemodynamic parameters would be necessary to properly augment heart function. As the sensor technology is continually evolving, sensor chip for data acquisition is more and more mature. This will not only make the monitoring of various parameters of the heart feasible, but also send parameters to external devices and doctors in real time for remote management and control. However, the sensor chips in the device may increase the complexity of the system; a better choice may be noninvasive estimation of the parameters if the estimation accuracy is accepted. To avoid myocardial trauma induced by invasive sensors, An Dawei et al. proposed a noninvasive estimation method to measure the assisting pressure. It has been shown that

polynomial model presents the best behavior to predict the assist pressure within and beyond the sample data range among the possible alternative models [46]. This estimation could promote the development of programmable control to fit for the blood perfusion requirements with minimally invasive treatment.

11.3.2 Future Considerations

11.3.2.1 Minimally Invasive Surgery

In minimally invasive surgery, doctors use a variety of techniques to operate with less damage to the body than with open surgery. In general, minimally invasive surgery is associated with less pain, a quicker recovery, and fewer complications. Therefore, the design of DCC devices should be fit for minimally invasive surgery, in which completely flexible materials should be adopted in future.

11.3.2.2 Portable Design

The traditional DCC devices are usually pneumatic driven. However, the air compressor is usually bulky, and the mobility of the patient is limited. The electric hydraulic drive method could greatly reduce the volume of the air compressor, which may provide a solution for portable design [53].

11.3.2.3 Physiological Control

Currently DCC devices mainly use asynchronous or synchronous assisted approach to improve hemodynamic parameters. However, assistance pressure may need to be adjustable to fit for different degree of heart disease. Therefore, a combination of custom control and instrumentation system of DCC devices is required to simultaneously monitor and record physiological performance parameters such as heart rate and ascending aortic pressure and flow rate. In this way, a physiological control could be designed to coordinate with the native cardiac cycle and fine-tune force generation and timing to provide disease-specific assistance.

11.4 Conclusion

Using an ultrasonic motor, an optimized inflow and outflow channel arrangement, this chapter reports the biocompatible VAD development and in vitro evaluation. The CFD and PIV show that flow pattern of blood chamber has good washing characteristics and favorable range of shear stresses, and the initial hemolysis test

results show a low hemolysis rate. Also, it is found that the synchronization with varying phase shifts has significant influences on the hemodynamics. Considering that electromagnetic motors operating at a constant rotation speed are inducing the severe adverse complications, this biocompatible VAD driven by ultrasonic motors is warranted further investigation for optimization in size and reliability because it may offer the benefits of small size and high reliability while providing the physiologic benefits of pulsatile end-organ perfusion. Furthermore, direct mechanical ventricular assist devices also have demonstrated the potential to avoid blood trauma.

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