

**Development of a Novel Centrifugal Left Ventricular Assist Device and the First
In Vivo Study: Istanbul Heart VAD**

By

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Development of a Novel Centrifugal Left Ventricular Assist Device and the First In Vivo Study: Istanbul Heart VAD

Koç University

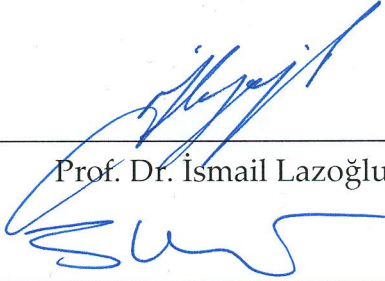
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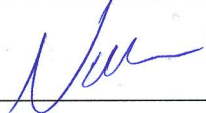
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**I DEDICATE THIS THESIS AND THE JOURNEY TO MY FATHER IRFAN, MY
MOTHER SEVGI, MY BROTHER EGEHAN AND MY FIANCEE SEVIM.**

ABSTRACT

Heart failure (HF) is a life-threatening disease that affects the structure and functions of the heart. The possible solutions for HF condition are mainly limited to the heart transplantation and mechanical circulatory support systems. Due to the shortage of available donor hearts, left ventricular assist devices (LVADs) have been used as a common treatment for HF patients as a bridge to transplant, bridge to recovery or destination therapy. LVADs have been a promising option for the survival of patients. However, high importing costs limit the use of VAD for every heart patient. Therefore, this study aims to develop a novel centrifugal blood pump for the HF patients who are not eligible for cardiac transplants to access a low cost, high-quality device.

Computational fluid dynamics (CFD) analysis has been used to accurately predict the hydraulic performance and flow field within the blood pump. Virtual design of the pump is constructed for CFD optimizations. A number of impeller/volute configurations were established in the design stage. CFD-based design optimization method has been developed, involving hydraulic performance, efficiency, and hemolysis. Shear stress and exposure time are considered as main factors to the hemolytic performance of blood pumps. CFD analysis revealed the regions of high shear and stagnation zones that could damage the red blood cells (RBC) and affect the hydroulic performance of the pump. This comprehensive CFD analysis of the pump performance and hemocompatibility provide a path for pump optimizations.

The presented method can also be utilized as an efficient CFD tool for new pump designs or multi-objective optimization.

Experimental evaluation of the prototype was performed to validate the computational results. Furthermore, an in vitro blood test of the final prototype has been conducted with hemolysis test rig by using the human blood. The in vitro test result demonstrates satisfying performance regarding the hemolysis index, pHb generation, hematocrit level, etc. in the range of clinically available LVADs.

In vivo device evaluation is vital for the validation of device performance before human clinical trials. The porcine animal model was selected in this study for initial acute evaluation. Three pigs weighing 77–92 kg have been used to assess the anatomical fitting and blood-handling characteristics during the acute experiments up to 6 hours. The study demonstrated an appropriate circulatory support, and the flow characteristics. Further acute in vivo studies are in progress for short-term evaluation.

ÖZETÇE

Kalp yetersizliği, insan kalbinin yapısını ve fonksiyonunu bozan ciddi bir sağlık sorunudur. Bu sorun için muhtemel çözümler ise kalp nakli ya da mekanik dolaşım destek cihazlarıdır. Mevcut donör organların yetersiz sayıda olmasından dolayı sol ventriküler destek cihazları (SVDC) sıklıkla kullanılan tedavi yöntemi olmuştur, bu yöntemler transplantasyona köprüleme, iyileşmeye köprüleme ve kalıcı tedavi olarak tanımlanabilir. SVDC'ler kalp yetersizliği hastaları için umut verici bir yöntem olmuştur, fakat yüksek ithalat maliyetleri bu cihazların her hasta tarafından kullanılabilmesini engellemektedir. Bu yüzden, yürütülen bu çalışma yenilikçi bir tasarıma sahip sentrifügal akışlı bir kan pompasını kalp nakline uygun olmayan hastalar için yüksek kalitede ve düşük maliyetle üretmeyi hedeflemektedir.

Hesaplamalı Akışkanlar Dinamiği (HAD) analizi pompa içindeki akış alanlarının ve hidrolik performansın hassas bir şekilde tahmin edilmesinde kullanılır. HAD analizleri ile optimizasyon çalışmalarının yürütülmesi için sanal ortamda pompa dizayn edilmiştir. Birden fazla rotor/volute konfigürasyonu oluşturulmuştur. HAD analizi ile yapılacak optimizasyon çalışması için geliştirilen metot ile hidrolik performans, verimlilik ve hemoliz incelenmiştir. Kayma gerilimi ve gerilime maruz kalma süresi pompanın hemolitik performansının temel faktörleri olarak hesaba katılmıştır. HAD analizleri ile yüksek kayma gerilimi ve durağan alanlar tespit edilmiştir, bu alanlar hidrodinamik verimliliği düşürmekte, tromboz ve hemoliz riskini arttırmaktadır. Yapılan kapsamlı HAD analizi, pompanın performansını ve

kan uyumluluğunu arttırmak için yapılacak ileri çalışmalar için de yol haritası olmuştur. Burada anlatılan yöntem başka pompa geliştirme çalışmaları için de etkili bir HAD analiz aracı olarak kullanılabilir.

Üretilen prototipin sanal ortamdaki simülasyon sonuçlarını doğrulamak için fiziki performans testi yürütülmüştür. Kan özelliklerini taklit eden bir akışkanın kullanıldığı test düzeneği kurulmuştur ve son prototipin kan testleri gerçekleştirilmiştir. Kan testi sonuçları, hemoliz indeksleri, hemoglobin miktarı ve hematokrit seviyesi dikkate alındığında tatmin edici bir performans ortaya koymuştur.

Geliştirilen bu cihazın insanlarda denemeye başlanmadan önce hayvan modeli üzerinde test edilmesi çok önemlidir. Bu çalışmada yürütülecek öncül akut deneyleri için domuz hayvan modeli seçilmiştir. Kiloları 77-92 kg arasında değişen üç domuz üzerinde akut deneyler yürütülerek pompanın anatomik olarak yerleştirilme pozisyonu ve kana verdiği zararlar incelenmiştir. Yapılan hayvan çalışmaları uygun bir kardiyak dolaşım ve akış karakteristiği ortaya koymuştur. Pompanın kısa dönem değerlendirilmesi için ileri akut deneyler devam etmektedir.

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NOMENCLATURE

ASTM	American Society for Testing and Materials
BPM	Beats per Minute
BTR	Bridge to Recovery
BTT	Bridge to Transplantation
CFD	Computational Fluid Dynamics
CHF	Coronary Heart Failure
CVD	Cardiovascular Disease
DT	Destination Therapy
FDA	U.S. Food and Drug Administration
HCT	Hematocrit
HF	Heart Failure
HGB	Hemoglobin
LVAD	Left Ventricular Assist Device
MCSS	Mechanical Circulatory Support System
NIH	Normalized Index of Hemolysis
PIV	Particle Image Velocimetry
Q	Flow Rate
RBC	Red Blood Cell
rpm	Revolution per Minute
RVAD	Right Ventricular Assist Device
TAH	Total Artificial Heart
UDF	User Defined Function
VAD	Ventricular Assist Device

η_h	Hydraulic efficiency
P_h	Hydraulic power
T	Torque
ω	Angular velocity
ρ	Fluid density
g	Acceleration due to gravity
H	Pressure head
v	Velocity
Re	Reynolds number
μ	Dynamic viscosity
dHb	Damaged hemoglobin content
τ	Scalar stress
Hb	Hemoglobin content
D	Blood damage index
D_l	Linear blood damage index

Chapter 1

INTRODUCTION

1.1 Introduction

This thesis discusses the development and evaluation of a novel ventricular assist device (VAD), called Istanbul Heart VAD (iHeart VAD) which is recently developed in Manufacturing and Automation Research Center (MARC), Koç University, Turkey. A VAD is a mechanical device that provides cardiac support for the end-stage heart failure (HF) patients as a bridge-to-recovery, bridge-to-transplantation or destination therapy. The use of this technology has increased as the number of advanced heart failure patients escalates while the number of suitable donors stands in the same level. In the first chapter of this thesis, a brief overview of the VAD and the motivation of the current study is introduced.

1.2 Significance

Heart failure (HF) is a severe medical condition, and it is the primary cause of death as reported by World Health Organization (WHO) [1]. Despite the advances in medical technology, the heart failure remains as a most common death cause [2]. It occurs due to the insufficient blood supply to the heart muscle, e.g., as a complication of myocardial infarction, myocarditis or cardiomyopathies.

Globally around 26 million people experience the heart failure problem [3]. Currently, 6.5 million people have this health problem in the US, and it is projected that at least 8 million people will have HF by 2030 [3,4]. Also, more than 5 million people die due to coronary artery diseases in Europe last year [5]. Likewise, 4.2 million people in China and 1 million people in Japan currently have HF [6,7]. Around 5% of HF patients suffer from advanced heart failure which is called as end-stage HF [8]. There are approximately 300,000 patients in the US and 500,000 patients in Europe with end-stage HF. Although there are many available treatments based on the stage of heart failure, the most effective treatment of end-stage HF is heart transplantation. However, many people die each year waiting for transplantation since there is not enough of available heart donors. In last 25 years, the number of available donor organs has remained same while the numbers of patients who are waiting for a heart donor are doubled (Figure 1) [9].

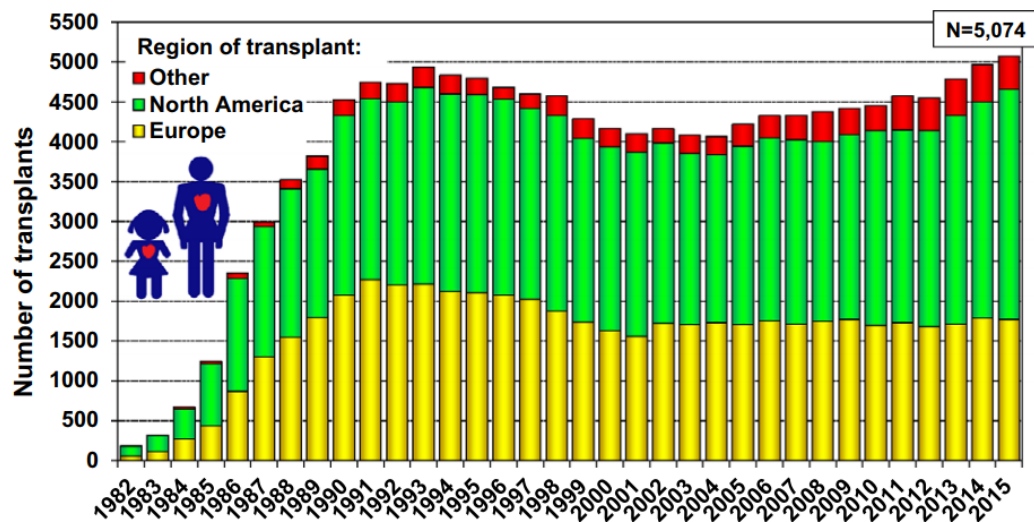


Figure 1 - Number of heart transplantations by year [10].

During the last decades, mechanical circulatory support systems (MCSS) has been widely used to assist heart failure patients as an alternative treatment method (Figure 2). These devices target to improve the life quality of HF patient by providing adequate cardiac output. A left ventricular assist device (LVAD) is the most frequent device among blood pumps to support the weakened left ventricle. In general, these devices increase the quality of life and offer the patients a potential for long-term survival.

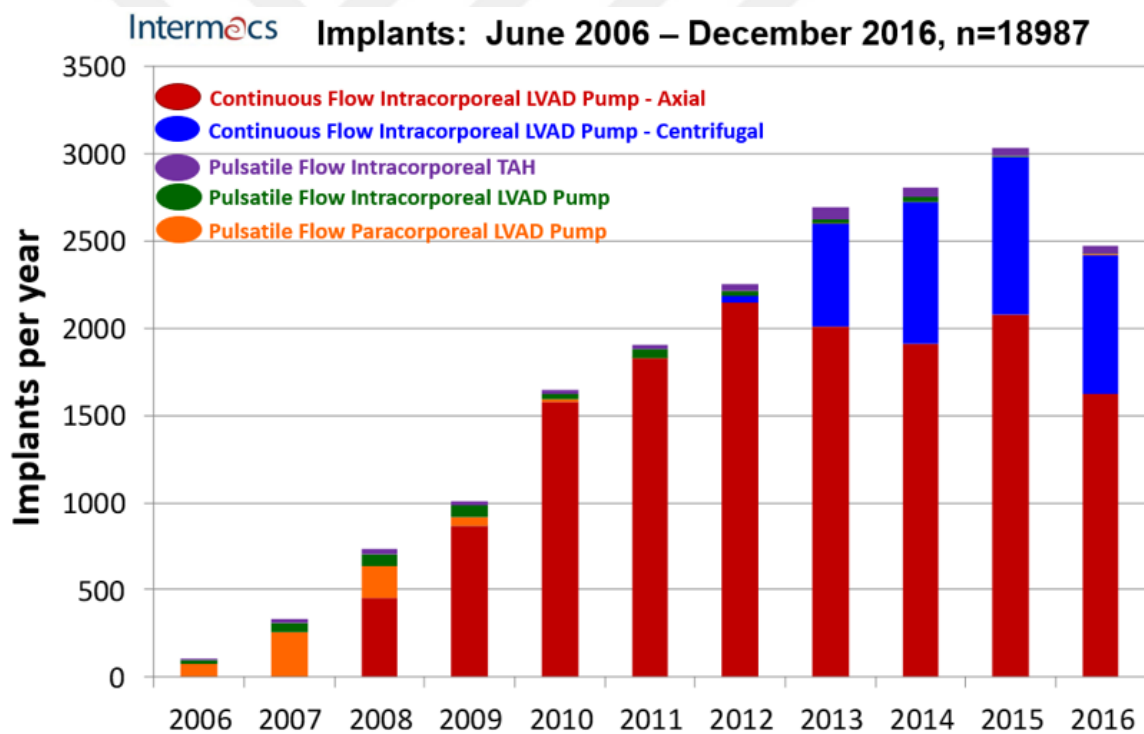


Figure 2 - Number of implants of mechanical circulatory support systems (MCSS) per year according to the eighth INTERMACS annual report [11].

The significance of this research relates to the development of a novel centrifugal blood pump to assist heart failure patients. This research will help the patients who are not eligible for cardiac transplants to access to a low cost and high quality VAD.

1.3 Research Aim

A novel centrifugal blood pump is under development in Manufacturing and Automation Research Center (MARC), Koç University. The research aims are to develop a centrifugal type blood pump prototype, investigate the flow characteristic, the hemodynamic performance, determine the level of blood damage and biocompatibility with both in vitro and in vivo evaluations. The findings of this study will be further utilized to optimize the device and eventually finalize the preparations for chronic in vivo studies.

1.4 Objectives

This thesis focuses on the development of a centrifugal flow pump by achieving the following objectives:

- Provide a literature review about the requirements for VAD design and characteristics of LVADs.
- Design a centrifugal flow pump which satisfies the design criteria of LVADs
- Propose different designs of impeller/volute geometries for design iterations.
- Create a computational fluid dynamics (CFD) model for numerical simulations.

- Explore the effects of impeller/volute configurations on hydraulic and hemolysis performance of the pump with numerical simulations.
- Perform a simple hydraulic experiment to validate the hydraulic output of impeller/volute configurations.
- Determine the design modifications based on this parametric study and finalize the pump design of Istanbul Heart VAD (iHeart VAD).
- Manufacture the finalized design with the hemocompatible material, Ti-6Al-4V ELI.
- Construct an experimental rig to investigate the flow characteristics with blood analogue fluid at different rotational speeds.
- Create an in vitro circulation loop to evaluate the blood damage potential of Istanbul Heart VAD (iHeart VAD).
- Perform an acute in vivo evaluation of Istanbul Heart VAD (iHeart VAD) to investigate the blood handling characteristic and anatomical fitting of the device in a large animal model.
- Finally, address the issues occurred during this research and present some suggestions for future studies.

1.5 Thesis outline

This thesis is divided into seven chapters describing the design and development of a novel centrifugal blood pump. The thesis begins with a general review of VADS, followed by a detailed background regarding heart failure, statistics, and types of blood pumps. Chapter 3 continues with the description of the design phase

including the design evolution, design criteria and proposed impeller/volute geometries for the optimization. Chapter 4 provides a description of the computational approach, blood damage models, optimization phase, numerical results, hydraulic validation and an overview of the final design. Different blood damage models are discussed and compared in this chapter. It involves hemolysis and hydraulic performance prediction of different impeller/volute configurations, design iteration and the overview of the finalized prototype which is selected for the in vitro evaluation. Chapter 5 outlines the manufacturing process of Istanbul Heart VAD (iHeart VAD), the in vitro evaluation procedure and results. The pump is constructed with a specific method for an in vitro blood test. The in vitro test setup and the blood damage potential of the pump are also explained in detail. Chapter 6 is dedicated to the initial in vivo evaluation of Istanbul Heart VAD (iHeart VAD). The rationale for in vivo evaluation and the animal model is described. Surgical procedure successfully implemented to the animal model, and the results are presented in this chapter. A discussion is also available for the further in vivo evaluations. Chapter 7 concludes the thesis with a summary of this study and recommends some suggestions for future studies.

Chapter 2

BACKGROUND

This chapter gives a brief overview about literature including the cardiovascular system, heart's characteristics, and existing VADs. Cardiovascular system and the human heart are introduced at the beginning of this chapter. Then, the congestive heart failure (CHF) which is also called as heart failure (HF) is discussed, and the treatment options for heart failure are described to provide an understanding about the rationale behind the development of blood pumps. Statistical information about heart failure and VADs is provided for the motivation of this study. Furthermore, types and generations of existing VADS are outlined for an extensive literature review. A summary is given at the end of this chapter.

2.1 Cardiovascular System

The cardiovascular system contains the blood vessels, heart, veins, arteries, and capillaries. It supplies oxygen and delivers nutrients to all cells in the body and carries waste products to the organs responsible for elimination. The human body has two connected circulatory system: The systemic circulation provides oxygenated blood and nutrients to the body cells while removing wastes. The deoxygenated blood is carried to the lungs with the pulmonary circulation to deliver carbon dioxide and obtain oxygen [12,13].

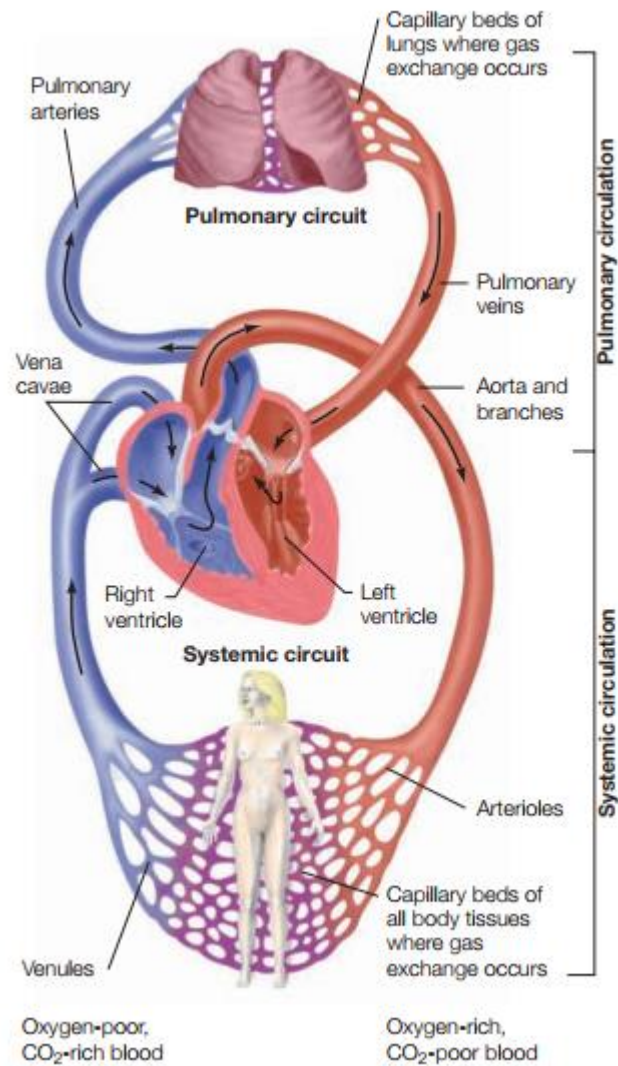


Figure 3 - The circulatory system [14].

2.1.1 The Human Heart

The heart is a key organ to humans and one of the components in the cardiovascular system, the other one being the blood vessels. It generally beats

between 60 to 100 times/minute, corresponding to almost 30 million beats per year [13].

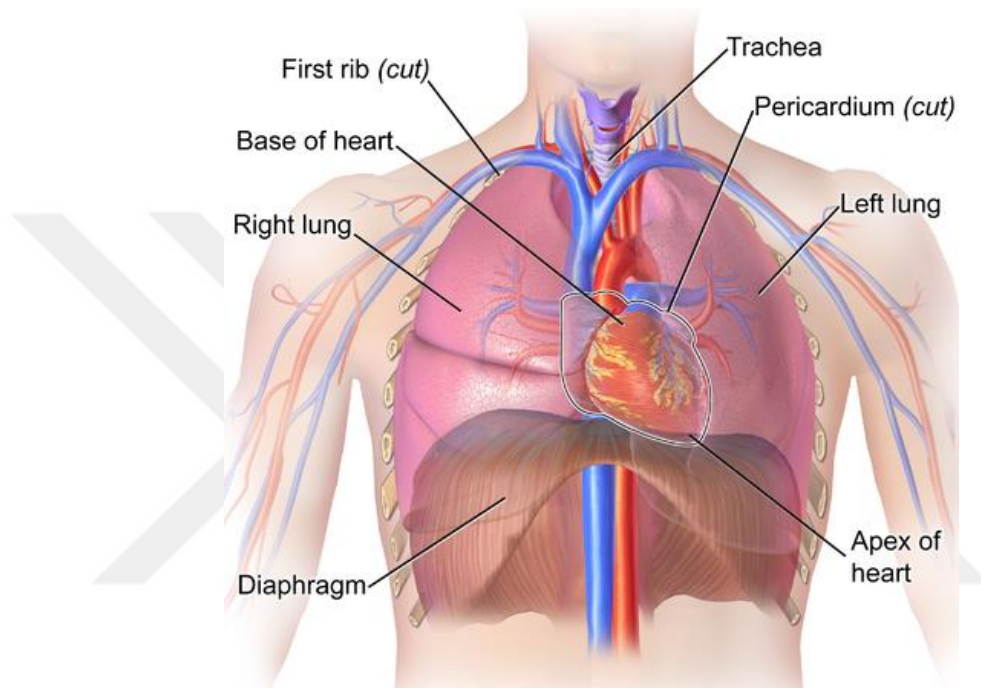


Figure 4 - Heart position in the human body [15].

The heart is located between two lungs as illustrated in Figure 4. It has four chambers; an atrium is located at upper chambers, and the lower chambers called ventricle. It serves as simultaneous two pumps, right and left. The right part of the heart assures the flow through the lungs (pulmonary circulation) where the left side pumps blood to the body (systemic circulation). The atria pumps returning blood into ventricles, and the ventricles send blood outside the heart. The right atrium receives de-oxygenated blood from the vena cava (systemic return) and then pumps it through the right ventricle where the blood is pumped into the lungs for

oxygenation. Then, the oxygenated blood is sent to the left ventricle by passing through the mitral valve [16].

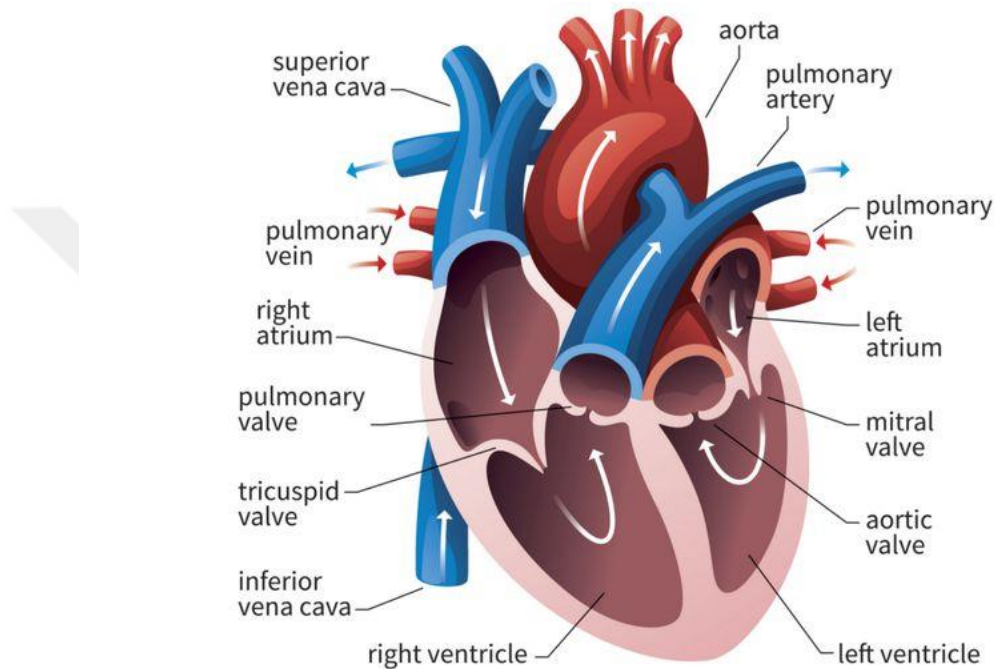


Figure 5 - Diagram of the human heart [17].

The reciprocating nature of the action of the heart results with a pulsatile and periodic flow characteristic. The cardiac cycle is defined as the stages of relaxation (diastole) and contraction (systole) while the heart pumps blood. The cardiac cycle can be evaluated in four separate phases. Each phase is categorized by the reciprocating movement of the heart valves. Normally, duration of a cardiac cycle is between 0.8 - 1.0 second (60 - 80 bpm), although the heart rate (HR) is adjusted in accordance to physiological requirements controlled by the autonomic nerves.

Figure 6 shows the cardiac cycle of the heart. The top four curves show aortic pressure, arterial pressure, ventricular pressure, and ventricular volume, respectively. The electrocardiogram (ECG) is shown in the fifth curve, and the last curve presents sound measurements (phonodiagram).

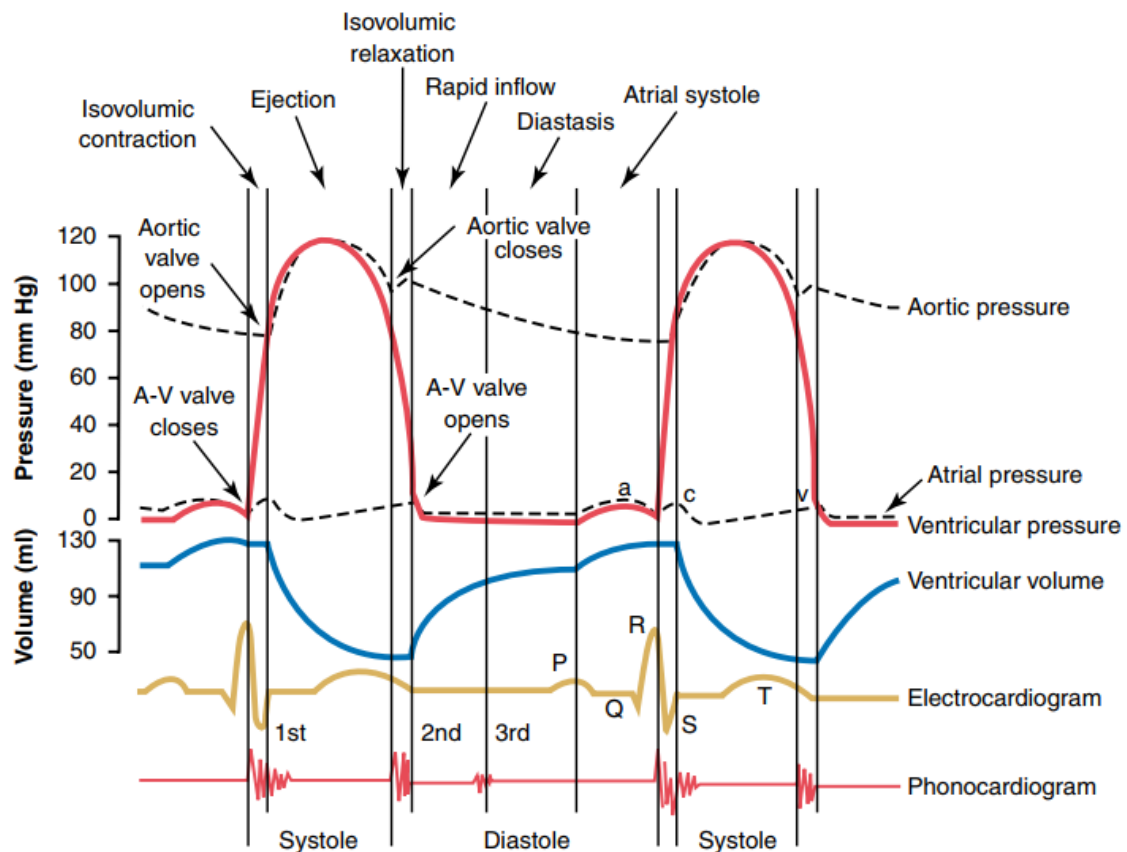


Figure 6 - Cardiac cycle of the left ventricle, left atrium and aorta from systole to diastole.

Electrocardiogram (ECG) signal is symbolized by P,Q,R,S and T wave [16].

2.1.2 Heart Failure

Heart failure (HF), frequently mentioned as congestive heart failure (CHF), is a clinical condition categorized by deterioration of left ventricular function. Basically, cardiac output is inadequate to satisfy the metabolic needs of the body which leads to systemic and pulmonary congestion. It is a progressive illness that damages the myocardium, eventually resulting in insufficient blood flow. Myocardial infarction or a long-term degradation of cardiac function may cause HF. It is a common end-stage of heart disease and has a profound impact on the survival. Ischemic heart disease, hypertension, valvular heart disease, primary myocardial disease and congenital cardiac malformations are considered as the most common reasons for the heart failure [18].

2.1.3 Statistics about Cardiovascular Diseases

The 2017 report of World Heart Organization (WHO) states that cardiovascular diseases (CVD) represent 31% of all global deaths, which means an estimated 17.7 million people died due to CVDs in 2017 [19]. Globally, HF has become the primary health concern, with an estimated 38 million patients worldwide [20]. In Europe, CVDs causes almost 5 million deaths corresponding to 45% of all deaths in Europe annually [21]. Likewise, almost 6 million patients in the US have HF, and there were almost 300,000 deaths annually [22].

Economic burden related to the heart failure is estimated as \$32 billion annually in the US [23]. Similarly, there are estimated 4.2 million HF patients in China and 1

million people in Japan [6,7]. Statistics of Turkey also indicates that CVDs are the first reason of death corresponding to 39.84% of all deaths in 2016 [24]. More than a million people have HF, and 20% of all patients reach the last stage annually. Every year, approximately 3000 patients need a heart transplant as a definitive treatment, but the number of transplantation in Turkey is less than 90 due to a shortage of available donor hearts as shown in Table 1.

Table 1 - Number of organ transplantation in Turkey between 2002 and 2016 [24].

	2002	2012	2013	2014	2015	2016
Kidney	550	2.903	2.944	2.924	3.204	3.419
Liver	159	1001	1.248	1.212	1.216	1.395
Heart	20	61	63	78	89	69
Heart Valve	15	5	1	0	0	0
Lung	0	25	32	33	30	22
Heart-Lung	0	2	0	0	0	0
Pancreas	0	6	4	9	7	6
Small Intestine	1	5	2	5	6	0
Total	745	4.008	4.294	4.261	4.552	4.911

2.1.4 The Treatment of Heart Failure

The treatment of heart failure is determined based on the stage of the disease. Early stage HF can be treated with medical drugs or daily routine adjustments. Treatment generally starts with drugs treatment, where the drug amount depends

on the patient condition or HF stage. However, surgical treatments are eventually required for the last stage HF patients. Heart transplantation is the essential treatment for these patients. However, the shortage of donor hearts limits this procedure. As an alternative treatment, mechanical circulatory support systems (MCSS) can be utilized.

Dr. Gibbon demonstrated the first successful mechanical circulatory assist in a clinical setting on a human during a cardiopulmonary bypass surgery in 1953 by using a heart-lung machine. This was the first proof that human can be supported with the mechanical device [25]. Later, Dr. DeBakey proposed the roller pump which is still in use and was combined with the heart-lung machine [26]. The first usage of LVAD as a bridge to transplantation (BTT) for heart and kidney was successful by the support from the USA government through the National Heart, Lung, and Blood Institute (NHLBI) during 70's and 80's [27]. Moreover, first electrically actuated model of LVAD was developed in 1984 as an alternative to the pneumatically driven LVADs [28].

The limitations of heart transplantation have enhanced the development of mechanical cardiac assist devices, and ventricular assist devices (VAD) have become widely used blood pumps to support the failing heart [29]. These devices are aimed to help patients in several treatment options such as bridge to heart transplant, recovery, or destination therapy. In general, these devices are implanted to the intra-abdominal position and connected to the controller and batteries by the tunneled

percutaneous driveline. The implantation of Istanbul Heart VAD (iHeart VAD) is illustrated as an example in Figure 7.

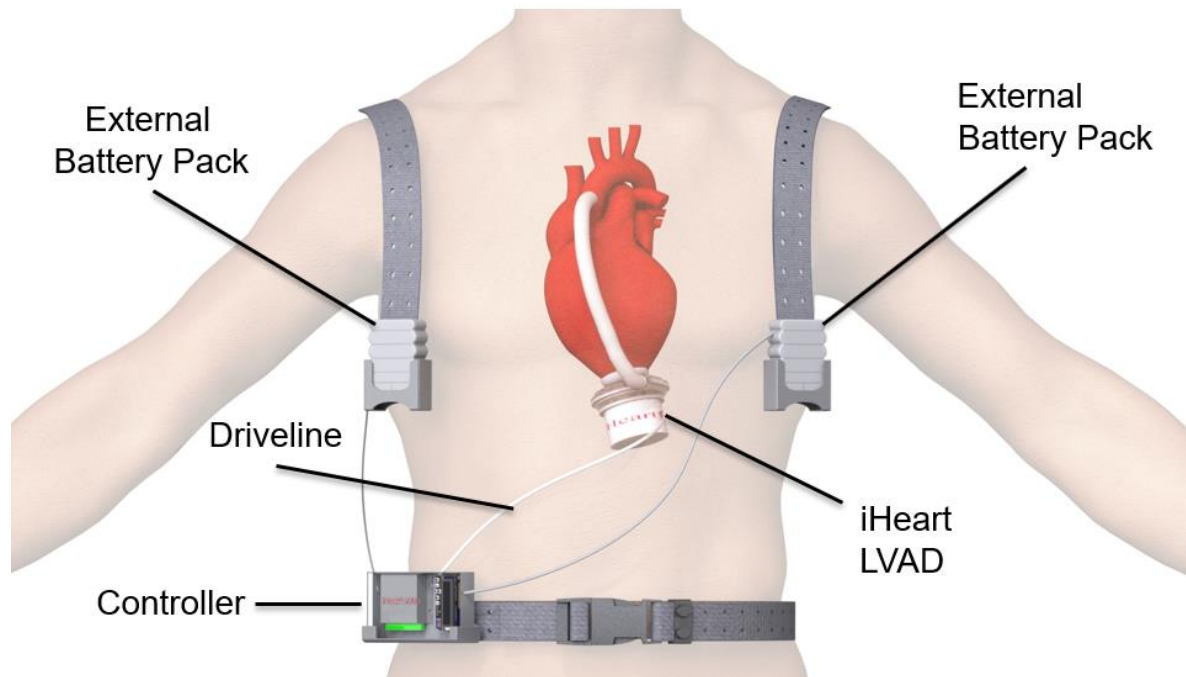


Figure 7 - Istanbul Heart VAD (iHeart VAD) surgically implanted to the left ventricle of heart.

2.2 Ventricular Assist Devices

VADs are progressively used in clinical practice and offers some different treatment options. For example, it can be utilized to bridge the recovery of a patient in short term. This is called as “Bridge to Recovery”. However, it can also be employed for long-term support as a definitive treatment which is called

“Destination Therapy”. Furthermore, the patient can be supported with VAD while waiting for the available heart as a “Bridge to Transplantation”.

- Bridge to Transplantation (BTT)
 - Implanted for short to intermediate term support for patients who are waiting for available heart.
 - It provides short-term treatment from severe HF while waiting for the heart.
- Bridge to Recovery (BTR)
 - Implanted for short-term support.
 - It provides recovery when implanted with a LVAD.
- Destination Therapy (DT)
 - Implanted for a definitive treatment as a permanent device.
 - For critical HF patients who are not suitable for transplantation.

The Interagency Registry for Mechanically Assisted Circulatory Support INTERMACS registry provides an extensive clinical data about VADs. Patients are classified based on the implant strategies such as BTT: likely to receive a transplant, BTT: moderate for transplantation, BTT: unlikely to receive a transplant, BTT: listed for transplantation, DT, Rescue, and BTR. Implant strategies are summarized by years in Figure 8.

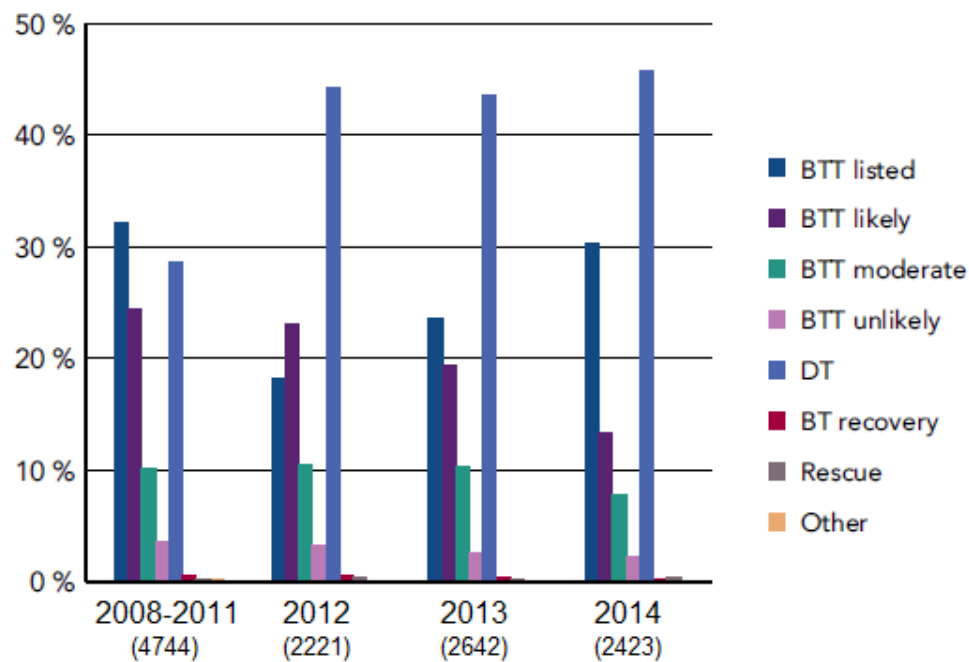


Figure 8 - Implant Strategies According to the INTERMACS Registry 2008-2014 [11,30].

VAD designs can be categorized in two groups considering the flow types, pulsatile and continuous flow. More than five decades ago, volume-displacement pumps were developed and used for the patients by generating a pulsatile outflow. Later, advances in the flow technology have improved the design of VADs and new continuous flow pumps have become widely used devices to assist HF patients [31].

Flow Type:

- a. Pulsatile Volume-Displacement Pumps
- b. Rotary Continuous Flow Pumps
 - Axial Flow
 - Centrifugal (Radial)

2.2.1 Axial Pump

An axial flow pump basically operates in a straight pipe casing transferring energy to the blood via an axial impeller [32]. Due to its geometric structure, the axial flow pump is appropriate for low head pressure and high flowrate pumping applications. The axial rotor is the main part for generating the energy for blood flow. The compact structure of axial pumps offers a good advantage for implantation inside the human body, but high operating speeds increase the potential of blood damage and mechanical wear. In general, the operating speed of axial flow pumps ranges between 6,000-12,000 rpm for adults and the pediatric axial pumps could even operate more than 30,000 rpm [32,33].

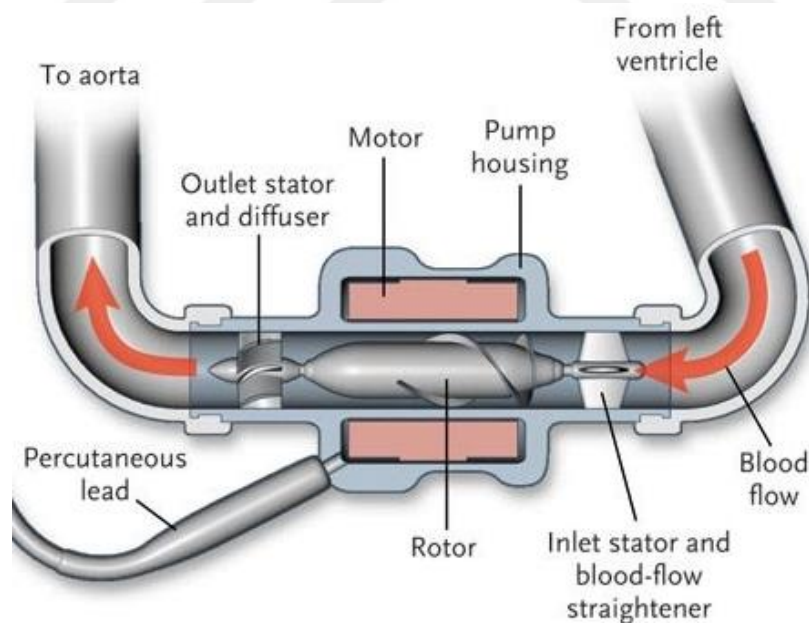


Figure 9 - Structure of the axial blood pump [34].

2.2.2 Centrifugal Pump

The centrifugal pump contains a radial impeller and a spiral volute. The impeller consists of radially curved blades. As the operation begins, the inflow fluid flows through the inlet and then centrifugal kinetic energy is transferred to the fluid by the rotating impeller. The fluid is pushed to the gap between blades and then to the spiral volute where this kinetic energy is converted to the potential energy. The centrifugal pumps generate higher pressures at low flow rates and the typical operating speed ranges between 2,000-4,000 rpm [32].

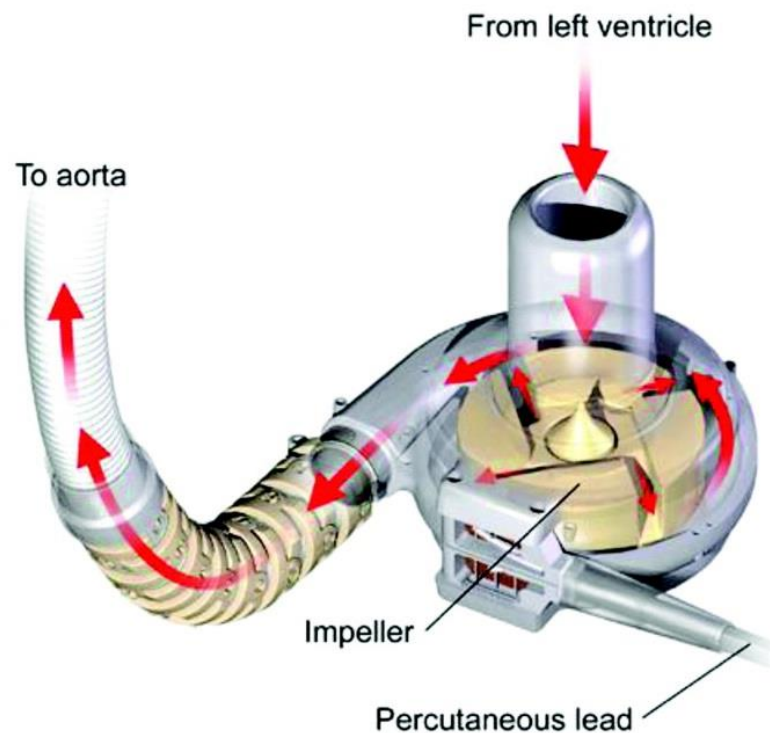


Figure 10 - Structure of the HeartWare® LVAD centrifugal pump [35].

The characteristics of pulsatile, axial and centrifugal types of blood pump are compared in Table 2.

Table 2 - Comparison of the characteristics of blood pumps [32,36].

	Pulsatile Pump	Centrifugal Pump	Axial Pump
Speed	~60 bps	2000-4000 rpm	6000-14000 rpm
Size	Large	Medium	Small
Relative Hemolysis	High	Small	Medium
Thrombosis	Low	Medium	High

2.2.3 Pump Generations

Considering the flow technology, VADs can be classified as three generations [31]:

- a. 1st generation: Reciprocating (Volume-Displacement) pumps,
- b. 2nd generation: Rotary pumps with mechanical bearings,
- c. 3rd generation: Rotary pumps with magnetic levitation or hydrodynamic bearings

First-generation blood pumps:

First-generation blood pumps are known as pulsatile pumps. They increase the pressure in a closed chamber with a piston-like mechanical system. Increased pressure provides unidirectional blood flow through outflow valve. These types of pumps provide pulsatile blood flows by generating a natural heart beat. However, this technology has some disadvantages due to the large size, limited durability, degradation of valves and large percutaneous driveline of the pump. The HeartMate XVE (Thoratec Corporation) is leading example of the pulsatile pumps.

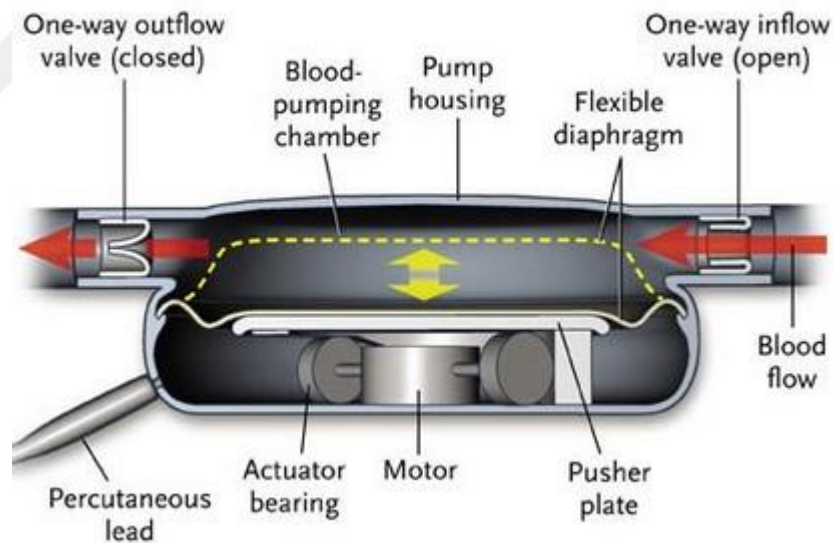


Figure 11 - Pulsatile pump, HeartMate XVE as a first generation blood pump [37].

Second-generation blood pumps:

Second-generation blood pumps are non-pulsatile pumps. In the 1990's, the second-generation pumps were developed to reduce the size and provide better durability. These pumps provide a continuous blood flow with a rotating impeller. Contact bearings and/or seals are generally used in second-generation VADs to stabilize rotating components of the pump. The structure of these pumps features an impeller rotating at high speed to generate the pressure. Both centrifugal and axial flow structures were available as a continuous flow second-generation VADs. Major limitation of these devices is rotating parts related problems such as mechanical wear, high shear forces, hemolysis, and thrombosis. However, these pumps are still widely accepted devices for clinical usage. Examples of second-generation pumps are Heartmate II, Jarvik 2000, MicroMed DeBakey and EVAHEART. The novel centrifugal blood pump presented in this thesis, Istanbul Heart VAD - iHeart VAD (Koc University, Istanbul, Turkey) can also be considered as an example for second-generation blood pumps.

EVAHEART (Sun Medical Technology Research Corporation, Japan) pump can be a good example for second-generation centrifugal blood pumps. Figure 12 illustrates the pump structure and working mechanism of EVAHEART.

A)



B)

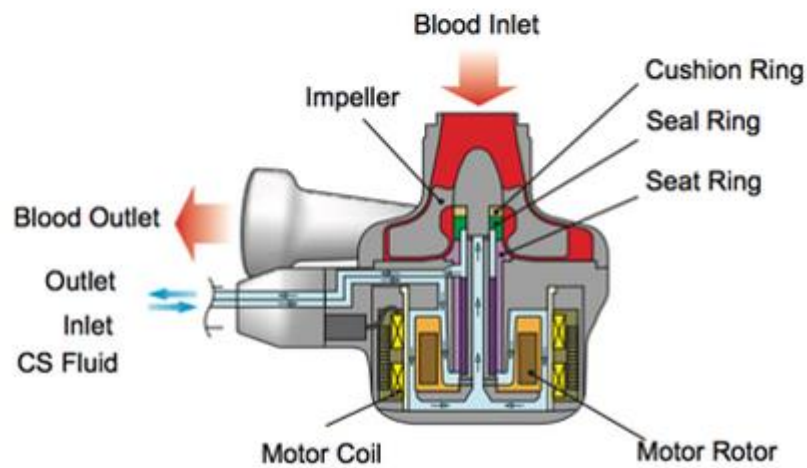


Figure 12 - (A) EVAHEART as a second-generation pump. (B) Cross-sectional view of the EVAHEART (Sun Medical Technology Research Corporation, Japan) [38].

The pump structure of EVAHEART consists of an impeller, mechanical seal, journal bearing, motor coils, rotor and cooling system. It features a size of 51 x 67

mm and weights 262g. It can generate a flow rate of 8 L/min and 90 mmHg at 2200 rpm as nominal. The mechanical seal is implemented to the shaft for avoiding a leakage to motor part. A thin layer of circulating sterile water is also used to cool down the temperature around the shaft.

Third-generation blood pumps:

The third-generation rotary blood pumps employ the magnetic levitation concept. In third-generation pumps, mechanical seals or/and bearings were removed as they have great potential to induce hemolysis. Magnetic force concept was proposed to hold the impeller in position without any contact. Coagulation was also reduced due to the simpler structure as compared to other generations. Nevertheless, high power consumption is considered as a major drawback for third-generation pumps while providing long-term support for patients. Moreover, the magnetic levitation concept could cause heating due to eddy currents and inserting more magnets increases the mass and size of the device. HeartWare LVAD (HeartWare Inc., Framingham, MA, USA) can be considered as an example for third-generation rotary blood pumps.

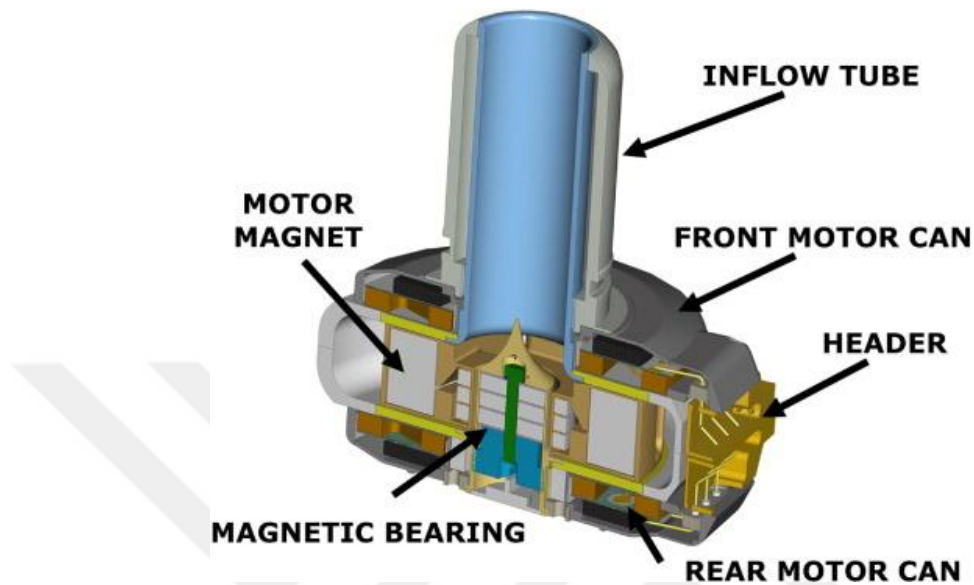


Figure 13 - Cross-section of the HVAD pump as a third-generation blood pump [39].

Another example of third-generation blood pump can be the Magnetic-Liquid Suspension Blood Pump (MLSBP) which is a centrifugal flow blood pump developed by the scientists from the China Academy of Launch Vehicle Technology (China) and TEDA International Cardiovascular Hospital (China). The pump features a single volute, an impeller with four blades and a magnetic levitation structure with magnetic-hydraulic suspension. The pump can operate at a rotational speed of 2600-3900 rpm with the flow range of 3–7 L/min and the pressure head of 60-180 mmHg. The MLS blood pump of China is still under chronic in vivo evaluation. So far, the pump has been investigated in 18 animals and the longest survival time was 108 days.

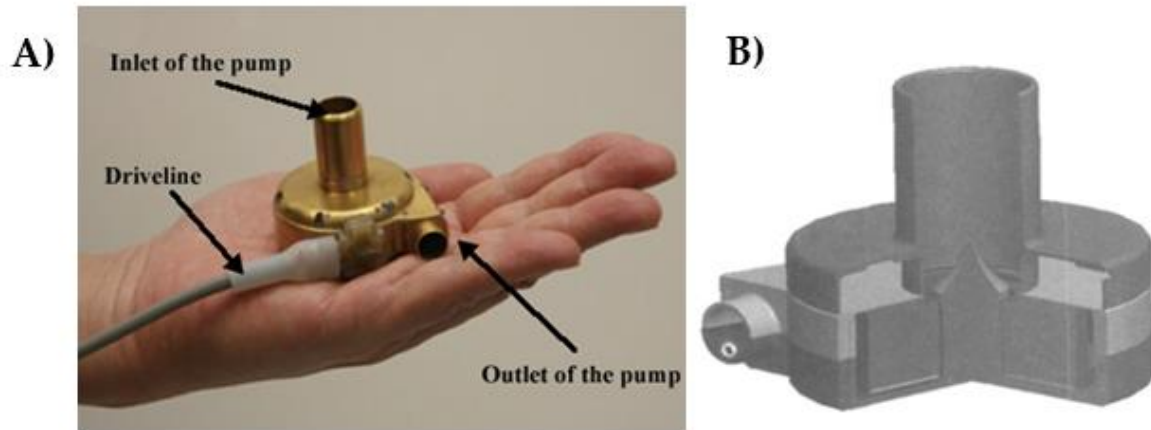


Figure 14 - (A) MLS blood pump of China. (B) The diagram of MLS blood pump [40].

Overall, the most common LVADs are summarized considering the pump generations, as shown in Table 3:

Table 3 - Clinically used left ventricular assist devices

	First Generation	Second Generation	Third Generation
Flow Type	Pulsatile flow	Continuous-flow	Continuous-flow
LVAD Model	HeartMate I Berlin ExCor Novacor Thoratec PVAD	Jarvik 2000 DeBakey VAD HeartMate II Impella MicroMed DeBakey Evaheart	HVAD DuraHeart Heartmate III

Based on the pump generations, the distribution of used devices in the last decade is reported by the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) as presented in Figure 15.

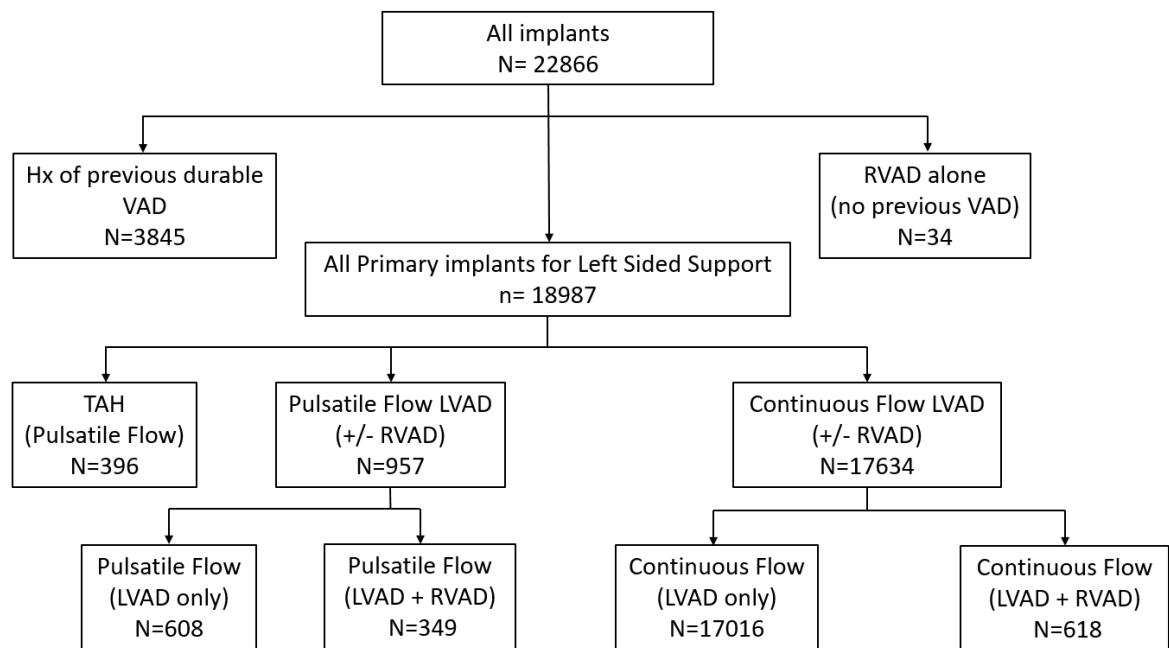


Figure 15 - Summary of INTERMACS implants between June 2006 and December 2016 [41].

2.3 Summary

This chapter presented the background information about the cardiovascular system, HF physiology, VADs as a treatment of HF patients. The rationale of this study was described by providing statistics about cardiovascular diseases and HF. The history, usage, classification, flow types and generation of blood pumps were also discussed briefly. As a whole, the second chapter indicates the motivation behind the development of a novel LVAD, Istanbul Heart VAD (iHeart VAD) by reviewing the literature.

Chapter 3

PUMP DESIGN AND DEVELOPMENT

This chapter presents the development of a centrifugal pump, Istanbul Heart VAD (iHeart VAD), including to address design criteria and optimization procedure. Designing a rotary blood pump requires the comprehensive investigation of pump structure and flow dynamics. The pump geometry may significantly influence the performance of blood pumps as it alters the flow field. Hence, incorporating the design parameters into hydraulic and hemolysis requirements plays an essential role when designing a pump.

At the beginning of this chapter, the hydraulic and hemolytic requirements are addressed in detail as they are important to generate an appropriate pump structure for an optimal performance. Later, the previous prototype of the pump was introduced to point out the origin of this research. Volute and impeller structures were produced by varying the design parameters, and a parametric study was carried out for the optimization.

3.1 Design Criteria of Istanbul Heart VAD (iHeart VAD)

Designing a second-generation centrifugal flow pump which has a high pump performance and good biocompatibility is the main objective of this thesis. The primary stage for the design of blood pump is to understand the specifications and

requirement for treatment of patients. As shown in Figure 16, the criteria of designing a blood pump can be categorized into two topics that are the hydraulic and clinical requirement.

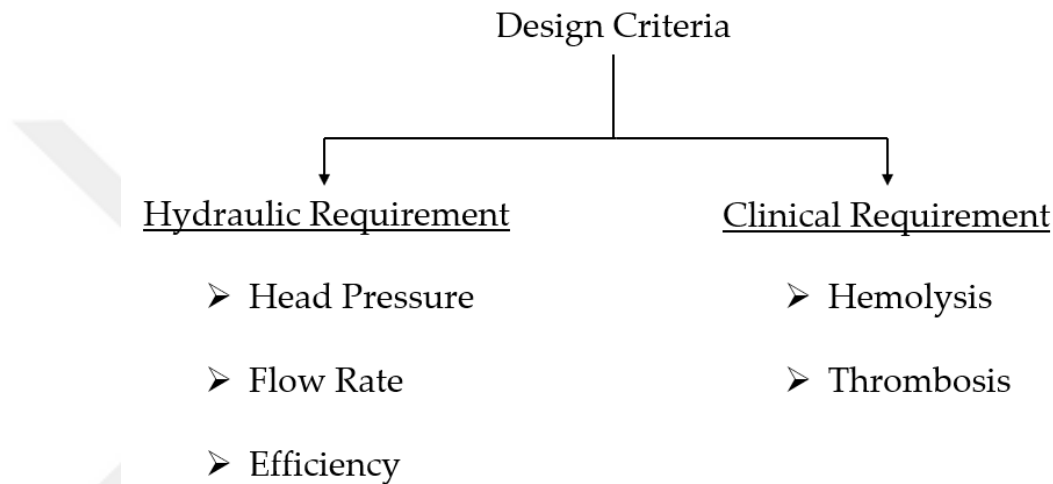


Figure 16 - Design criteria for blood pumps.

Hydraulic requirements are mainly the head pressure, flow rate, and hydraulic efficiency. The flow rate and head pressure should satisfy the physiologic needs of the patient. Based on these physiologic requirements, the flow rate and head pressure range can be calculated after determining the size of the pump. The clinical requirements can be summarized as hemolysis and thrombosis in the design step. To reduce the thrombosis risk, the pump should be structured in a way to provide washout mechanism for rotating and non-rotating components. Moreover, the hemolysis and platelet activation occur due to the high shear stress acting on the RBCs which mainly locates near the tip region of the impeller.

3.1.1 Head pressure

Head pressure is usually determined as the pressure difference between the inlet and outlet port of the pump. It can be calculated by the following equation:

$$H = \frac{\Delta P}{\rho g} \quad (1)$$

Where H is the pressure head, ΔP is a pressure difference between inlet and outlet and ρ is fluid density.

The plot of the head pressure against the flow rate (H-Q curve) is considered as the main indicator for hydraulic performance characteristic of blood pumps. Figure 17 illustrates the typical performance curve of a centrifugal blood pump [32].

Head pressure is mostly dependent on the geometry of pump and also the rotational speed impeller. The pump needs to be able to deliver sufficient head pressure to the circulation so that the pressure loss due to the weakened ventricle can be compensated. It must be able to provide adequate pressure range by considering all conditions of the patients such as sleep, rest, exercise, etc [32]. Hence, the pump is designed to have 60 to 120mmHg pressure range and ~100mmHg pressure at the normal operating condition for adult patients [42].

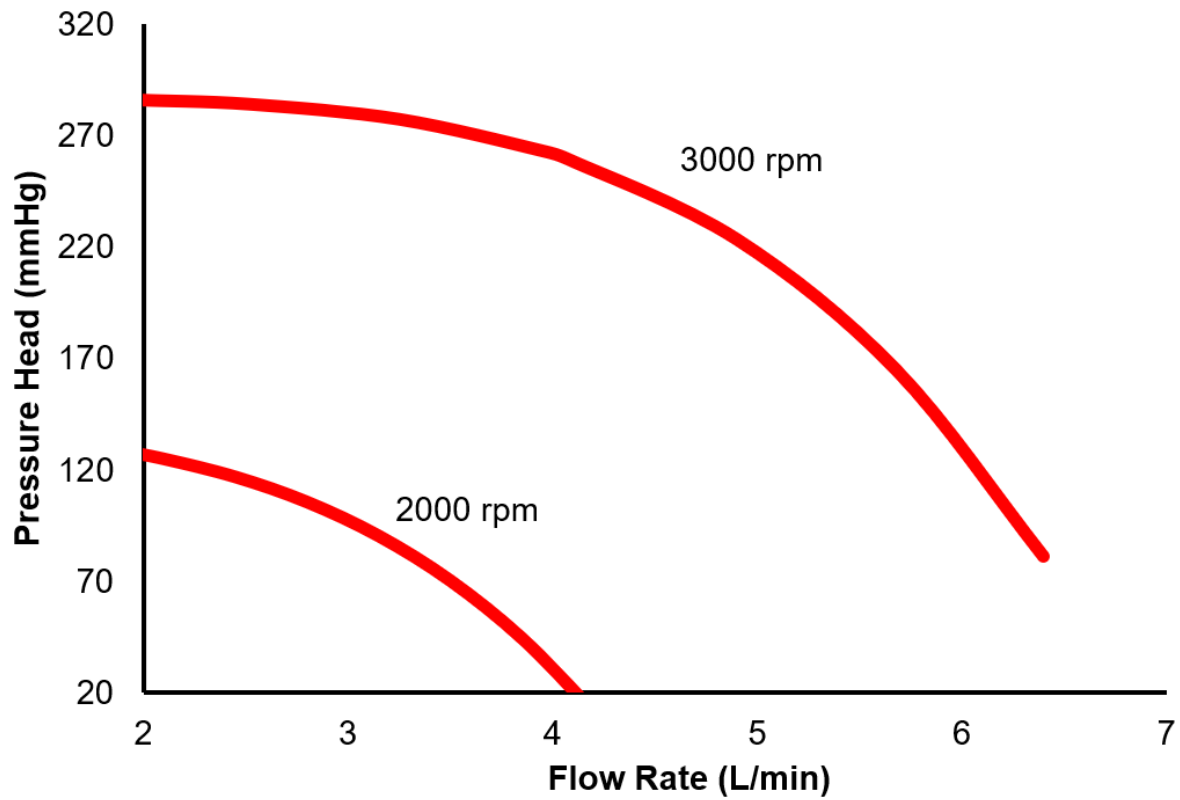


Figure 17 - Typical performance curve.

3.1.2 Hydraulic efficiency

The hydraulic efficiency is basically the transfer of the mechanical power into hydraulic power. It can be calculated as follows:

$$\eta_h = \frac{P_h}{P_s} = \frac{\rho g Q H}{T \omega} \quad (2)$$

Where η_h is hydraulic efficiency, P_h is hydraulic power, P_s is shaft power, T is torque, ρ is the fluid density, g is acceleration due to gravity and ω is the angular velocity.

A pump's hydraulic efficiency is determined by dividing the hydraulic power to shaft power. Generally, the efficiency of a centrifugal blood pump would be around 30-50%. An efficiency of 100% describes the condition that the flow is pumped at zero pressure and no torque is required to drive the impeller.

3.1.3 Hemolysis

Hemolysis is defined as the damage or destruction of the Red Blood Cells (RBC). During the hemolysis, the hemoglobin and other contents are released into the plasma [32]. Hemolysis could worsen the patient's condition by leading to multiple organ failures [43]. As the hemolysis is directly related to the exposure time and the shear force, it is considered as one of the major problems for blood pumps at the design phase. The small clearances between the rotor and housing or high rotational speeds are the primary reasons for the high shear stresses and hemolysis [44]. The surface roughness of the blood contacting surfaces (R_a) is also proportional to hemolysis. Surface roughness value of the blood contacting surfaces should be limited to below $0.2 \mu\text{m } R_a$ for anti-traumatic surfaces [45]. In order to evaluate the hemolysis in blood pumps, the standards recommended by American Society for Testing and Materials (ASTM F1841-97) are constituted for the researchers [46]. The details of ASTM F1841-97 standards will be given in next chapter. Generally, blood pumps are considered anti-traumatic, if the normalized hemolysis index (NIH)

would be less than 0.01 g/100L under 5 L/min flow rate and 100 mm Hg head pressure [45,47].

3.1.4 Thrombosis

Thrombosis is also another clinical concern for the blood pumps, and it is the formation of a blood clot as a hemostatic response of body to stop blood loss [43]. If the thrombosis occurs, it may affect the pumping mechanism leading to failure of the device. Furthermore, if the clot circulates in the blood stream, it might damage the blood vessels in vital organs. Many factors are associated with thrombosis such as the flow rate, pump speed, washout mechanism or level of anticoagulation [48]. In design step, the risk of formation of thrombosis could be minimized with a proper washout mechanism, particularly in small clearance zone around the impeller.

3.2 Design Evolution of Istanbul Heart VAD (iHeart VAD)

The initial starting point of current prototype of Istanbul Heart VAD in this thesis was based on the previous design, named as Heart Turcica Centrifugal (HTC). The research on this project started with a second-generation centrifugal blood pump including a rotating impeller with eight straight blade configuration and volute. Until now, the previous researchers at MARC have developed several design prototypes [49,50]. A centrifugal blood pump prototype was named as Heart Turcica Centrifugal (HTC) [49]. HTC consists of an inlet with three guide blades and impeller was structured by double-sided pivot pin-hole mechanism [50]. An external driver mechanism was used to actuate the impeller rotation, AC

servomotor which is controlled by servo driver and power units. Driving mechanism was illustrated in Figure 19. The pump dimensions were 81 x 87 x 35 mm and impeller featured a size of 48 mm in diameter.

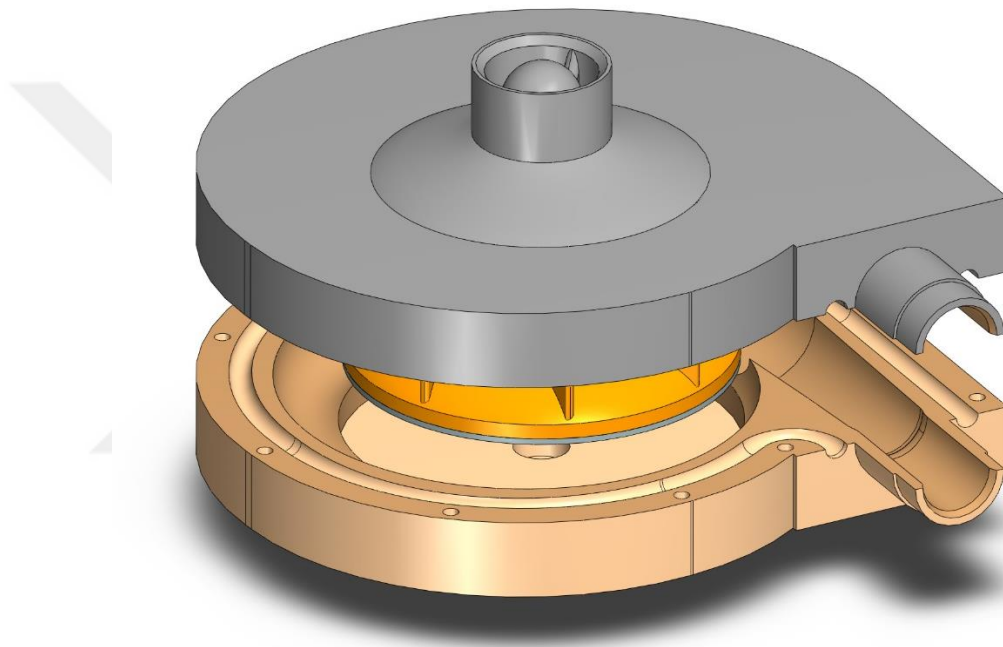


Figure 18 - Heart Turcica Centrifugal (HTC) geometry.

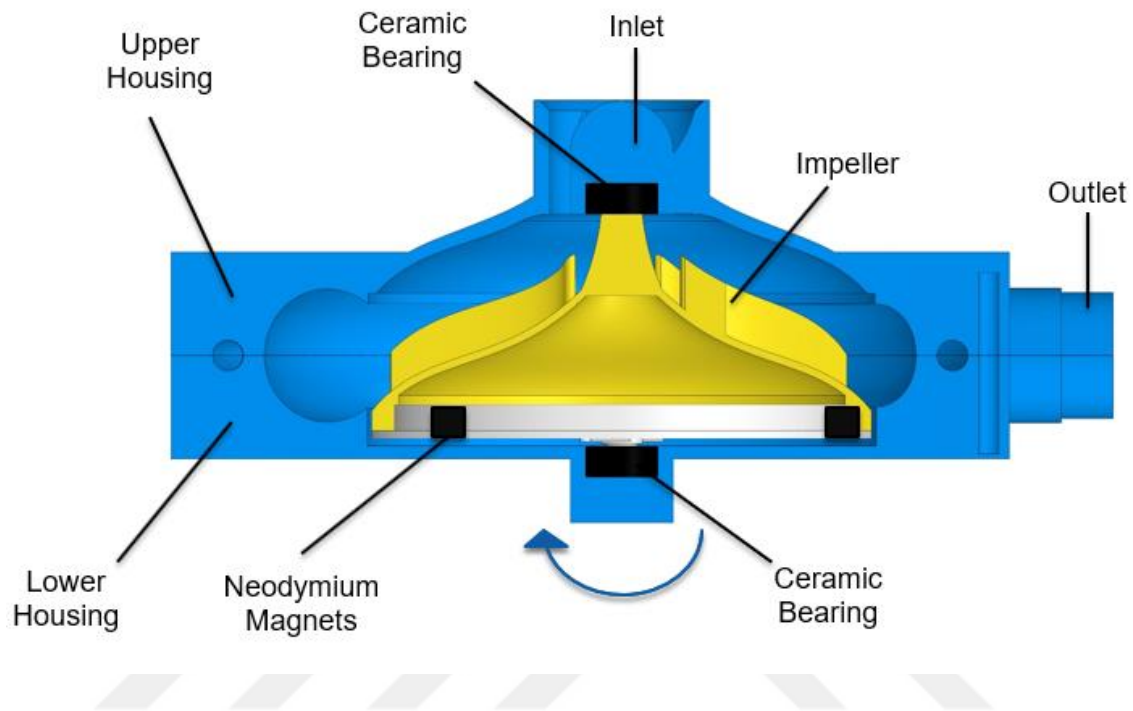


Figure 19 - Driving system of Heart Turcica Centrifugal (HTC) [50].

Hydraulic experiments and in vitro blood test trial were conducted on this prototype [50]. The Heart Turcica Centrifugal (HTC) has shown satisfying results in terms of hydrodynamic output and hemolysis level, but the pump geometry was not in the compact size due to the external drive mechanism and large gaps inside the pump geometry. This could cause whirl flow around the impeller zone which eventually could result in stagnation points and high shear stress based on the computational results. Therefore, the Heart Turcica Centrifugal (HTC) requires optimization in a way that it would be appropriate in size for implantation inside the human body and provide good biocompatibility for long-term use.

3.3 Pump Optimization

The input of design procedure of centrifugal blood pump can be determined based on the blood pump design criteria. In the design phase, the risk of hemolysis, thrombosis, and platelet activation in blood pump must be minimized while providing a good hydrodynamic output and efficiency. Iterative optimization of design is the key process to avoid these traumatic conditions during the design phase. The detailed development cycle is demonstrated in Figure 20.

A classical pump design method for centrifugal flow pumps was described in the book of “Centrifugal and Axial Flow Pumps: Theory Design and Application” [51]. Theoretical calculation of the required design parameters, such as rotational speed, attack, and trail angle of blade, wrap and volute are explained in detail for pump designers.

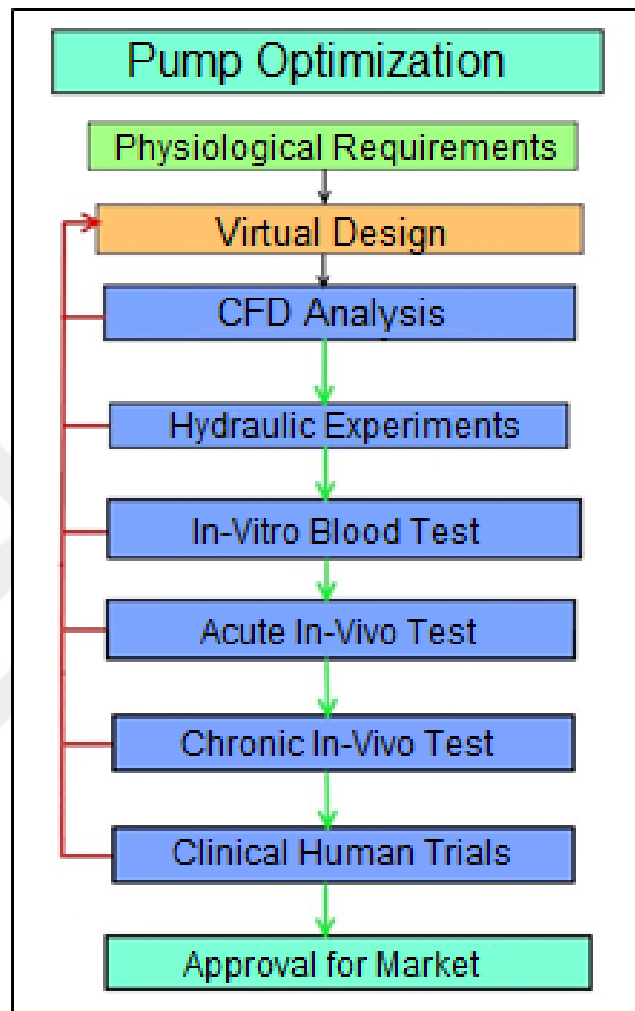


Figure 20 - Typical development cycle of the blood pump.

In general, the optimization of Istanbul Heart VAD was achieved by focusing on two main components as impeller geometry and volute structure. Furthermore, the drive mechanism is updated by integrating a motor under the volute casing of the pump. The design optimization includes parametric analysis of impeller blade angle and volute tongue position. These parameters relate the performance characteristic

with the pump geometry in this thesis. The hydraulic output, efficiency, the radial force acting on the impeller, hemolysis generation, etc. are evaluated for the optimization of Istanbul Heart VAD (iHeart VAD).

3.3.1 Impeller Design

The energy conversion of a pump starts via impeller transferring the energy to flowing fluid. Therefore, the impeller is one of the most important regions in blood pumps as it defines flow field. The blade design parameters including the wrap angle are important due to the fact that these parameters determine the local absolute velocity which has a great influence on its kinetic energy.

As the blades and impellers are commonly a focus of the optimization for turbomachinery, the wrap angle parameter was introduced this study to increase hydraulic output and avoid stagnation zones and high shear stress in the flow field. Optimizing the impeller blades by adjusting the wrap angle could lead to higher efficiency, more power, and less vortical structures compared to the straight blade configuration.

The effect of blade wrap profile on hemolytic and hydraulic performance was studied in this thesis by incorporating the wrap angle parameter into blood pump design. As a design parameter, the wrap angle allows the blade camber line to feature on fixed attack and trail angles, and thus the swirl of blade profile can be easily controlled (Figure 21).

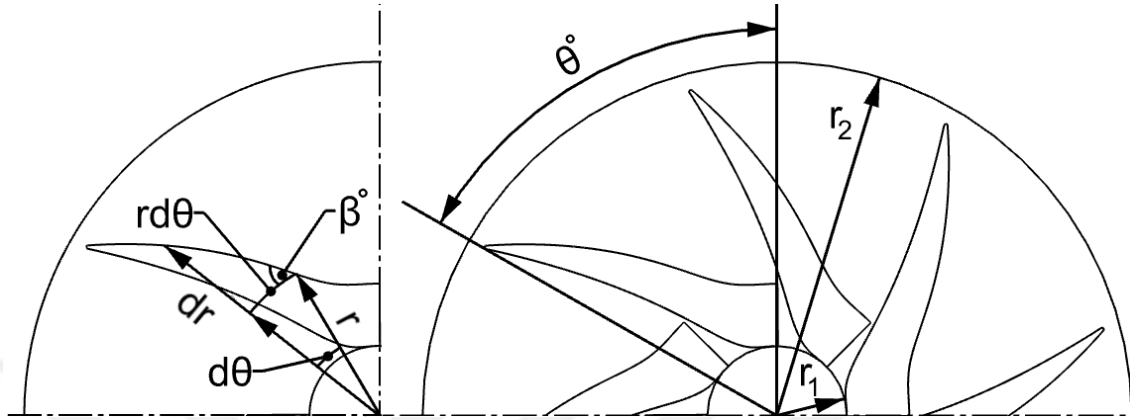


Figure 21 - The wrap angle definition of the impeller blade.

According to Scheit et al. [52], the blade wrap angle can be described by a geometric relation as follows:

$$\tan(\beta(r)) = \frac{dr}{rd\theta} \quad (3)$$

The wrap angle θ can be obtained by rearranging Equation 3 and integrating through radius:

$$\theta = \int_{r_1}^{r_2} \frac{1}{r \tan(\beta(r))} dr \quad (4)$$

where θ is the blade wrap angle, β is the blade flow angle, and r is the calculation point radius. A detailed description of three-dimensional blade bone lines is explained in the study of Scheit et al. [52].

Five different wrap angles were used to design the impellers, the wrap angles of blades (θ°) were ranged from 0° to 240° for Cases I-V, respectively. Table 3

demonstrates the physical configurations for the five impellers. All impellers were designed to operate at a rotational speed of 2000 rpm, corresponding to the 5 L/min pump flow rate and 100 mmHg pressure head. The outer diameter and height of the impellers were 45 mm and 18 mm respectively. ANSYS Bladegen (ANSYS 17.0, ANSYS, Inc., Pittsburgh, Pennsylvania, USA) software was used to generate blade geometries. The relative position of the remaining components was fixed.

Table 4 - Geometric characteristic of the impellers with wrap angle variation.

	Case I	Case II	Case III	Case IV	Case V
Wrap Angle (°)	0	60	120	180	240
Blade Number	8	8	8	8	8
Outer Diameter (mm)	45	45	45	45	45
Blade Thickness (mm)	1.25	1.25	1.25	1.25	1.25
Blade Height (mm)	4	4	4	4	4
Total Height (mm)	20	20	20	20	20

The pump geometry was designed using the Siemens NX software (NX 10.0, Siemens Product Lifecycle Management Software Inc., Plano, TX, USA).

In addition to wrap angle, the effect of the number of blades was investigated. The wrap angle of 120° was fixed as a reference wrap angle due to its promising results. Eight bladed impeller design was initially selected, and the number of blades was adjusted to ten and six. Splitters were additionally integrated into designs to

investigate the splitter effect on flow characteristic. Table 5 reveals the geometric features of geometries constructed to evaluate blade numbers.

Table 5 - Geometric characteristic of the impellers with blade numbers.

	Wrap Angle	Num. of Main Blades	Num. of Splitter
Case III	120°	8	0
Case VI	120°	4	4
Case VII	120°	10	0
Case VIII	120°	5	5
Case IX	120°	6	0
Case X	120°	3	3

3.3.2 Volute Design

In centrifugal pumps, the volute is very important structure as it transfers the kinetic energy generated by the impeller to hydrostatic pressure. Principally, volute designs are based on the logarithmic spirals whose radius increases with angular position. Even though the impeller geometry plays an essential role in the overall performance of a centrifugal blood pump, the volute structure is equally important for assuring steady flow lines, a good kinetic energy to potential energy conversion [53]. Moreover, the uniformity of the pressure distribution around the impeller is a key parameter for radial forces acting on bearings in second-generation centrifugal blood pumps. As the nature of centrifugal pumps, non-axisymmetric volute geometry generates a non-uniform pressure distribution around the impeller and thus inducing a radial force.

Volute tongue region is one of the key parameters which has been widely studied in various engineering fields for improving the pump endurance, noise reduction, magnetic levitation and improvement of the hydraulic performance. A well-designed volute tongue reduces the vibration, flow separation and radial forces acting on the impeller. Also, it increases the bearing life and overall pump performance [54].

In Figure 22, the tongue angle and the circumferential angular position were represented by the volute tongue angle. Radial gap (δ) between impeller periphery and volute tongue was identified as a percentage based on the standard of Stepanoff [51].

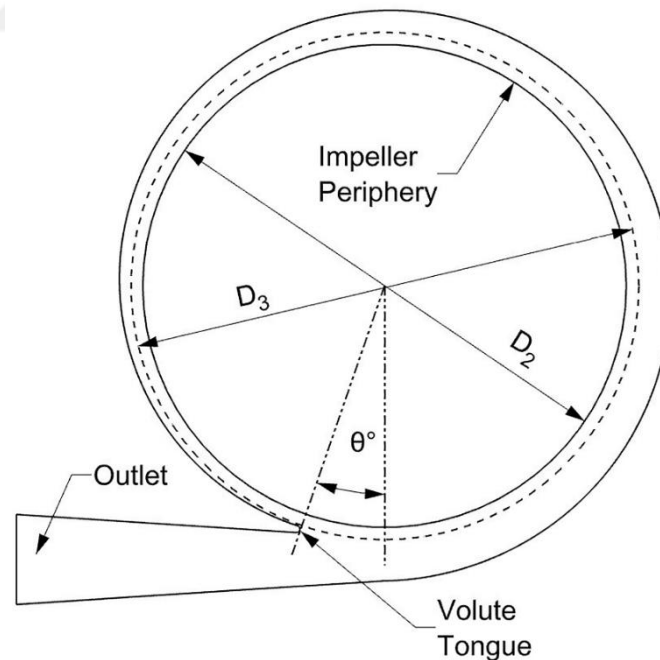


Figure 22 - Definition of the volute tongue angle [53].

The distance from origin to initial point of the volute tongue is represented by diameter D_3 . Impeller outlet diameter is also shown as D_2 . Then, the ratio of D_3/D_2 is described as base circle diameter [53].

$$\delta = \frac{D_3 - D_2}{D_2} \times 100\% \quad (5)$$

In this study, five volutes were designed to study the effects of volute tongue geometry on both hydraulic and hemolysis performance. The volute tongue region was parametrized as the tongue angle (θ°). The constant mean velocity method was used to design the volute geometry by Stepanoff design rule [53]. The pump specific speed (N_s) was 790 in the design rule and fixed. The tongue position was represented by the volute tongue angle. Table 6 demonstrates the physical configurations for the five volute designs.

Table 6 - Geometric characteristic of volute designs.

	Case I	Case II	Case III	Case IV	Case V
Volute Angle ($^\circ$)	10	20	30	40	50
Radial Gap ($\delta\%$)	5	5	5	5	5
Volute Cross Section	Round	Round	Round	Round	Round
Diffuser End Cross Section	Circle	Circle	Circle	Circle	Circle
Diffuser End Diameter (mm)	9	9	9	9	9

In the specified pump geometry, volute tongue angles (θ°) were ranged from 10° to 50° for all cases, respectively. The relative position of the other geometrical components was fixed. The pump geometry was designed using the Siemens NX

software (NX 10.0, Siemens Product Lifecycle Management Software Inc., Plano, TX, USA) and CAD geometries are shown in Figure 23.

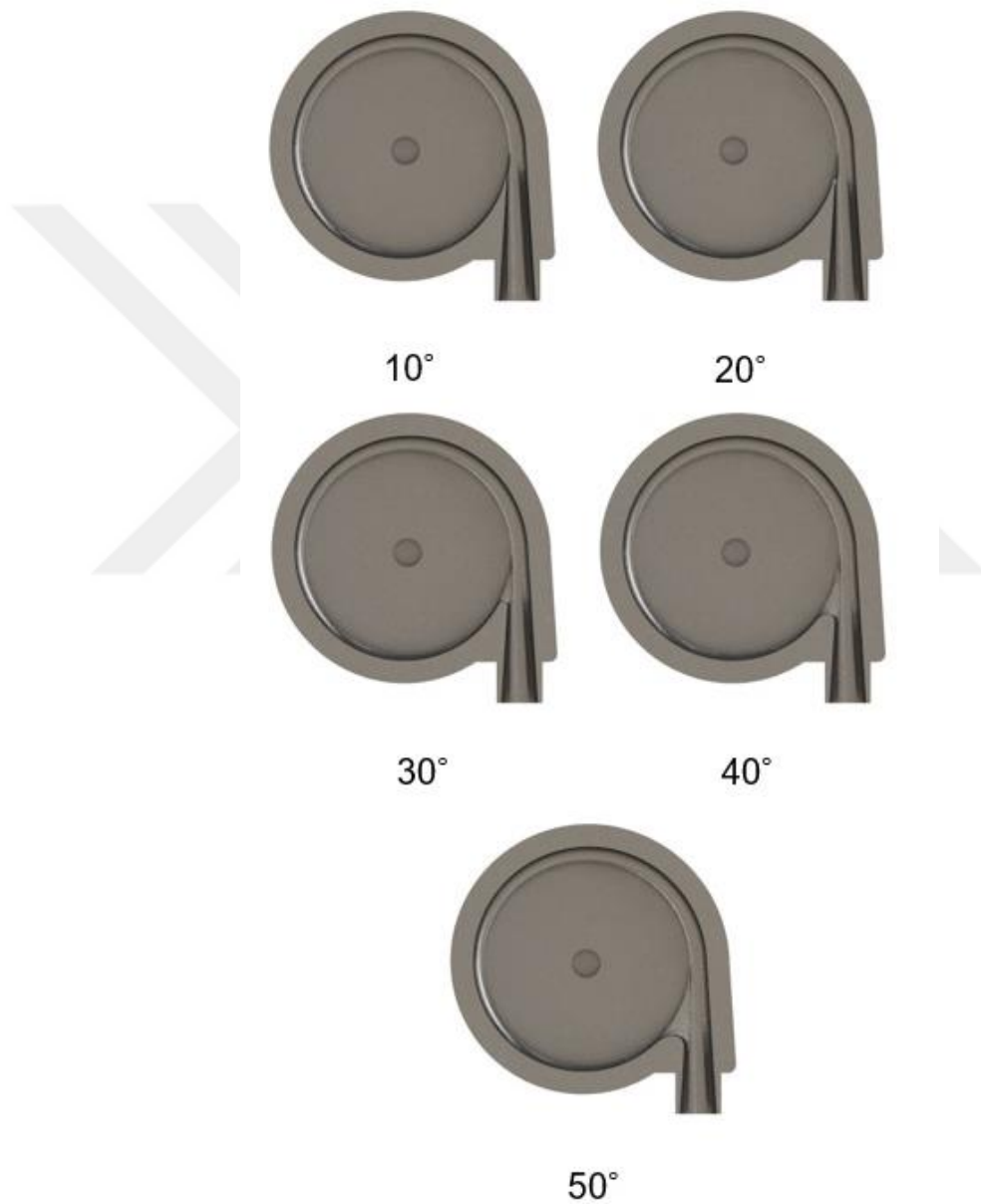


Figure 23 - Virtual design of different volute tongue angles (θ°).

3.3.3 3D Pump Geometry

Overall, the physical design of the pump system contains five parts: a motor stator (shroud), a magnet, an inlet guided by three straight blades, a rotating impeller to exert kinetic energy to the fluid, and a volute to convert the kinetic energy to potential energy. The geometry of the pump is shown in Figure 24.

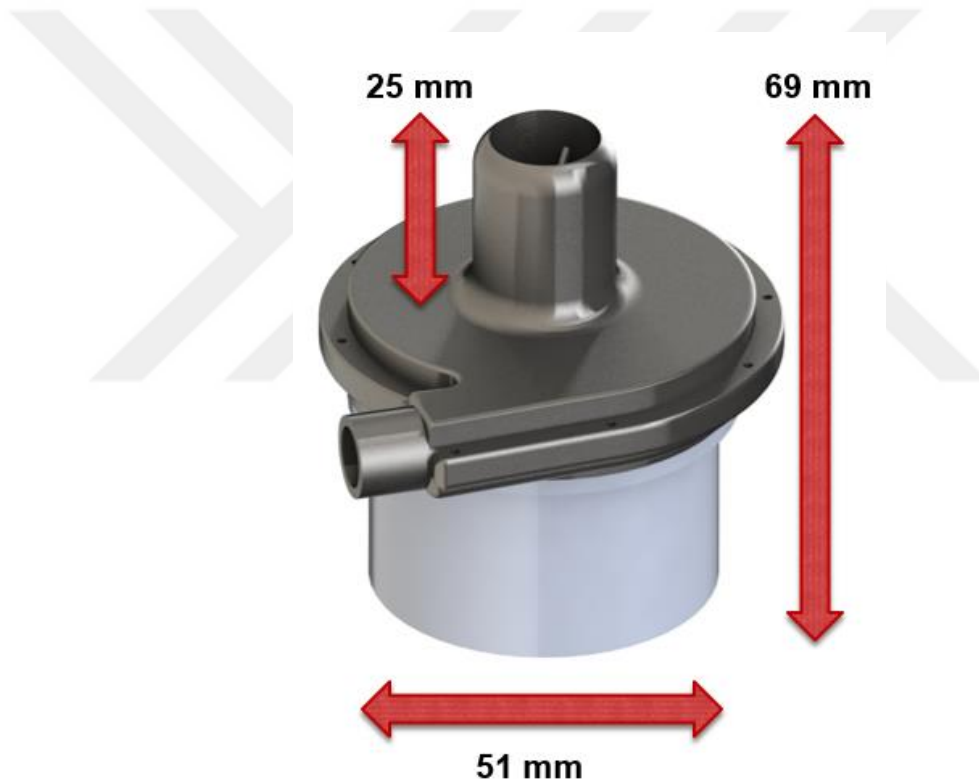


Figure 24 - 3D Pump Geometry

The main dimensions of the pump are 25 mm inflow height, 69 mm total height and 45 mm impeller diameter inside. The pump was designed to operate at the

speed of 2000 rpm, corresponding to the 5 L/min pump flow rate and 100 mmHg pressure head which satisfy the physiologic needs.

3.4 Summary

In this chapter, the design evolution of Istanbul Heart VAD (iHeart VAD) is described and the requirements for the performance optimization outlined with determining the design criteria. The method for design optimization was presented by aiming to produce the final prototype by considering available manufacturing capacity and testing equipment at Koc University. A focus of the research is working toward the most efficient geometrical configuration with a good hydrodynamic and hemolytic output to create a more competitive device which can be accessible for more patients with low cost. The casing structure of the pump was modified to embed a motor for driving mechanism. The volute and impeller parts were also modified with the most efficient geometrical structure. The design parameters (blade wrap angle, number of blades, volute tongue position) were studied for optimization by means of a numerical parametric study.

Chapter 4

NUMERICAL SIMULATIONS

This chapter introduces the computational methods which have been used for simulations of the Istanbul Heart VAD (iHeart VAD) to analyze the flow field and hemolytic performance for optimization. Computational fluid dynamics (CFD) is a helpful tool to predict hydraulic performance and analyze the flow structure of rotary blood pumps at design phase [44,55]. It is a widely used method for designing, analyzing and optimizing medical devices such as blood pumps. In the beginning of this chapter, a general procedure and the description of the principles of computational simulations of rotary blood pumps are presented. Next, the description of blood damage modeling is given. The result of numerical simulations is compared, and then the hydraulic output is tested in simple hydraulic rig for validation. Finally, the optimized design is introduced at the end of this chapter.

4.1 Computational Fluid Dynamics

Optimizing the design of a pump is an iterative process. The investigation of each design parameters needs to validate the design theory but performing an experiment for any modification would not be a cost-effective method and consumes a significant amount of time [31]. Computational fluid dynamics (CFD) offers an efficient method to improve the design of blood pumps by analyzing the flow field instead of the trial and error by performing experiments. Development

cycle time and cost of physical tests could also be minimized by utilizing CFD approach.

Commercial CFD packages Fluent and CFD-Post were utilized in this study (ANSYS Inc., Pittsburgh, PA, USA). It basically splits fluid domain into small cells and solves the related equations for every cell by iteration. Flow model should be evaluated by including other desired equations along with Navier-Stokes equations. The analysis reveals the dynamic of fluid under distinctive conditions such as turbulence, heat transfer or acoustics.

4.1.1 Navier-Stokes Equations

CFD software basically solves the Navier-Stokes equations which contains a continuity equation, conservation of momentum equations and conservation of energy equation. Equation 6 describes the conservation of mass equation based on the concept that mass flow into a controlled volume must equal mass flow out of the volume:

$$\frac{Dp}{Dt} + \rho \nabla \cdot v = 0 \quad (6)$$

where ∇ is the divergence, t is time, v is velocity and ρ is the fluid density.

The conservation equation of momentum is also achieved by the conservation relation.

$$\rho \frac{Dv}{Dt} = \rho g - \nabla p + \mu \Delta v \quad (7)$$

Where v is velocity, ∇p the gradient of surface forces, P is the pressure, μ is the dynamic viscosity.

4.1.2 Turbulence Model

In fluid dynamics, flow regimes are characterized by a non-dimensional number, Reynolds number (Re). Reynolds Number defines flow characteristics as laminar or turbulent based on the velocity fields. It corresponds to the ratio of inertial forces to viscous forces.

$$Re = \frac{\rho v L}{\mu} \quad (8)$$

Where v is the velocity of the fluid, L is the characteristic length, μ is the dynamic viscosity.

Determining the turbulence model is a significant aspect in CFD simulations. In general, blood pumps in literature are simulated by $k-\varepsilon$ or $k-\omega$ turbulence models due to the high velocity gradient. k represents kinetic energy, ε is dissipation rate, and ω is frequency. The $k-\omega$ model is generally better for low-Reynolds number computations. However, $k-\omega$ is very sensitive to initial boundary conditions, and the convergence is difficult compared to the $k-\varepsilon$ model. $k-\varepsilon$ is commonly used model and isn't memory-intensive, also it offers good convergence. Hence, the $k-\varepsilon$ model is selected as turbulence model during the numerical simulations [56,57].

4.1.3 Mesh Generation

The mesh is a crucial component of a CFD simulation as it impacts the validity, accuracy, and convergence of the solution. Hence, it is appropriate to consider mesh quality regarding error analyses to enable an accurate simulation. The fine mesh must be structured for critical areas where the flow has high velocity and shear stress. Non-smooth contact regions, bearings, small clearance zones, rotor-inducer and rotor-diffuser gaps are usually considered as risky regions so, fine meshes must be applied.

Fine mesh sizes at boundary layer are applied to model the flow characteristic with Enhanced Wall Treatment method. The flow around viscous sublayer is practically laminar due to the no-slip condition, and the transition layer between laminar and turbulent flow is called buffer zone. The most exterior layer is named as a fully turbulent region [58]. In this study, the first node is placed in “viscous sublayer” by ensuring $y^+ < 5$ contours with fine meshing. During the grid generation process, orthogonal quality, aspect ratio, and skewness were set in the required range. The final meshes were contained approximately 10 million cells during the numerical simulations (Figure 25).

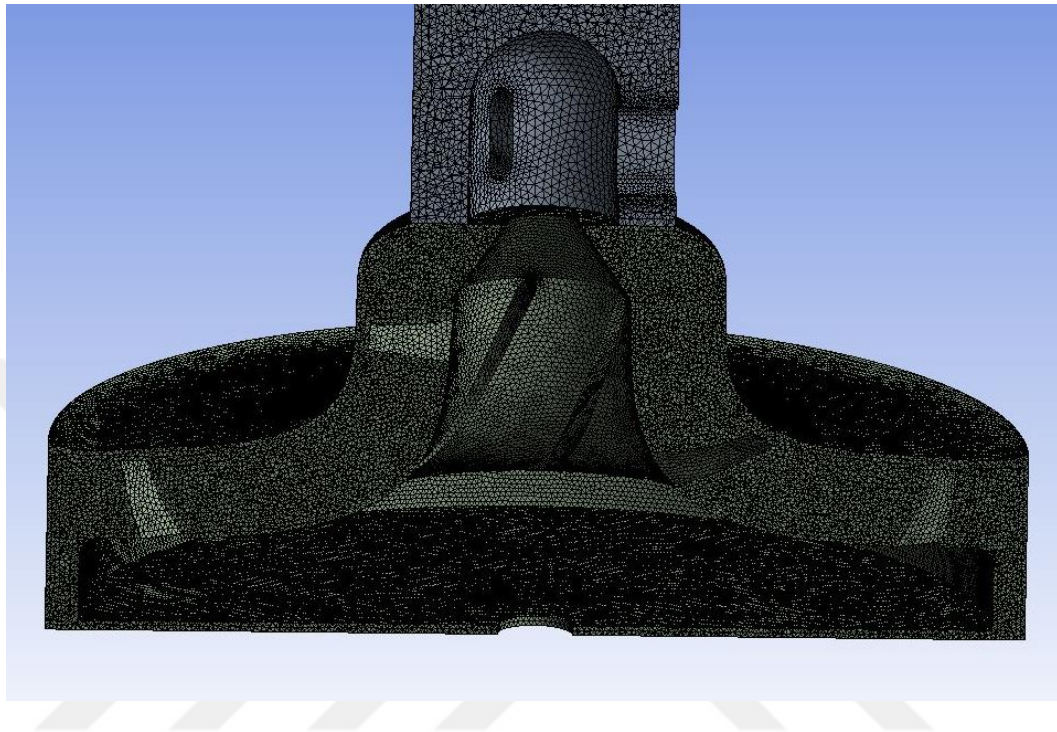


Figure 25 - Mesh generation of the impeller geometry of centrifugal blood pump.

4.1.4 Boundary Conditions

Commercial software Fluent (ANSYS 17.0, ANSYS, Inc., Pittsburgh, PA, USA) was used to model the flow pattern inside the pump. Finite volume method with multiple reference frame (MRF) was applied. Grids between impeller and volute region were combined by the frozen rotor interface. In this computational study, blood was modeled as an incompressible Newtonian fluid with 1060 Kg/m³ density and 0.0035 Pas dynamic viscosity. Although blood is known as non-Newtonian fluid, it only exhibits non-Newtonian properties at low shear rates (<100/s). Therefore, it is reasonable to assume blood as a Newtonian fluid due to the high

shear rates in rotary blood pumps. The convergence precision was set to 10^{-4} for the scaled residuals. Inlet and outlet ports were extended to the certain length in order to prevent boundary condition effects on the convergence. The inlet boundary condition was set to 5 L/min flow rate, and the outlet pressure was set to zero as nominal values at 2000 rpm. The pressure difference between the inlet and outlet port was reported as absolute.

4.2 Blood Damage Modeling

As the rotating surfaces contacts with blood cell during the flow circulation in blood pumps, there is a risk of hemolysis and thrombosis. Therefore, the potential of blood damage must be evaluated using the hemolysis prediction models.

An empirical power-law model has been mostly employed to compute the hemolysis in blood pumps. The hemolysis potential of the pump is quantified as a blood damage index (D) which essentially shows the increase in plasma-free hemoglobin. The power law model predicts the blood damage by correlating the plasma-free hemoglobin level with shear stress and exposure time of the fluid elements [59],

$$D = \frac{dHb}{Hb} = C \tau^\alpha t^\beta \quad (9)$$

where C , α and β are the constants obtained by post-processing the experimental data, τ is the scalar stress, t is the exposure time of blood cell, dHb represents the damaged hemoglobin content, and Hb indicates the hemoglobin content. As the constants vary based on the conducted experiment, several researchers have

proposed different values. The suggested constants by Heuser et al. [60] ($C = 1.8 \times 10^{-6}$, $\alpha = 0.765$, $\beta = 1.991$) were computed in this numerical study due to the reported results about their accuracy over experimental data [61].

$$D = \frac{dHb}{Hb} = 1.8 \times 10^{-6} \tau^{1.991} t^{0.765} \quad (10)$$

A scalar shear stress (SSS) parameter can be found by the following expression;

$$\tau = \left[\frac{1}{6} \sum (\tau_{ii} - \tau_{jj})^2 + \sum \tau_{ij}^2 \right]^{\frac{1}{2}} \quad (11)$$

and stress tensor components can be found by the summation of the viscous and Reynolds stress tensor.

Two well-known numerical methods, Eulerian and Lagrangian approaches, were implemented together to calculate the blood damage potential in this study. These estimation methods differ in their approach to calculate the blood damage index (D). Lagrangian approach calculates the blood damage index by integrating the shear stress and exposure time along the pathline, whereas Eulerian approach linearizes the power-law equation to solve as a scalar transport equation [61]. Nevertheless, both approaches were implemented to provide a crosscheck on relative hemolysis between the cases.

4.2.1 Eulerian approach

In the Eulerian approach, the power-law equation is linearized to obtain the blood damage index. This method directly computes the damage index from velocity and

shear stress field by volume integration over the entire flow domain [62]. The time dependency of the power law in Equation (9) was eliminated by the linearization. The linearized blood damage index was then expressed as:

$$D_I = D^{1/0.765} = (1.8 \times 10^{-6})^{1/0.765} \tau^{1.991/0.765} t \quad (12)$$

A hyperbolic equation was also obtained by taking the time derivative of Equation (12) and applying the Eulerian transform.

$$\frac{\partial}{\partial t} D_I = \left(\frac{\partial}{\partial t} + \bar{u} \cdot \nabla \right) D_I = \tau \quad (13)$$

$$\frac{\partial}{\partial t} D_I = (1.8 \times 10^{-6})^{1/0.765} \tau^{1.991/0.765} \quad (14)$$

By assuming that the damage is time-independent, and the fluid is incompressible, linear damage index can be linked to the volume integral of shear stress and it can be presented as the mass-weighted average.

$$D_I = \frac{1}{Q} \int_V \tau dV \quad (15)$$

The final damage index can be shown as:

$$D = D_I^{0.765} \quad (16)$$

4.2.2 Lagrangian approach

Several research groups had applied Lagrangian technique for hemolysis estimation [63,64]. The shear stress acting on the RBC was calculated with the

particle tracking method by using Euler forward integration technique [65]. Exposure time information was calculated by releasing massless particles from the inlet surfaces of each design. Blood damage index (D) was calculated by using an integrative approach as particles move to the next cell.

$$D = \int_{inlet}^{outlet} 1.8 \times 10^{-6} \tau^{1.991} t^{0.765} \quad (17)$$

$$= \sum_{inlet}^{outlet} 1.8 \times 10^{-6} \tau^{1.991} \Delta T^{0.765} \quad (18)$$

Parameters for calculating the particle tracks were chosen to get as many particles to exit as possible. Particles in the flow were numerically traced and recorded.

4.3 FDA Blood Pump Model as a CFD Benchmark

The numerical approach used in this study was also applied on a benchmark centrifugal blood pump provided by the U.S. Food and Drug Administration (FDA), as part of the “CFD Critical Path Initiative” project. The purpose of this is to validate our computational approach so that CFD can be effectively utilized to characterize fluid flow and to predict blood damage in our study. More detail about FDA’s “CFD Critical Path Initiative” project can be found in the work of Malinauskas et al. [66].

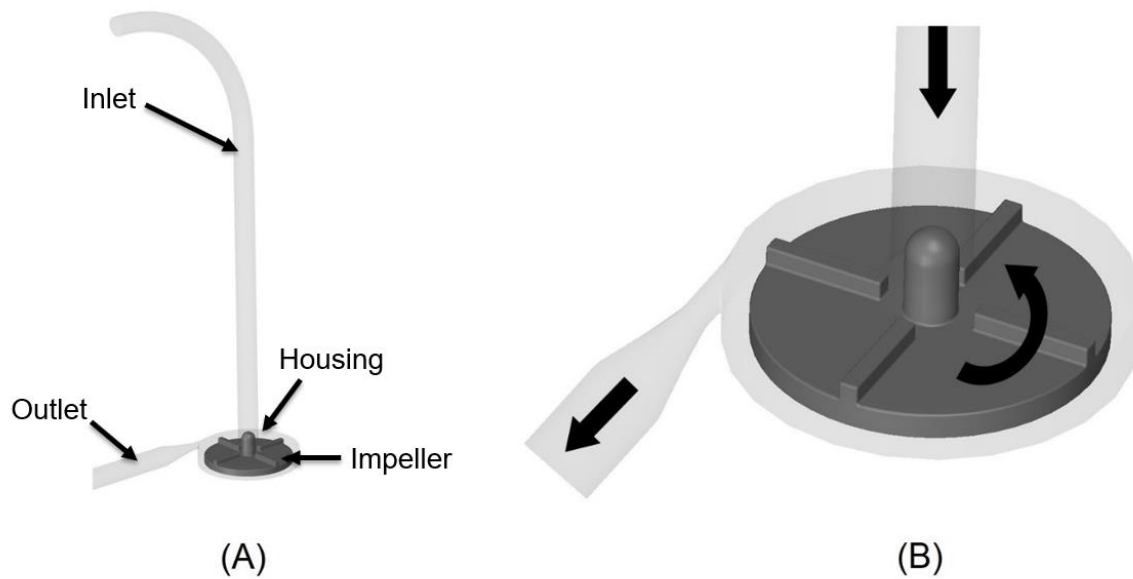


Figure 26 - (A) Geometry of the FDA's benchmark blood pump. (B) Enlargement of impeller zone.

The FDA blood pump is based on a simple centrifugal type design with four straight blades and a volute, as shown in Figure 26. It is designed as a standardized benchmark case to provide a comparison of the computational results with experimental data for pump designers as a reference to the accuracy of the CFD application. Currently, verification and validation studies for the FDA's centrifugal pump are still ongoing [66,67]. Computer-aided design (CAD) models were generated based on the dimensions supplied by FDA and implemented into our CFD model to calculate the flow field. The experimental data of Malinauskas et al. was also utilized in this study to validate FDA pump's computational results.

4.4 Computational Results

This section details the results of the optimization process of Istanbul Heart VAD (iHeart VAD). The pump design was iteratively optimized with the help of CFD analysis. The results start with the comparison of different impeller geometries that is followed by volute tongue position analysis. Next, the result of FDA's centrifugal blood pump was presented as a comparative benchmark case. Finally, experimental validation was illustrated on the hydraulic test rig.

4.4.1 Analysis 1: Impeller Geometry Variation

In blood pump design, there are several factors which can affect the blood damage. This analysis focuses on the impeller design which is considered as the most critical part of the pumping system. Blood damage index values from two hemolysis estimation models were carried out to assess a specific parameter called wrap angle in the design cycle. Hydraulic and hemolysis performances of five geometries were compared at the same rotation speed of 2000 rpm and flow rate of 5 L/min. The working conditions and overall performance are given in Table 7. The hydraulic performance was observed fairly similar in Case I, II, III and IV. Moreover, Case V which has the highest wrap angle (240°) revealed the poorest hydraulic performance with the efficiency of 46.9% and pressure head of 83.8 mmHg.

Table 7 - Effect of the wrap angle on hydraulic and hemolysis Performance.

	Case I	Case II	Case III	Case IV	Case V
Wrap Angle [°]	0	60	120	180	240
Rotation Speed [rpm]	2000	2000	2000	2000	2000
Outflow Rate [L/min]	5	5	5	5	5
Pressure Head [mmHg]	101	105.2	104.1	101.4	83.8
Hydraulic Efficiency [%]	52.1	54.3	53.5	54	46.9
Damage Index (Lagrangian)	1.37E-02	1.14E-02	9.84E-03	7.31E-03	1.85E-02
Damage Index (Eulerian)	1.26E-03	1.10E-03	9.47E-04	8.94E-04	1.40E-03

The difference in pressure head and hydraulic efficiency was observed less than 4% between Case I to IV. However, as the wrap angle varied from 0° to 180°, hemolysis indices indicated up to 46.6% and 29.1% improvement based on the Lagrangian and Eulerian approaches, respectively. Nevertheless, the improvement trend was not observed in Case V due to the high hemolysis rates and poor hydraulic performance with the hydraulic efficiency of 46.9%.

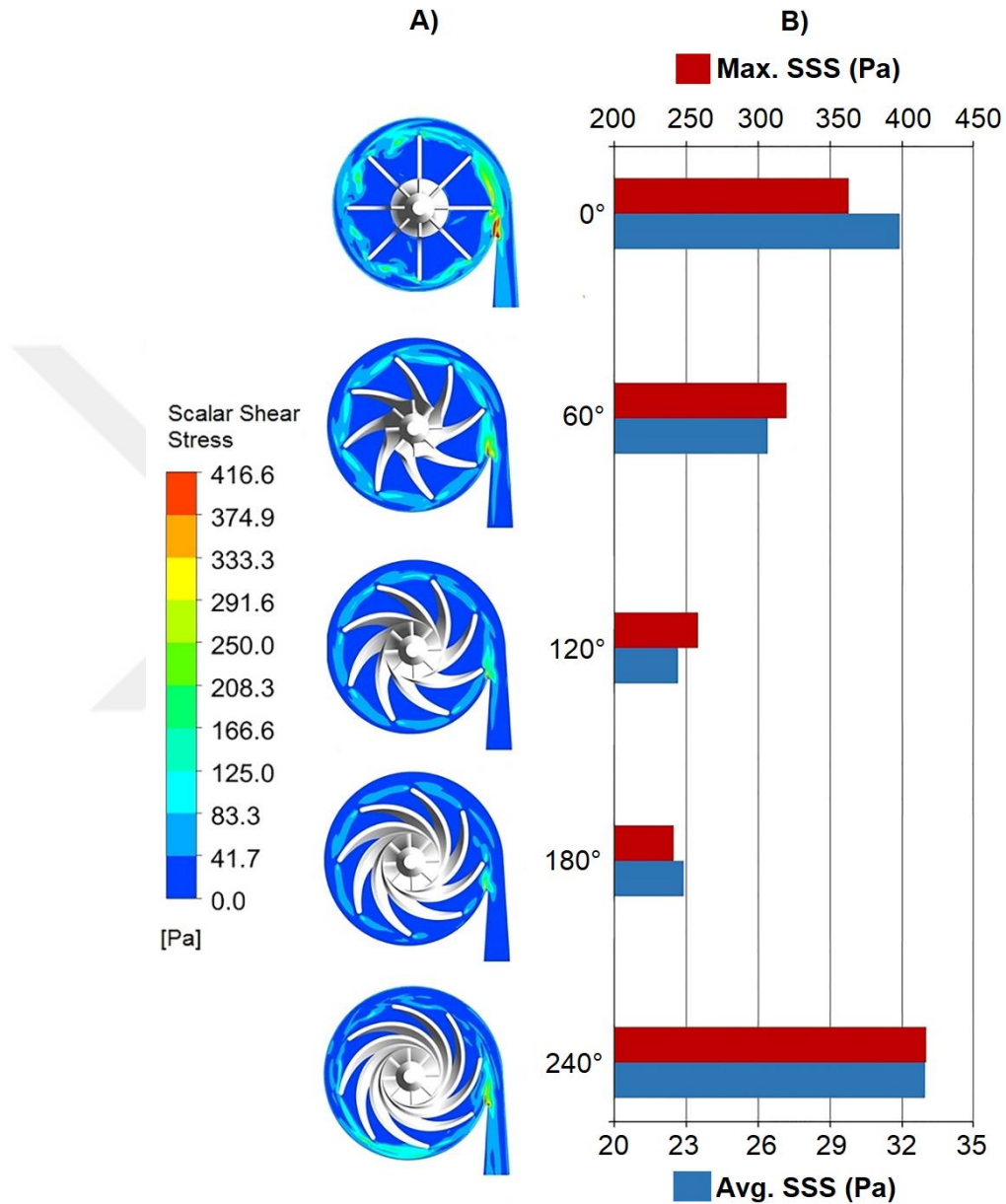


Figure 27 - (A) The distribution of scalar shear stress (SSS) at different wrap angles. (B) The maximum and averaged scalar shear stress values in the entire flow domain of different wrap angles.

Figure 27 (A) illustrates the scalar shear stress (SSS) distribution for all designs. It can also be found in Figure 28 (B) that maximum scalar shear stress induced in all five designs were about 362.8, 319.8, 258, 241.5 and 416.6 Pa, respectively. The average shear stress values were ranged from 22.7 to 33 Pa.

4.4.1.1 Eulerian Approach

The high blood damage index was usually observed at the tips of the blades and around the volute tongue region. A mid-volute layer of the geometry was used to demonstrate the blood damage formation inside the pump. Figure 28 depicts an illustration of linear blood damage indices (D_I) for Case II, which has a relatively high hemolysis index at the wrap angle of 60° . Flow zones where RBCs are more prone to hemolysis is simply observed. As the wrap angle is increased to 180° , the improvement in the distribution of the D_I was observed in Figure 29(b).

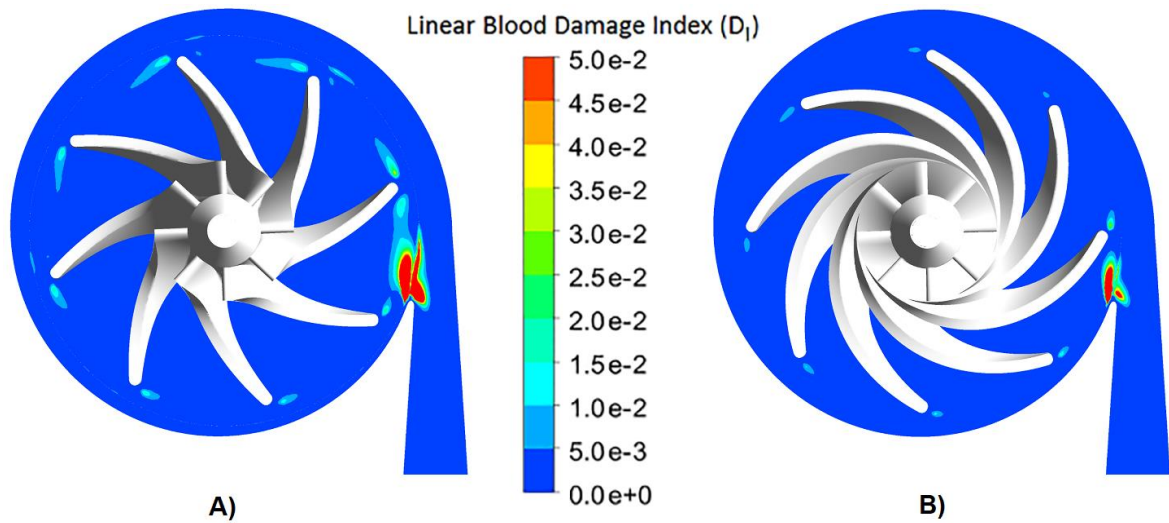


Figure 28 - (A) The distribution of D_l in Case II by the Eulerian approach. (B) The distributions of D_l in Case IV by the Eulerian approach.

4.4.1.2 Lagrangian Approach

In Lagrangian approach, the flow paths of the particles originated from the inlet port of the pump and completed at the outlet. The number of particles released was varied between 2280 and 2338 depending on the number of the mesh faces at the inlet port and the residence time of the particles ranged from 0.14 to 3.24 second for changing blade geometries. Figure 29 shows the blood damage index distribution of five designs by the particle tracking method. Blood damage indices ranged from 0 to 0.48; hence the results of blood damage indices were presented in three sets of the interval for illustration purposes. In Figure 29, the horizontal axis indicates the blood damage index and the vertical axis shows the percentage of released particles at

different intervals. 74.6% of the particles traced in the wrap angle of 180° were concentrated in the low blood damage interval ranged from 0-0.005. However, the wrap angle of 0° and 240° had the largest blood damage by the percentages of 27.4% and 28.6%, respectively, at the range of 0.015-0.48.

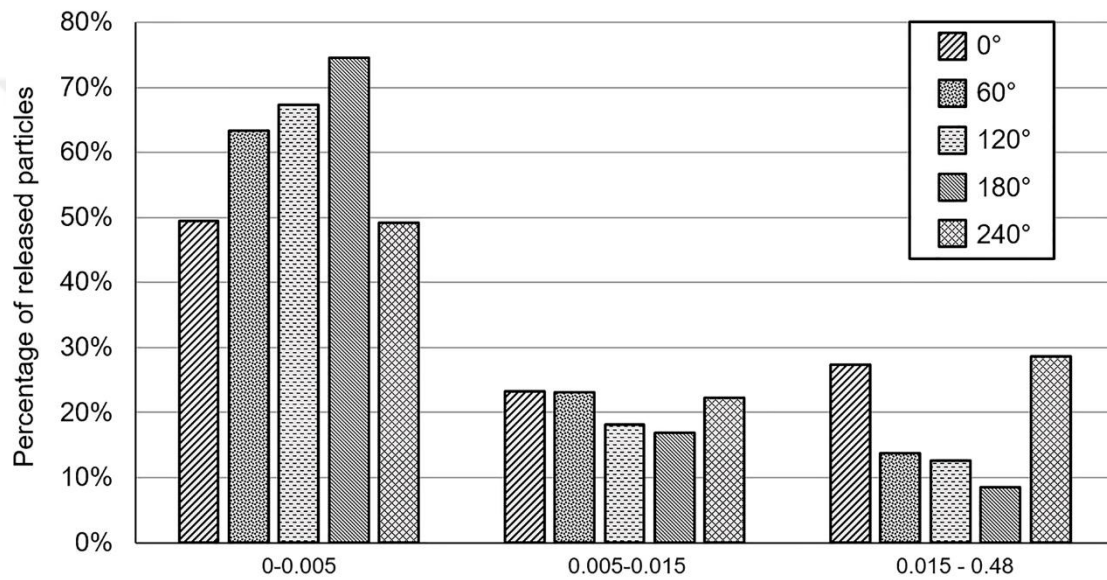


Figure 29 - Blood damage indices of the different wrap angles by particle tracking method.

Additionally, the number of blades were compared at the wrap angle of 120° . Results are shown in Table 8. It indicates that an increase in blade number could result in a high blood damage index, which means that RBCs are more prone to hemolysis.

Table 8 - Effect of the number of blades on hydraulic and hemolysis Performance.

	Case III	Case VI	Case VII	Case VIII	Case IX	Case X
Wrap Angle [°]	120	120	120	120	120	120
Num. of Blades	8	4	10	5	6	3
Num. of Splitter	0	4	0	5	0	3
Rotation Speed [rpm]	2000	2000	2000	2000	2000	2000
Outflow Rate [L/min]	5	5	5	5	5	5
Pressure Head [mmHg]	104.1	103.1	104	99.6	96.8	94.9
Damage Index (Lagrangian)	9.84E-3	1.20E-2	1.08E-2	8.41E-3	1.94E-2	9.44E-3
Damage Index (Eulerian)	9.47E-4	1.32E-3	1.09E-3	9.39E-4	1.68E-3	7.56E-4

Besides the effect of blade number, splitter blade was studied separately in Case III, VII, and IX. Splitters were integrated by removing blades in order to reduce the streamline fluctuations in the region between two blades. Table 8 shows that splitters provide lower blood damage indices compared to the design without splitters. This result indicates that introducing splitters to the impeller geometry shows decay in hemolysis estimation. The design which has five splitters, five main blades at the wrap angle of 120° performed the best hemolysis performance based on both damage prediction models.

4.4.2 Analysis 2: Volute Geometry Variation

The numerical simulations were also conducted to evaluate the volute geometry variation. The hydraulic and hemolysis performance of five volute geometries were investigated. Table 9 illustrates the working conditions and overall performance of

the cases. The tongue angle (position) shifted from 10° to 50° at the intervals of 10° . With increasing the tongue angle, pressure head and hydraulic efficiency were decreased correspondingly. The poorest hydraulic performance was observed in Case V with the hydraulic efficiency of 44.4% and pressure head of 94.8 mmHg. Both hemolysis estimation approaches indicated that the volute angle of 20° revealed the minimum blood damage index.

Table 9 - Effect of the volute tongue on hydraulic and hemolysis performance.

	Case I	Case II	Case III	Case IV	Case V
Volute Angle ($^\circ$)	10	20	30	40	50
Pressure Head (mmHg)	103.4	102.1	99.6	96.8	94.8
Hydraulic Efficiency (%)	53.3	51.9	50	48.3	44.4
Net Radial Force (N)	0.29	0.26	0.23	0.21	0.18
Damage Index (Lagrangian)	1.20E-02	1.18E-02	1.35E-02	1.58E-02	1.56E-02
Damage Index (Eulerian)	3.26E-03	2.84E-03	4.14E-03	8.39E-03	1.24E-02

In Figure 30, pressure distributions of five different cases were compared. The pressure contours of the mid-volute layer were plotted for all cases, respectively. Pressure field was observed more uniform around the impeller region at the tongue angle of 50° . The net radial force acting on impeller was also reduced by the effect of increasing tongue angle.

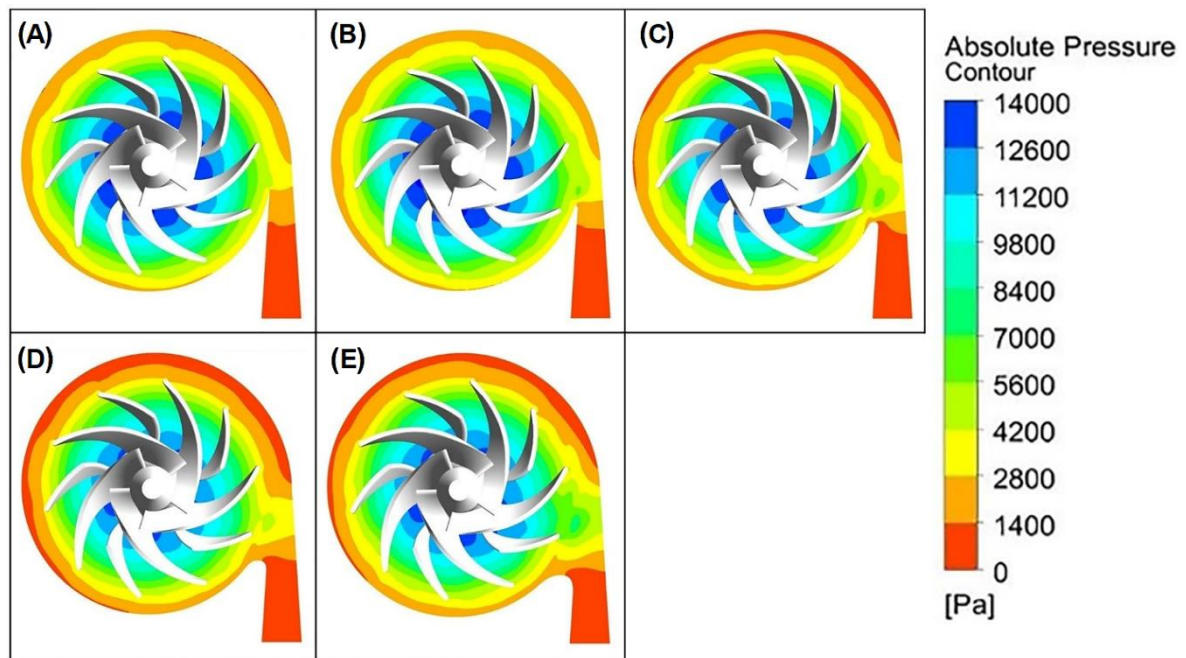


Figure 30 - Absolute pressure contours in various tongue angles. (A) 10°. (B) 20°. (C) 30°. (D) 40°. (E) 50°.

To investigate the flow patterns around the tongue region, the outlet flow angle was demonstrated for all five cases (Figure 31). The flow angle was computed between the outlet velocity and the outlet axial velocity. At minimum tongue angle, less variation in flow angle was observed near the tongue region.

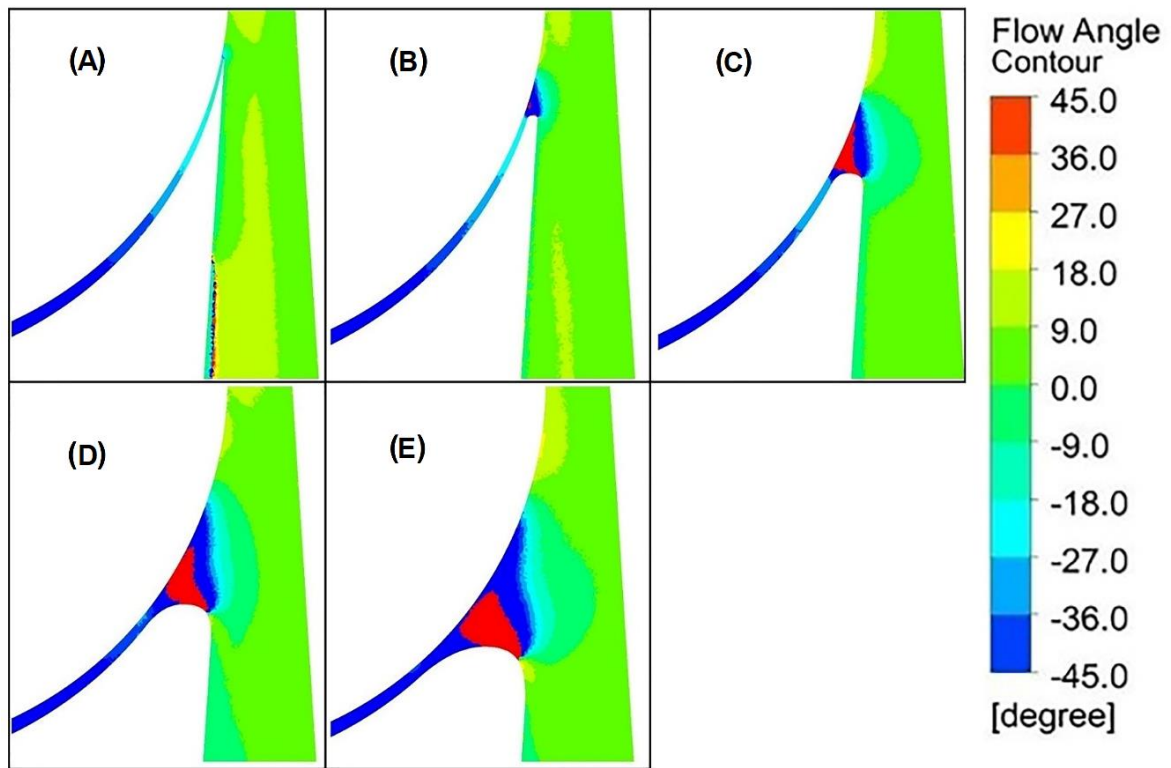


Figure 31 - Outlet flow angle at different tongue angles. (A) 10°. (B) 20°. (C) 30°. (D) 40°. (E) 50°.

The relative velocity field presents the flow interaction between outlet and impeller outflow (Figure 32). At a low tongue angle, the flow was well-guided along the volute region through the outlet. However, as the tongue angle increases, the flow was separated through to the suction side of the blades and eventually resulted in the whirl flow.

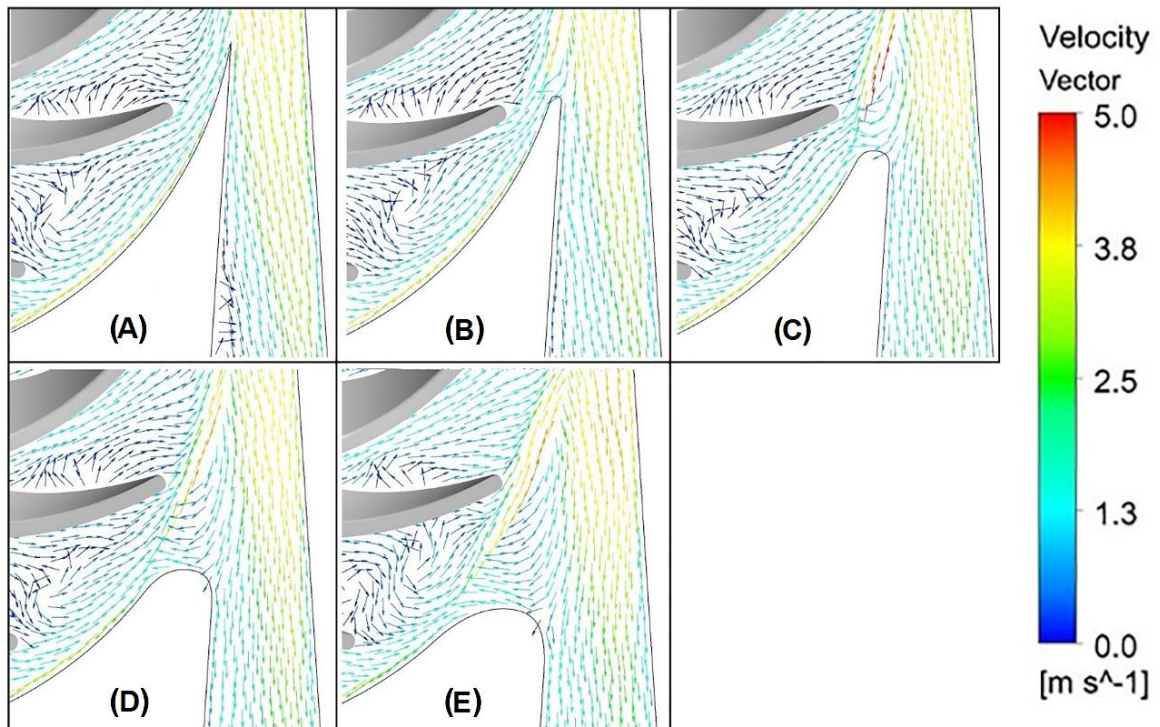


Figure 32 - Velocity vector field at different tongue angles. (A) 10°. (B) 20°. (C) 30°. (D) 40°. (E) 50°.

The SSS distribution based on Equation (11) was also illustrated in Figure 33 (A). High shear stress zones were mostly concentrated around the trailing edges of the blades and the volute tongue region. The maximum and averaged SSS in the entire flow domain were plotted in Figure 33 (B). The largest damage was observed at the tongue angle of 50°, the maximum SSS was found to be 394.2 Pa, and the average SSS was calculated as 15.6 Pa.

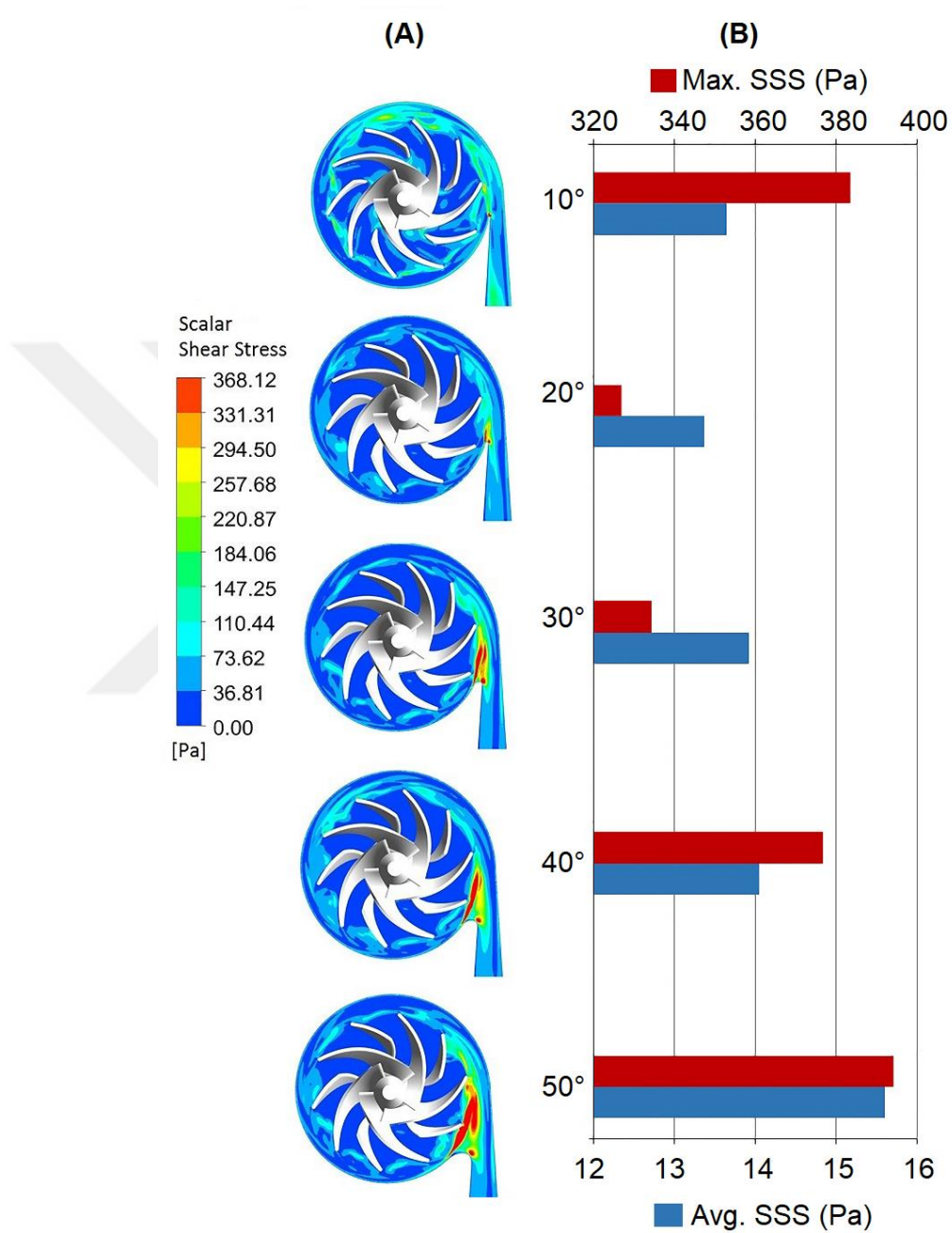


Figure 33 - (A) The distribution of scalar shear stress at different tongue angles. (B) The maximum and averaged scalar shear stresses in the entire fluid domain.

4.4.2.1 Eulerian Approach

In Figure 34, a mid-plane was used to demonstrate the blood damage formation inside the pump. Linear blood damage indices (D_l) based on the Equation (15) were illustrated for the tongue angle of 50° and 20° , as they have the poorest and largest hydraulic and hemolysis performance. Final blood damage index (D) was obtained by integrating the D_l along the volume of the fluid domain and found to be $1.24\text{E-}02$ and $2.84\text{E-}03$ for the wrap angles of 50° and 20° , respectively.

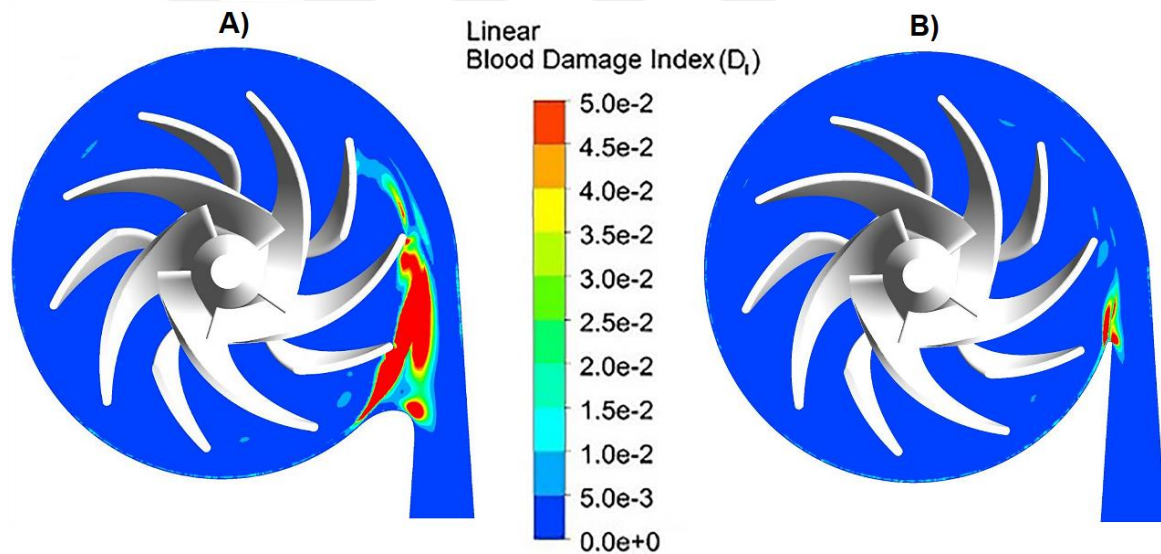


Figure 34 - Distribution of the linear blood damage index (DI) by the Eulerian approach.

(A) the tongue angle of 50° . (B) the tongue angle of 20° .

4.4.2.2 Lagrangian Approach

Massless particles were released from the inlet port of the pump and terminated at the outlet port. The number of pathlines for these particles was varied between 2489 and 2542 depending on the mesh variation at the inlet port and the residence time of the particles ranged from 0.1 to 2.12 s. Figure 35 plots the distribution of blood damage index for five cases by the Lagrangian approach. Blood damage indices of the pathlines ranged from 0 to 0.38. Therefore damage was reported in three sets of an interval for illustration purposes. 57% of the total particles in the tongue angle of 20° remained less than 0.005 and only 10.1% of particles were ranged between 0.015-0.38. A further increase in the tongue angle worsened the condition, and the distribution of the particles was more concentrated through the larger blood damage index zone. When the tongue angle was 50° , 15.8% of particles were traced at the range of 0.015-0.48 which means a greater possibility of hemolysis for large tongue angle.

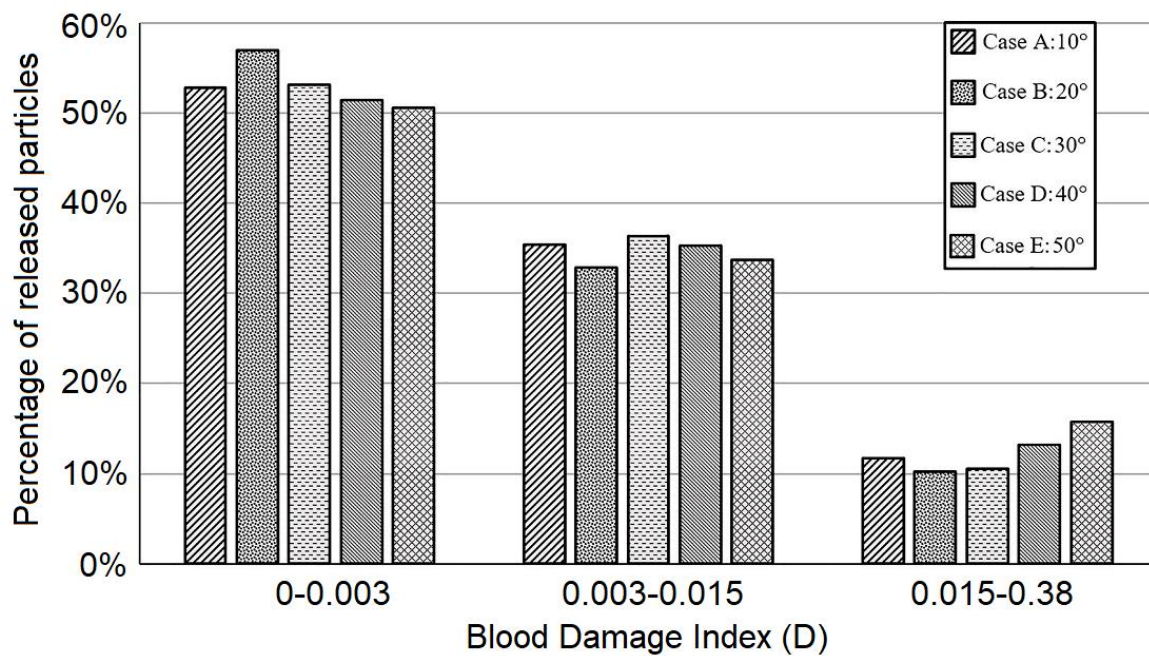


Figure 35 - Distribution of blood damage indices of volute variations with particle tracking method (Lagrangian approach).

4.4.3 Analysis 3: FDA's Benchmark Model

The FDA's pump performance was evaluated at 2000, 2500 and 3500 rpm to validate our CFD approach in this study. For each speed, the flow rate and pressure head were calculated.

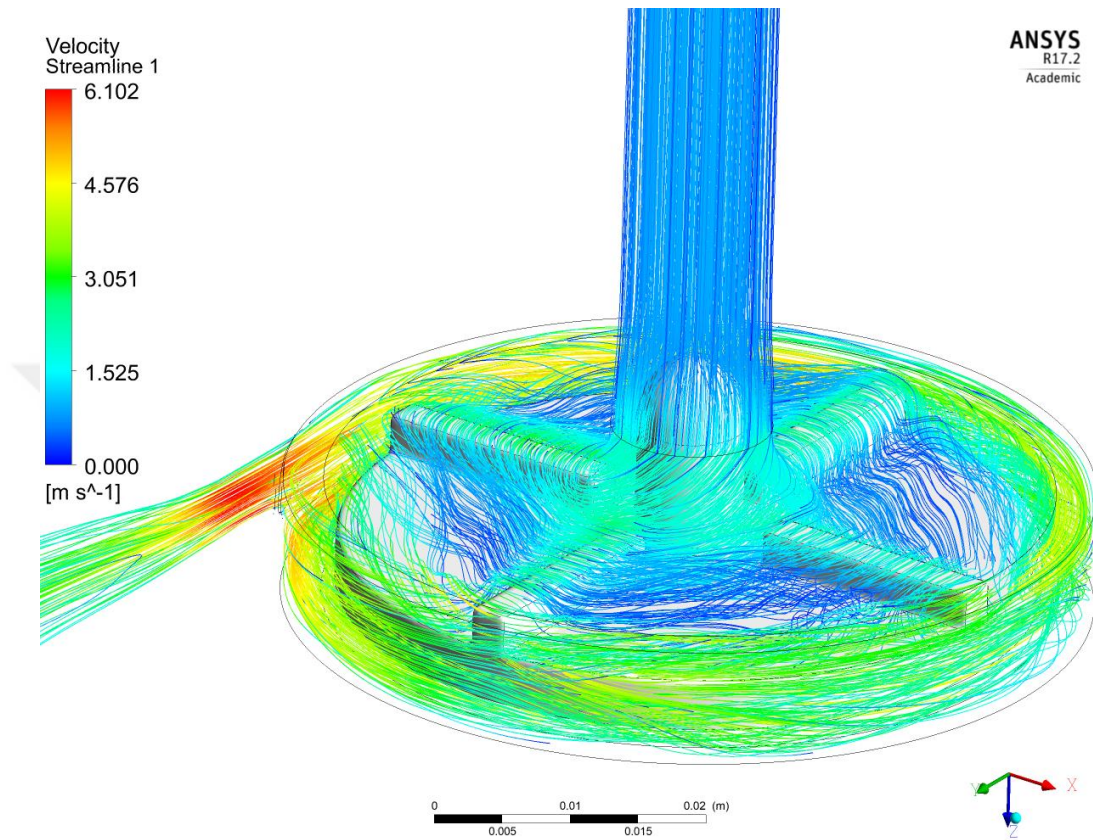


Figure 36 - Streamlines of FDA's blood pump at 2500 rpm.

The CFD results compared to the experimental data are shown in Figure 37 with hydraulic performance curves retrieved from Malinauskas et al. [66].

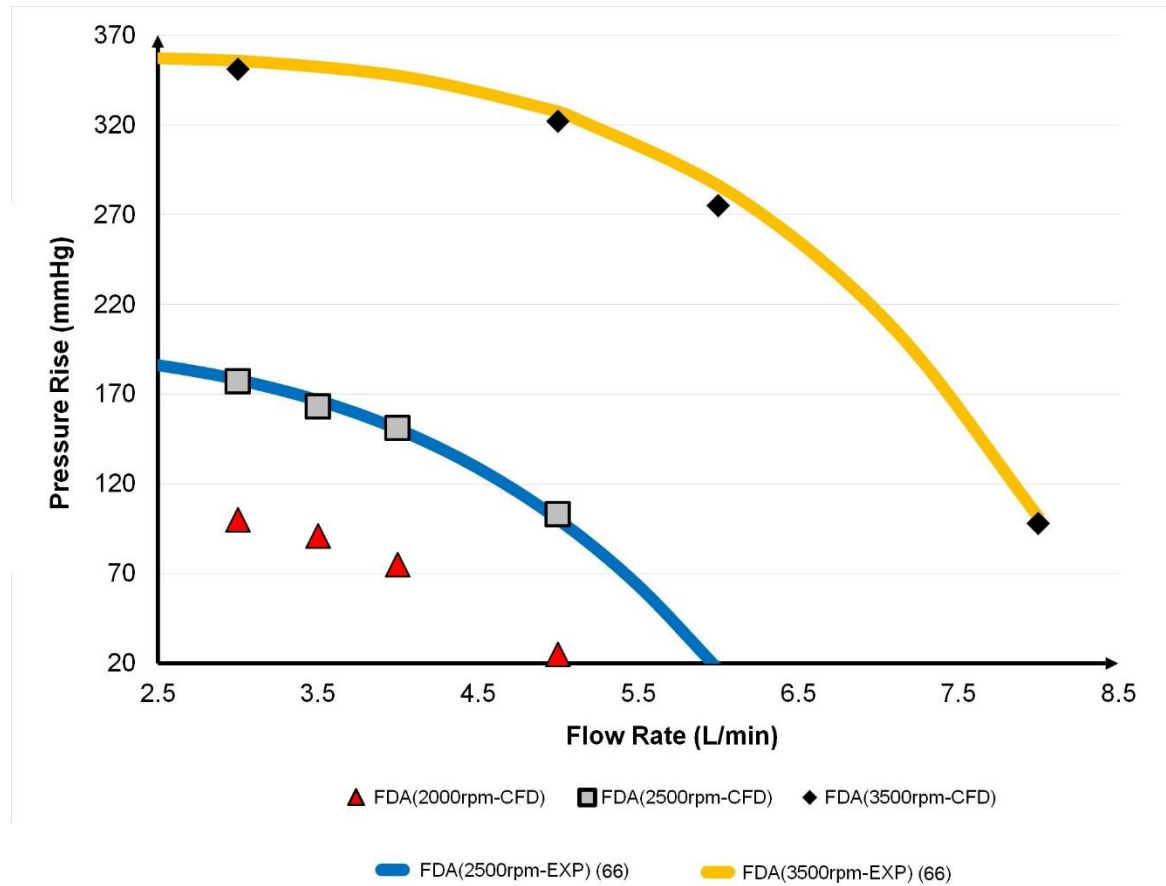


Figure 37 - Pressure-flow rate profile of FDA's blood pump with the experimental data reported in the literature [66].

As FDA's benchmark blood pump is constructed with very simple design, large oscillations in pressure head were observed, and the vortex structure was occurred in the flow field due to large gaps between blades and housing.

4.5 Validation of Computational Results

The numerical investigation of impeller and volute variation has demonstrated different performance characteristics based on the geometry. A hydraulic test rig was established, and experimental investigation of hydrodynamic output was performed to verify the CFD results.

4.5.1 Prototype Construction

Each prototype pump (impeller and volute) was constructed using a rapid prototype manufacturing process. The various configurations were modeled in CAD software (NX 10.0, Siemens Product Lifecycle Management Software Inc., Plano, TX) and exported as STL files. The pump prototypes were manufactured of ABS plastic with a 3D printer (Ultra 3SP Envisiontec GMBH, Gladbeck, Germany). The machine prints highly accurate parts from STL files by using a UV laser to cure the resin. The laser scans the resin and then cures at the data points layer by layer.

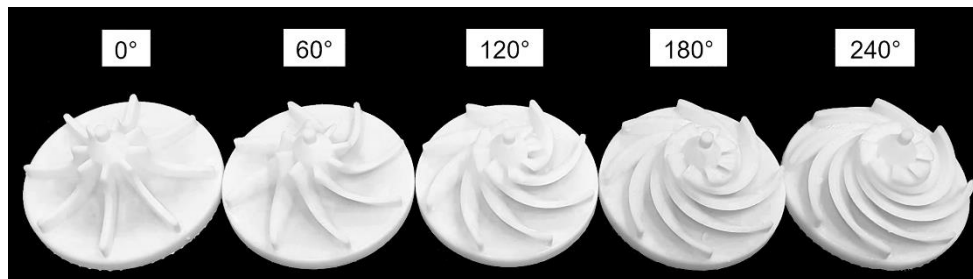


Figure 38 - Prototyped geometries with different wrap angle positions.

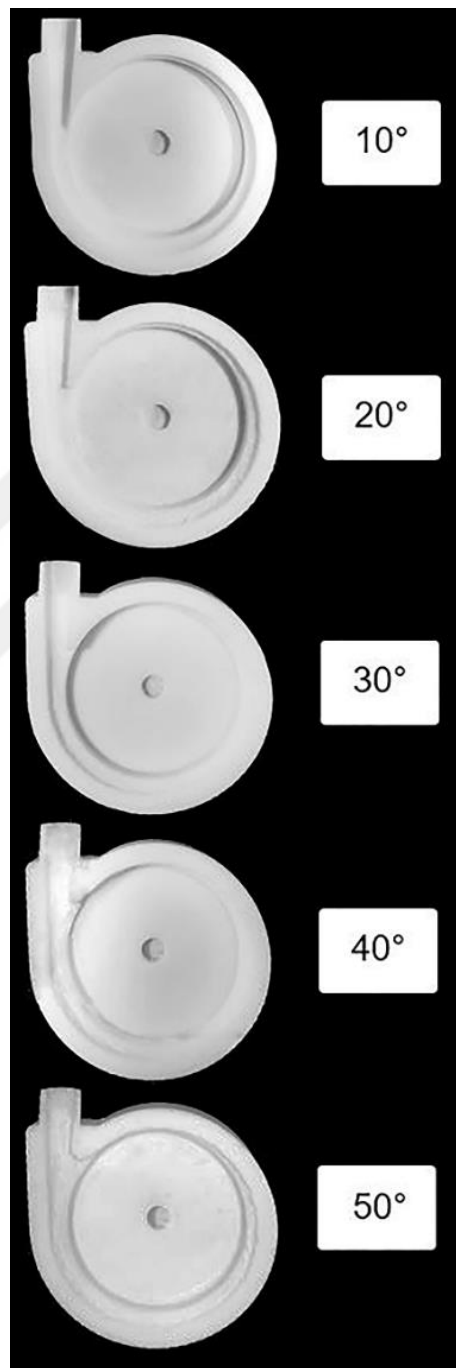


Figure 39 - Rapid prototyped geometries with different volute tongue positions.

Figure 38 demonstrates the rapid prototyped impeller geometries with different wrap angles for the impeller variation analysis. The volute structure was also investigated as described previously. The experimental evaluation focused then second analysis, volute tongue variation. Rapid prototyped volute casings are also shown in Figure 39.

4.5.2 Analysis 1: Hydraulic Output of Impellers

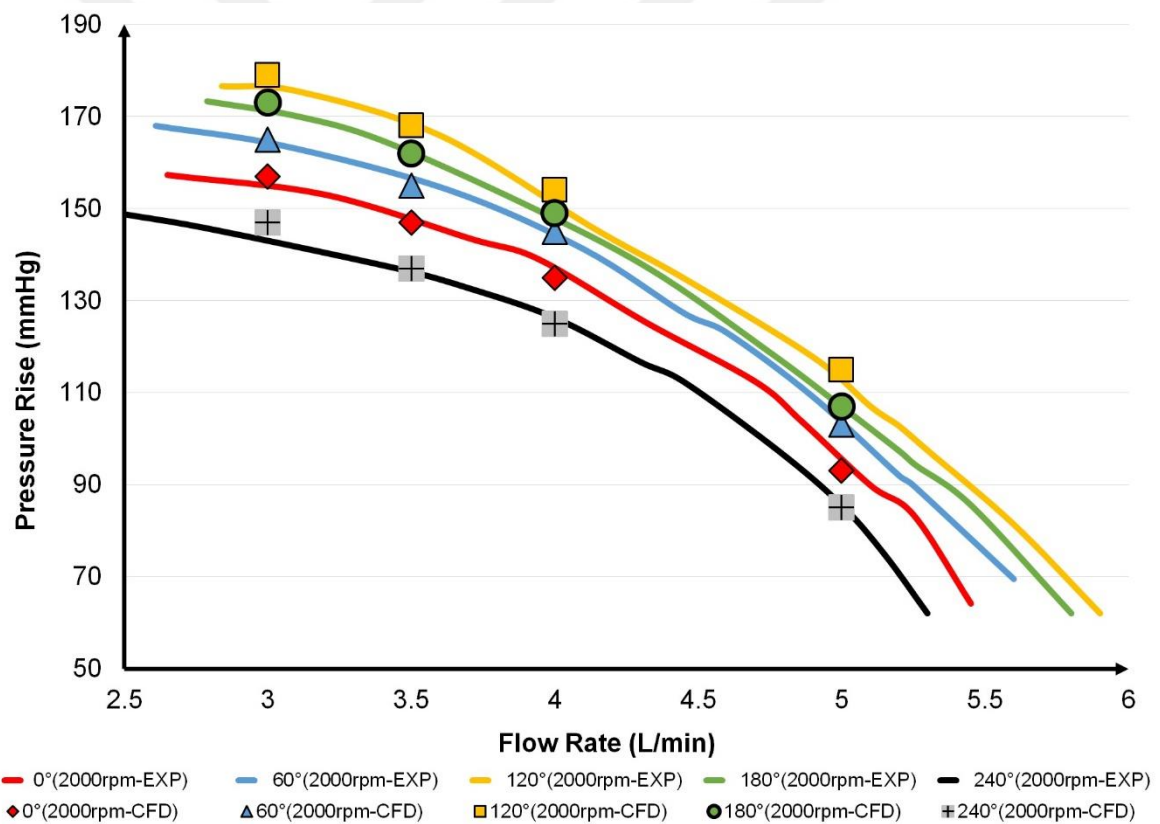


Figure 40 - The pressure-flow rate characteristic of different blade wrap angles at 2000 rpm.

The pressure-flow rate characteristic of prototypes was also examined by physical experiments (Figure 40). Hydraulic experiments revealed that 240° wrap angle has the poorest performance curve. Nevertheless, increasing the wrap angle from 0° led to a major improvement in hydraulic performance. 120° and 180° configurations were observed fairly similar and generated the largest pressure-flow rate profile. The variability of pressure rise between designs was observed near 35%. The trend of computational results matches the experimental data.

4.5.3 Analysis 2: Hydraulic Output of Volutes

Findings of hydraulic experiments were also reported in Figure 41. The pressure-flow performance was measured at 2000 rpm. Performance characteristics revealed that the configuration of 50° tongue angle has the poorest performance curve. Overall, hydraulic performance was observed to be negatively influenced by increasing the tongue angle.

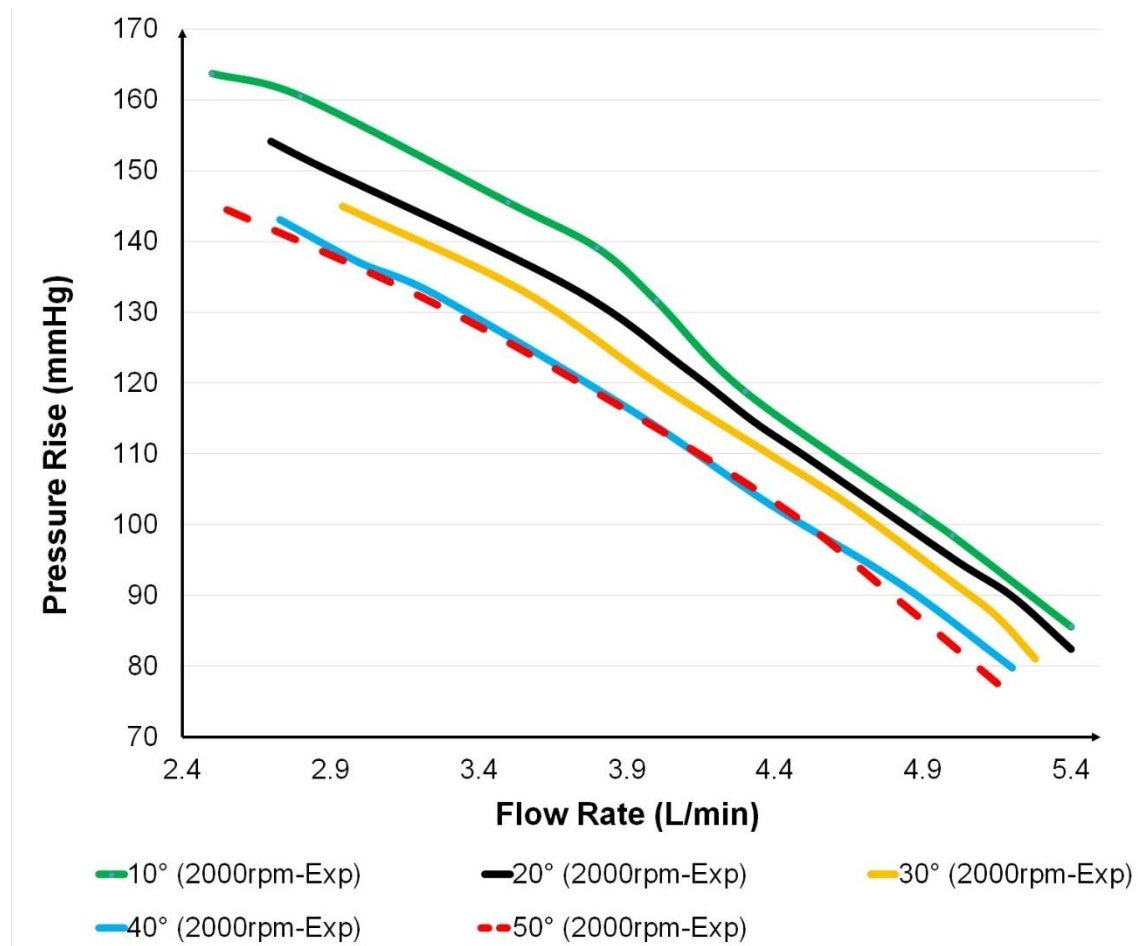


Figure 41 - Measured pressure-flow rate characteristic of different tongue angles at 2000 rpm.

4.6 Discussion

According to the numerical results, the flow pattern of straight blade configuration (the wrap angle of 0°) resulted in flow separation around the trailing edge of the blades where vortex formation is observed. Hence, the wrap angle of 0°

is more prone to high SSS generation due to the recirculating flow pattern in the relatively large blade passage. Introducing a wrapped blade profile provides a narrower flow path, thus reduces the flow separation and provides better guidance to the fluid, consequently vortical structures can be reduced. However, an excessive wrap angle increases the blade length, reduces the priming volume which can negatively influence SSS and velocity distributions causing a poor performance as observed in the wrap angle of 20° .

For volute structure, pressure contours of the cases indicated that increasing volute tongue angle promotes the decrease in the corresponding net radial force on the impeller. However, hydraulic efficiency and head pressure are reduced by the effect of increasing tongue angle. Hydraulic experiments also confirm the pressure-flow rate characteristic of the pumps. It was observed that the SSS distributions were negatively impacted by the larger tongue angle. The tongue angle of 20° represents better hemolysis performance by 5.7% and 12.9% improvements based on Eulerian and Lagrangian approaches, respectively. However, the net radial force acting on the impeller was a major drawback in lower tongue angles. Near the volute tongue region and the trailing edge of blades, blood damage risk is usually higher due to relatively higher acceleration and deceleration values. A well-matching volute tongue and impeller outflow should minimize the flow separation and net radial force acting on the impeller, eventually, lower blood damage can be obtained.

Though the presented two hemolysis estimation models provided different orders of magnitude for blood damage indices, they indicated the same trend. The

difference between these two blood damage indices might be explained by the fact that both estimation techniques follow different numerical approach [61]. According to Taskin et al. [61], none of the blood damage approaches have yet to validate their reliability and accuracy, but they could be used for calculating the relative hemolysis, comparing different pumps or optimization studies. It should also be noted that the scope of this thesis does not include questioning the accuracy and reliability of hemolysis estimation methods.

The presented study reveals encouraging outputs, but there are also some limitations. The MRF method which uses an approximation accounts only the steady state effects. In fact, as the impeller blades pass near the volute tongue region, flow field alters due to the non-axisymmetry of the centrifugal pump volute. Dynamic effects were able to be investigated only by hydraulic experiments. Furthermore, limitations exist in the experimental study as well. Tolerances of the rapid prototyped parts were around 100μ and removal of the remaining support material was done by hand polishing. These factors may influence the tolerances of pump geometry. Nevertheless, hydraulic performance of the physical prototypes was in a good agreement with the CFD analysis.

4.7 Summary: Resulting Design from Optimization

In this chapter, the optimized geometry was achieved based on numerical and experimental investigations. Comparison of the geometries revealed that the design parameters such as wrap angle of blade, splitter blade, volute tongue position, have

a significant influence on both hydraulic and hemolysis performances of the blood pump. Presented hemolysis estimation models have enabled us to investigate the hemolysis characteristic of centrifugal pump geometries in the design process. The reported effects of the design parameters can serve as a guideline for the pump optimization and can be adjusted based on the design requirements such as hemolysis, hydraulic efficiency, net radial force, etc.

The finalized geometry consists of an impeller with the wrap angle of 120° , five main blades, five splitter blades and a volute which has a tongue position of 20° , as presented in Figure 42.

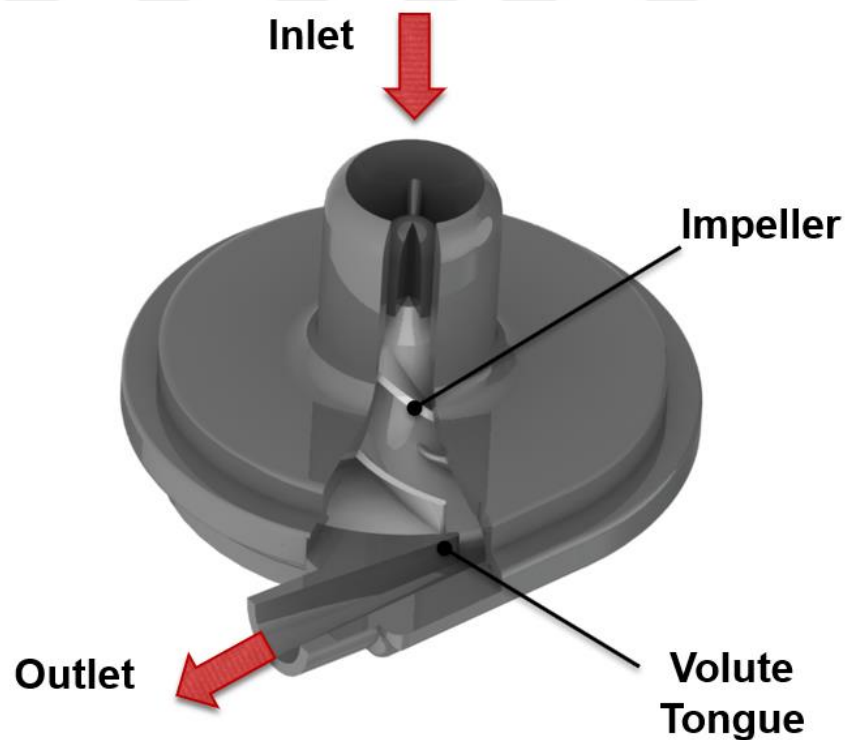


Figure 42 - Final Prototype of Istanbul Heart VAD (iHeart VAD).

Chapter 5

EXPERIMENTAL EVALUATION

The final prototype of Istanbul Heart VAD (iHeart VAD) was achieved based on the optimization study explained in the previous chapter. This chapter describes the in vitro blood test procedure which has been carried out in order to validate the blood damage potential of Istanbul Heart VAD. The pump prototype was manufactured with hemocompatible material, and the hemolytic performance was evaluated in the hemolysis test loop based on the ASTM International Standard F1841 –97 [46].

5.1 Introduction

Medical devices such as blood pumps are intended to be developed for implantation inside the human body. Hence, the evaluation of these devices must be performed in a controlled laboratory environment before tests on the living organism. Even if the blood damage potential is calculated accurately, in vitro tests must be conducted in the final stage of the development of blood pumps [68]. The main concern of in vitro hemolysis tests is to examine the biocompatibility of blood pumps.

5.2 Experimental Method

This section presents the general details of the experimental setup with the description of the procedure and sensors. The manufacturing of prototype, preparation of test setup, testing procedure and evaluation of the results are explained in detail.

5.2.1 Manufacturing Process

Ti-6Al-4V material is considered as one of the most common used titanium alloy in biomedical applications. It features good hemocompatibility, machinability and structural properties. For machining operations, Computer Aided Manufacturing (CAM) modules were implemented (NX 10.0, Siemens Product Lifecycle Management Software Inc., Plano, TX Siemens NX). In this module, tool geometry, blank workpiece, machining toolpaths and regarding G-Codes were generated. These G-codes are the computer languages which are used to guide CNC machines for performing machining operation. A sample of G-code and toolpath is demonstrated in Figure 43.

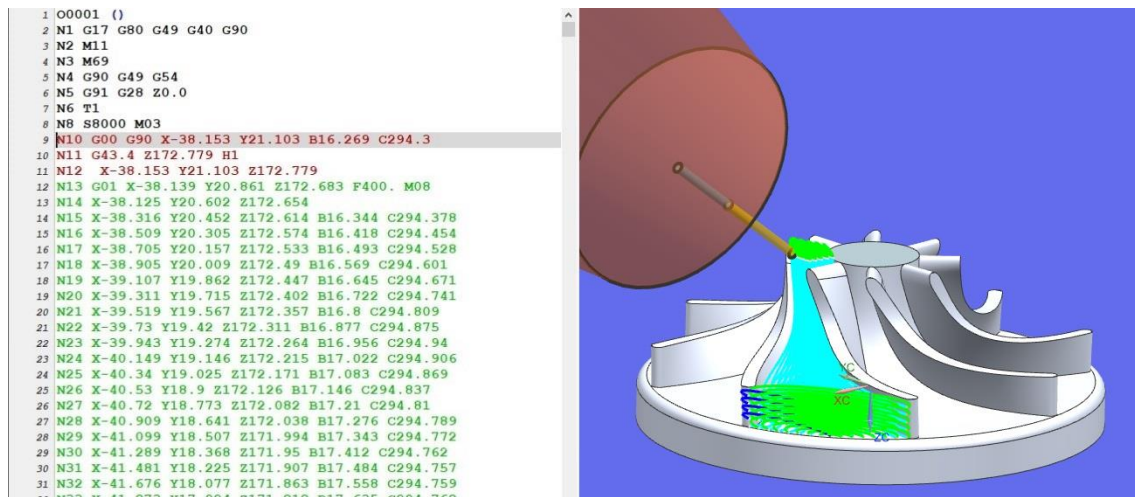


Figure 43 - Sample G-code portion and toolpath representation.

The machining of a geometry mostly includes roughing, semi-finishing and finishing operations. The highest volume of material is usually removed in the roughing operation as a first step. Large machining tools are used in this type of operations. In next stage, semi-finishing and finishing operations are performed to reach final surface. These operations are presented in Figure 44.

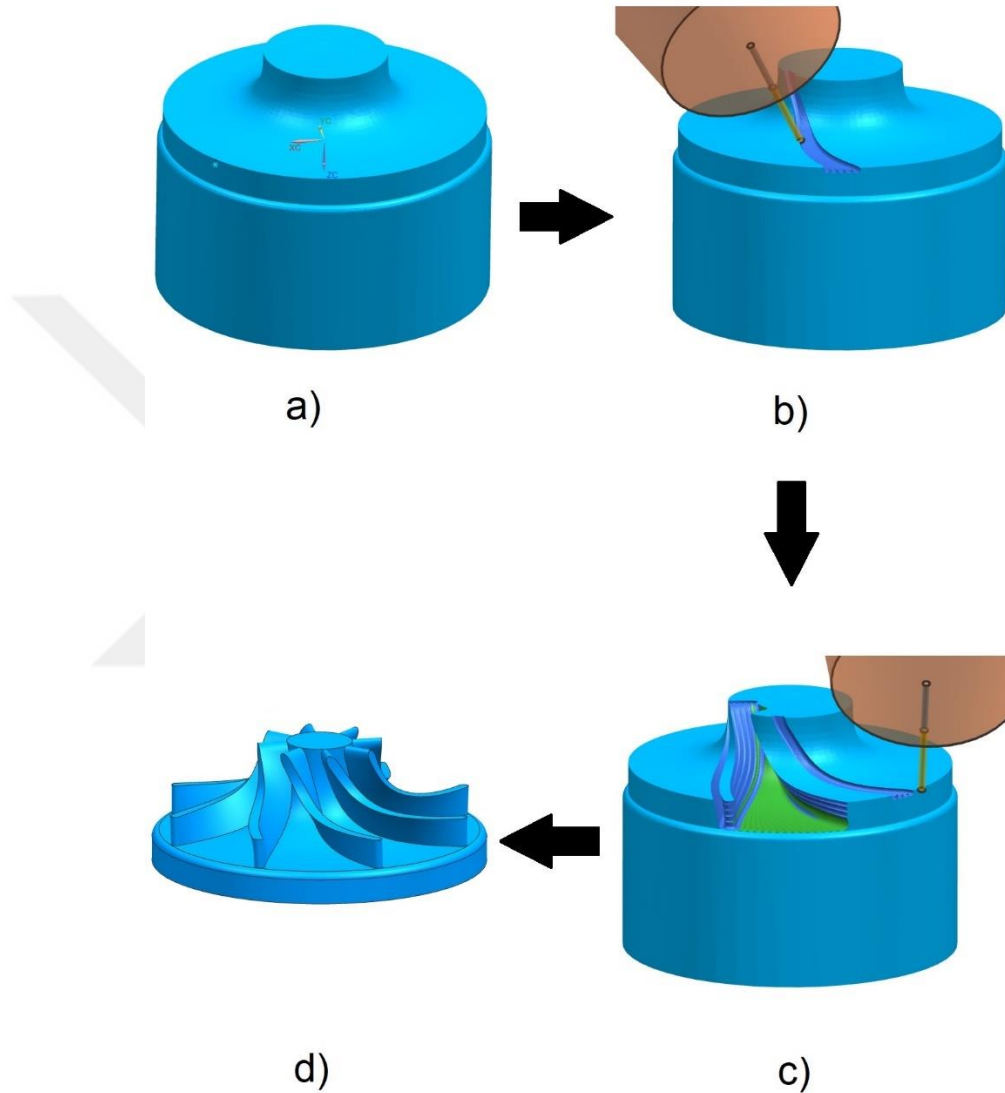


Figure 44 - Impeller machining operations: (A) workpiece, (B) roughing, (C) semi-finishing, (D) final shape of the geometry after finishing operation.

Although the Ti-6Al-4V alloy offers high strength with low density, the machining process is very challenging. In general, the manufacturing process of the

pump components from Ti-6Al-4V alloy takes approximately 200 hours. All operations were conducted on a five-axis vertical milling center (NMV 5000, DMG Mori Seiki Co., Nakamura-ku, Nagoya, Japan) which is shown in Figure 45.



Figure 45 - MORI SEIKI NMV 5000 DCG five-axis vertical milling center.



Figure 46 - Impeller machining during the semi-finishing operation.

As explained in Chapter 3, the surface roughness value (R_a) of blood contacting faces should be maximum $0.2\ \mu\text{m}$ to prevent the breakdown of the blood cells [45]. Therefore, polishing techniques were implemented to machined parts by using the special polishing equipment after machining process. Abrasive sandpapers (400-1200 grit) were iteratively performed on the surface of machined components.

Moreover, diamond paste compound of 1 micron was applied to the surface by using the hand-type rotary head tool.

5.2.2 Hydraulic Test Setup

In order to hydraulically evaluate the final prototype of Istanbul Heart VAD (iHeart VAD), a flow loop was employed. The constructed hydraulic test loop contains a pump prototype, flow meter, pressure transducers, controller box, LabVIEW DAQ card (National Instruments, Austin, TX, USA), a total of 2m flexible tubing (3/8 inch ID) and a reservoir (Figure 47). A blood analogue fluid (67% water, 33% glycerol) was utilized at 25°C. A valve was implemented for adjusting the resistance and thus changing the flow rate. The flow rate was observed via an ultrasonic flow meter (FD-Q 10C, Keyence Corp., Osaka, Japan) which was placed on the outlet tubing. Two pressure transducers (Kistler AG, Winterthur, Switzerland) were placed through the inlet and the outlet tubing. The performance measurements were recorded at a sampling rate of 1000 Hz. The pressure-flow rate characteristic was recorded at the range of 1000-3200 rpm motor speed.

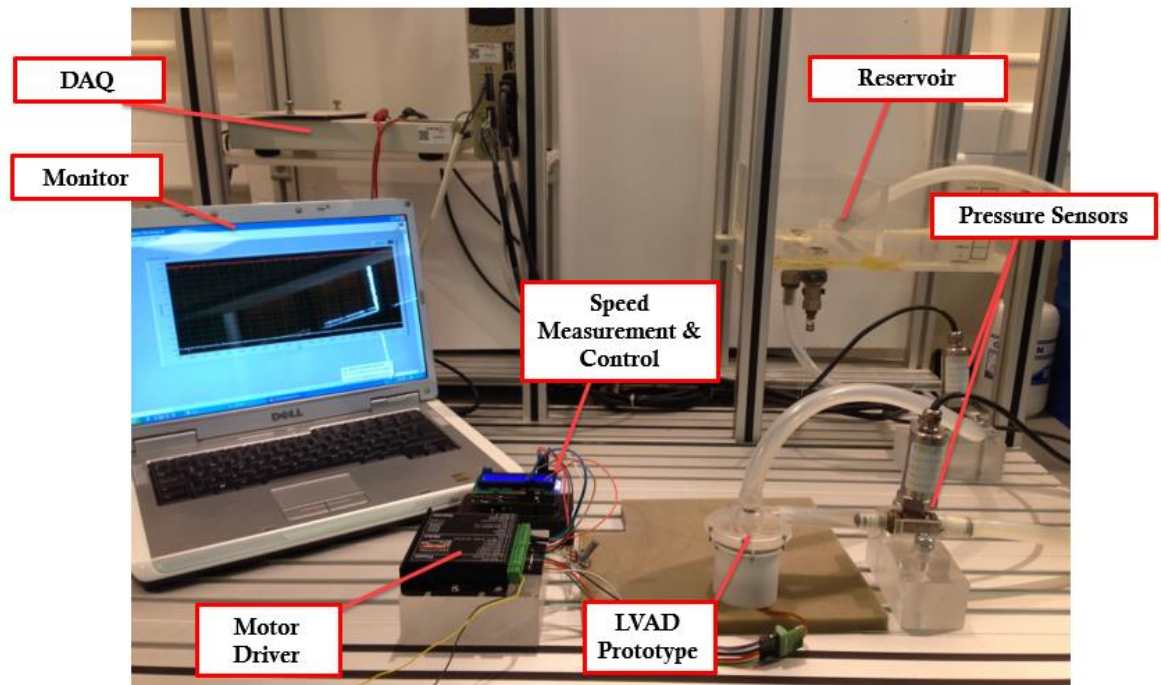


Figure 47 - Hydraulic flow loop.

5.2.3 In-Vitro Hemolysis Test Setup

Test loop (Figure 48) was created according to ASTM F1841-97 standards. This standard contains detailed information about selection, collecting and storing procedures of blood before in vitro experiments [46].

Blood samples (90 ml) were obtained from a healthy volunteer, aged 27 years, anticoagulated with sodium heparin. The blood count was achieved by an electronic hematology analyzer (ABX Micros OT, ABX Diagnostics, Montpellier, France). Red blood cells (RBC) were isolated by centrifugation (1400xg, 5 min). Re-suspension of the packed cells was performed at a hematocrit 26% in PBS solution. Hematocrit (Ht)

is the percentage of the volume of RBCs in the total blood volume. The microhematocrit method ($10,000\times g$, 4 min) was applied to determine RBC suspension hematocrits.

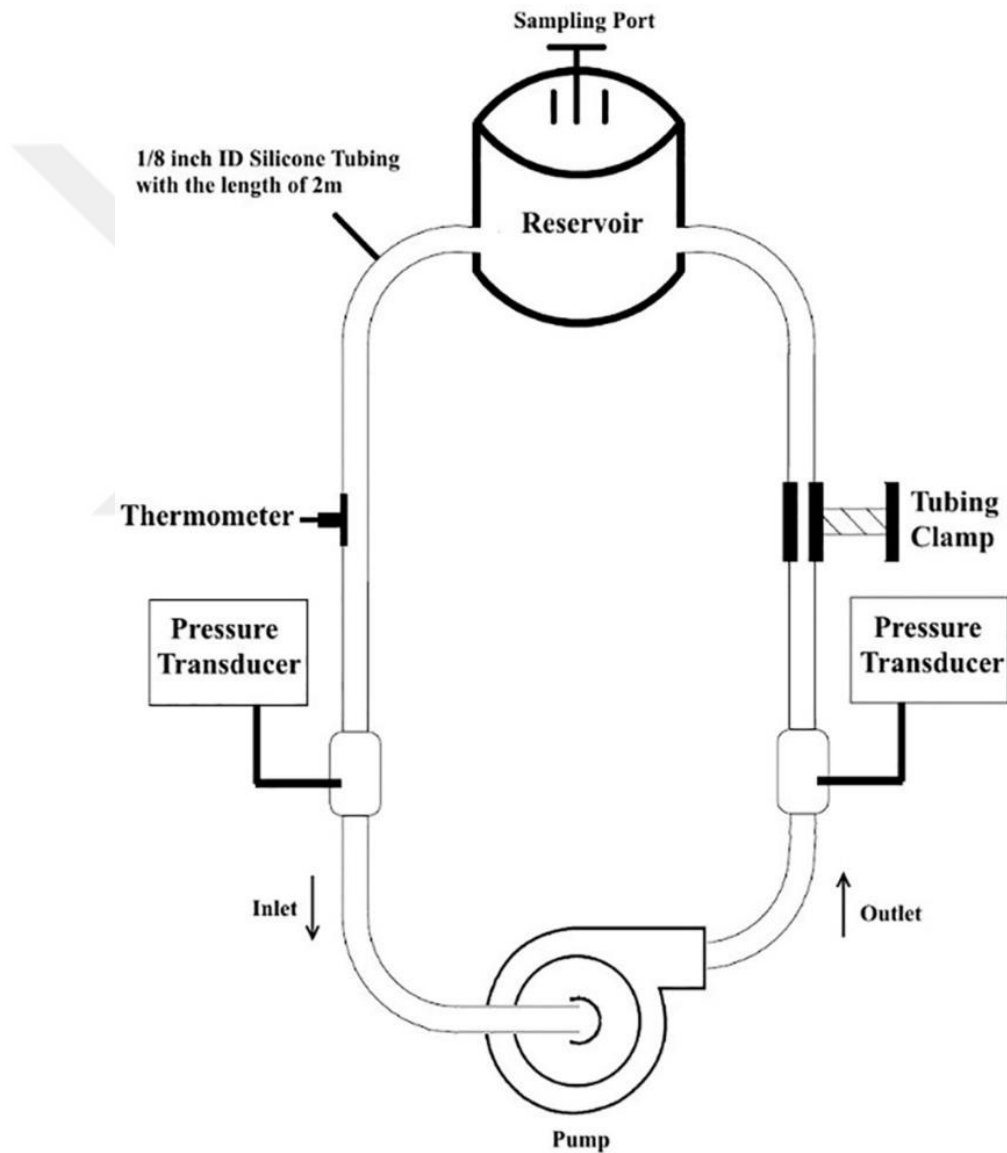


Figure 48 - Test loop for in vitro hemolysis tests.

The circuit was filled with 90 ml blood (26% Ht), and any air was removed from the circuit before the data acquisition. 1 mL blood samples were taken from the reservoir at specific time intervals. Instant hematocrit rates were calculated for each test at the discrete sampling intervals.

Normalized Index of Hemolysis (NIH) is the most applicable index for assessing the hemolysis level of blood pumps. According to ASTM F1841 –97, this evaluation can be calculated by following formulas:

$$NIH \text{ g / 100l} = \Delta freeHgb \times V \times \frac{100 - Hct}{100} \times \frac{100}{Q \times T} \quad (19)$$

Where V is the circuit volume [L], Q corresponds to flow rate [L/min], T corresponds to sampling time interval [min], Hct corresponds to hematocrit percentage [%], Hgb corresponds to the total hemoglobin concentration before the test [mg/L], $\Delta freeHgb$ corresponds to increase in the plasma free hemoglobin concentration over the sampling time interval [g/L]. The calculated NIH values reported at every sampling intervals.

5.3 Results

5.3.1 Hydraulic Performance

The manufactured pump is tested under various conditions considering physiological limits. The pressure and flow data at the different motor speeds were recorded to characterize the hydraulic performance. The performance data is plotted in Figure 49.

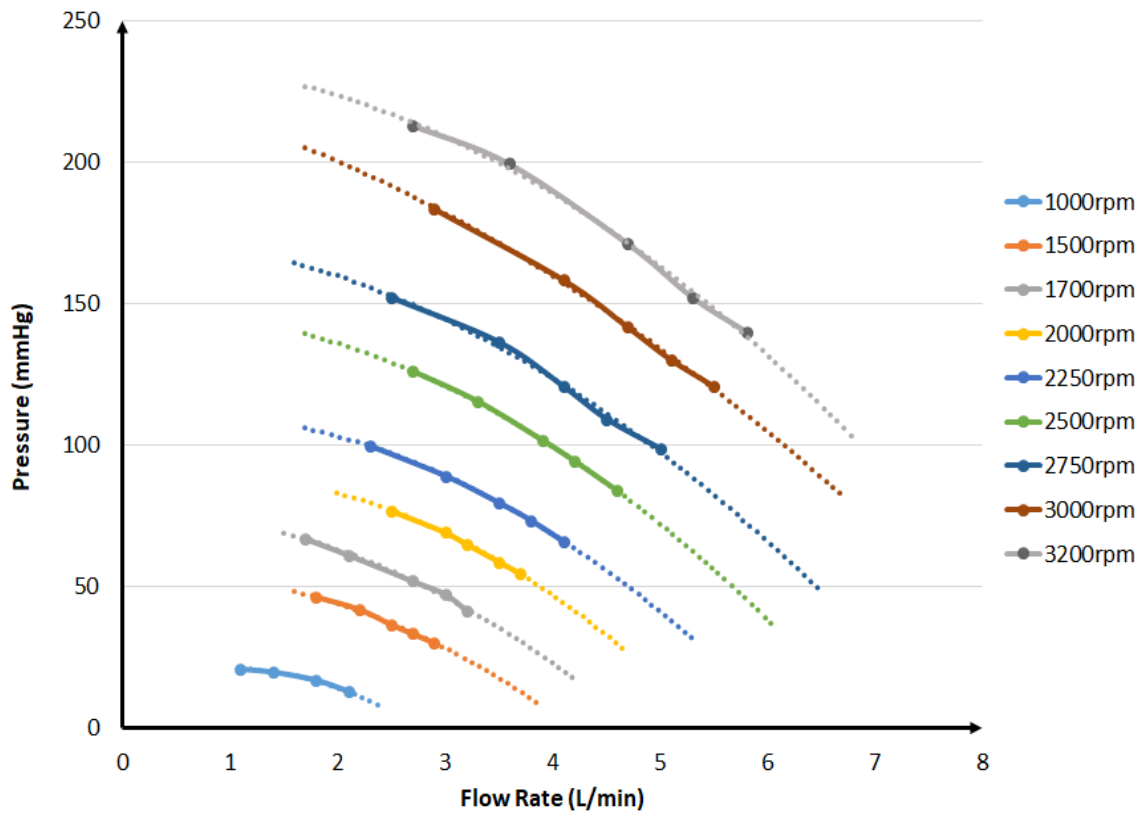


Figure 49 - Performance Characteristic of Istanbul Heart VAD (iHeart VAD).

The rise in pressure head was observed with the increasing impeller speed as expected. Furthermore, the mass flow rate evidently affected the pressure head at any constant speed. Maximum pressure head of 218.9 mmHg was measured at 3200 rpm. The ideal operating point was logged at 2750 rpm where the pump delivers 5 L/min at 100 mmHg.

5.3.2 Hemolysis Performance

The measured plasma free hemoglobin levels (pHb) during the blood test are shown in Figure 50. The horizontal axis represents the testing period, and the vertical axis shows the change in hemoglobin content in mg/dL. All measurements were normalized with respect to the initial sample. The trend of data was close to linear fit.

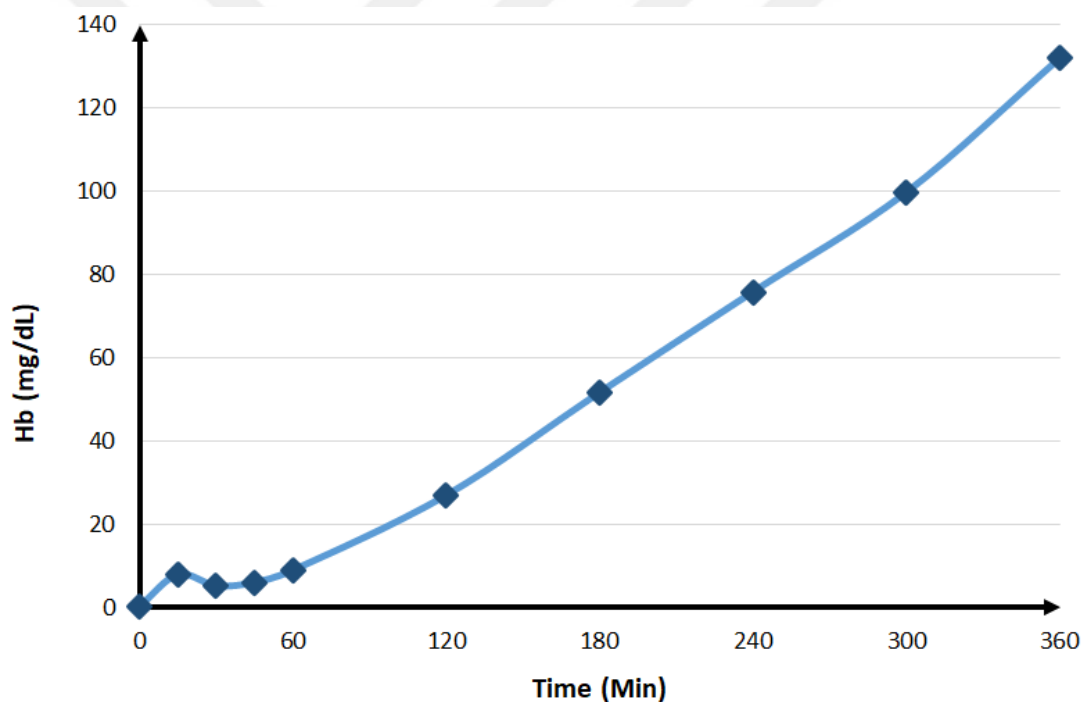


Figure 50 - Plasma free hemoglobin level during the experiment. Data were normalized with respect to initial blood volume.

The rates of hemolysis also summarized as calculated NIH values in Figure 51. NIH values were calculated for a total of 360 minutes by taking pHb measurements

at 15 minutes intervals in the first hour and then every hour. Any change in the hematocrit rate was not observed during the blood test, and NIH values ranged between 0.00053 and 0.00159 g/100L. The mean of NIH during the in vitro blood test was 0.00098 g/100L.

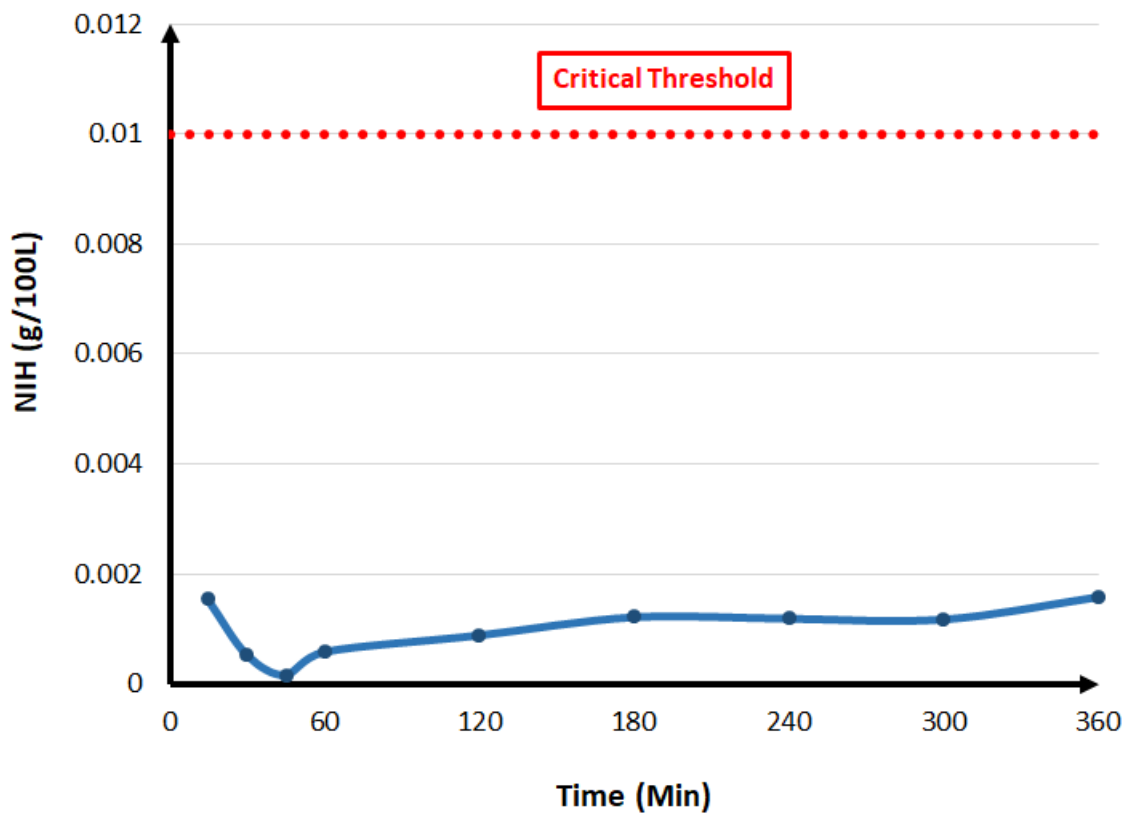


Figure 51 - NIH Results during the in vitro blood test.

No sign of malfunction or distortion was observed within the device during and after the experiment. Furthermore, any sign of thrombosis was not observed. Collected blood samples were also illustrated in Figure 52. It was evident that the

hemoglobin was released into the blood plasma during the testing. The released hemoglobin caused the transparent serum to appear red in color.



Figure 52 - Hemolysis of blood samples.

5.4 Discussion

In-vitro hemolysis test is dependent on numerous reasons such as blood type, blood storage, temperature, test loop, etc. In this hemolytic performance analysis, 100 mmHg of pressure head was selected based on the ASTM F1841–97. However, the amount of blood (90 mL) used in this experiment was less than the suggested blood volume (450 ± 45 mL) according to ASTM F1841–97. The reason for this limitation can be explained by the fact that current laboratory equipment and the approved ethical protocol restricts our usage of blood volume in the blood tests.

However, as the nature of fluid dynamics, experimenting with a smaller volume of blood can be considered as a challenging environment as compared to larger volume. Because the hemolysis is calculated based the blood which is continuously circulated in the pump over a 6-hour period. Nevertheless, new in vitro tests must also be performed with a larger volume of blood (450 ± 45 mL) to exactly follow the ASTM F1841–97 standards.

Another limitation of the in vitro test is that the hemolysis results may only be applicable to the specific blood properties. If we use another type of blood such as porcine, bovine blood or aged more than 24 hours, we could not accurately reproduce same hemolysis levels.

Tough CFD model and in vitro hemolysis test results of final prototype provided different orders of magnitude for the blood damage index; they indicated the same trend corresponding to the variation of wrap angle and the variation in damage indices was consistent with other studies in the literature [61,64]. According to Taskin et al., the hemolysis estimation approaches have yet to validate their reliability and accuracy, but they could be used for calculating the relative hemolysis for design changes and optimization studies [61].

5.5 Summary

In summary, the final prototype was manufactured with biocompatible material of Ti-6Al-4V by using a high precision 5-axis CNC machining center at Manufacturing and Automation Research Center (MARC), Koc University. Later, in vitro blood test evaluation has been performed and described in this chapter. The pump demonstrated promising performance regarding hydraulic output, biocompatibility, and durability. Overall, the prototype of Istanbul Heart VAD (iHeart VAD) indicated satisfactory results by producing a NIH level of 0.00098 g/100L which is almost one tenth of the critical threshold value (0.001 g/100L). The results of this experiment may be utilized to improve the predictive computational blood damage models.

Chapter 6

PRELIMINARY ACUTE IN-VIVO EVALUATION

Istanbul Heart VAD (iHeart VAD) is designed to satisfy physiological requirements of the human heart, both computational and in vitro evaluation have been described in previous chapters. This chapter demonstrates the initial in vivo evaluation of the device in a large animal model, porcine model. As the animal experimentation has played a fundamental role in biomedical research, this section aims to evaluate the performance, hemocompatibility, anatomical fitting and end-organ effects of our ventricular assist device on the porcine model.

6.1 Introduction

In vivo test means the test performed within living organisms which includes an animal. The use of animals in biomedical applications has great importance for evaluating the biocompatibility of medical devices. It is considered as the last development stage before clinical trials on humans. In vivo evaluation can be divided into two sections such as acute trials for short-term and chronic trials for long-term. Acute trials must be performed initially to assess the anatomic fit and short-term biocompatibility. Chronic tests can be performed as the next stage of acute trials. Overall, Istanbul Heart VAD (iHeart VAD) system consists 171x121x55mm of size controller, a pump driver, two lithium ion batteries providing 17 hours continuous operation.

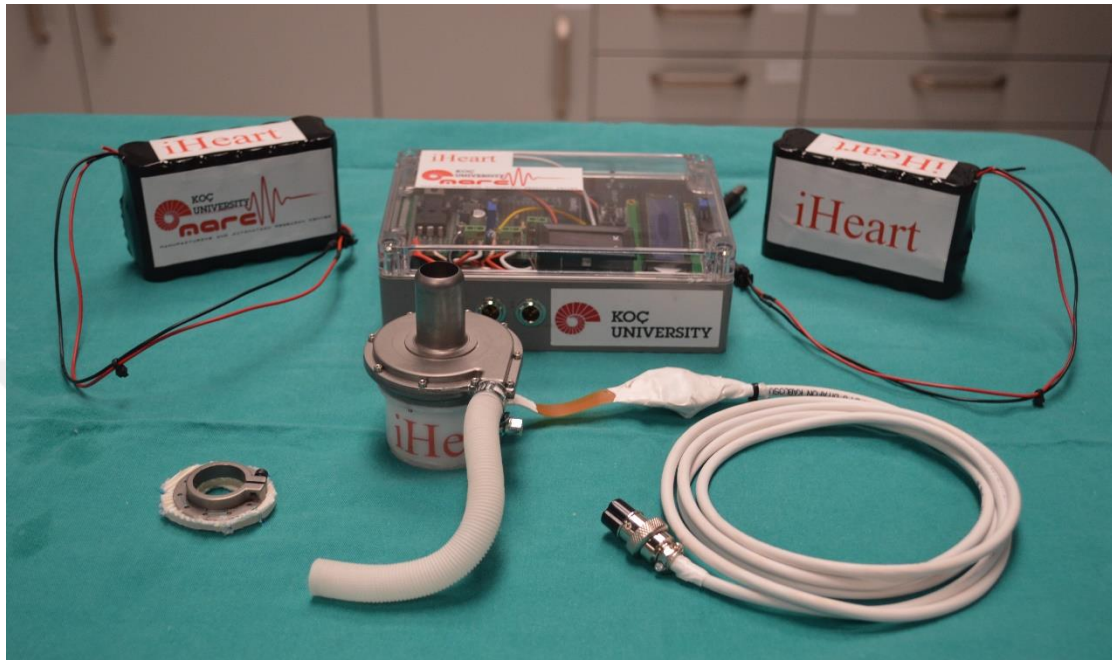


Figure 53 - Istanbul Heart VAD (iHeart VAD) system.

The objectives of this in vivo study were to develop an animal model for the implantation using a pig and to establish a standard surgical procedure. This chapter presents our initial experience with an acute in vivo test which was conducted in collaboration with CASE Laboratory (Center of Advanced Simulation and Education), Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey. The surgical implantation was performed by Prof. Dr. Deniz Suha Kucukaksu and his surgical team.

6.2 Method

6.2.1 Animal Model

Three acute (one 3-hour, one 4-hour, and one 5-hour) animal studies were conducted in the porcine model to evaluate in vivo hemodynamics and hemocompatibility. All animals were received humane care based on the “Guide for Care and Use of Laboratory Animals” [69]. The study protocol was approved by the Ethics Committee of the Acibadem Mehmet Ali Aydinlar University.

Three pigs weighing 77–92 kg, were used for this in vivo study. The animals were sourced from a private farm affiliated with Acibadem Mehmet Ali Aydinlar University. Pigs were then brought to the experiment facility two days prior to the surgery.

6.2.2 Surgical Procedure

Three healthy pigs, with an average weight of 84 ± 7.6 kg, were used for the fitting study. The pig was anesthetized and intubated, and ventilation was provided during surgery. Heparin (4 mg/kg) was given intravenously to avoid blood clotting. The ventilation and gas content were maintained at the normal pH and carbon dioxide (pCO₂) level in the venous blood. The pump was filled with saline and run for 5 minutes for the final check. After heparin was supplied, an outflow graft (PTFE) was anastomosed to the descending aorta (Figure 54).

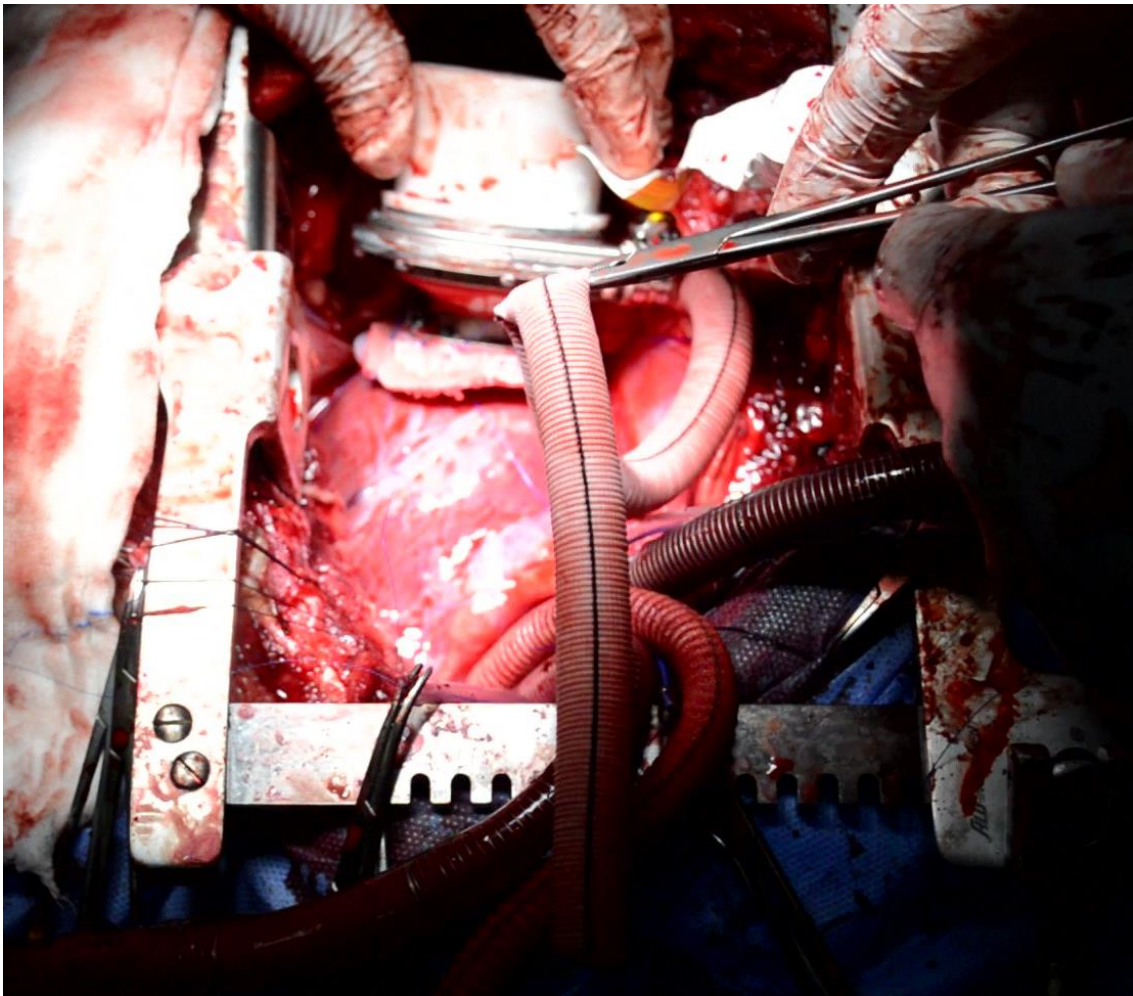


Figure 54 - The process of outflow graft anastomosis.

The apex of the left ventricle was cored with a circular knife as shown in Figure 55. Sewing-ring apparatus placed radially on the myocardium to secure the inserting position of inflow cannula (Figure 56).

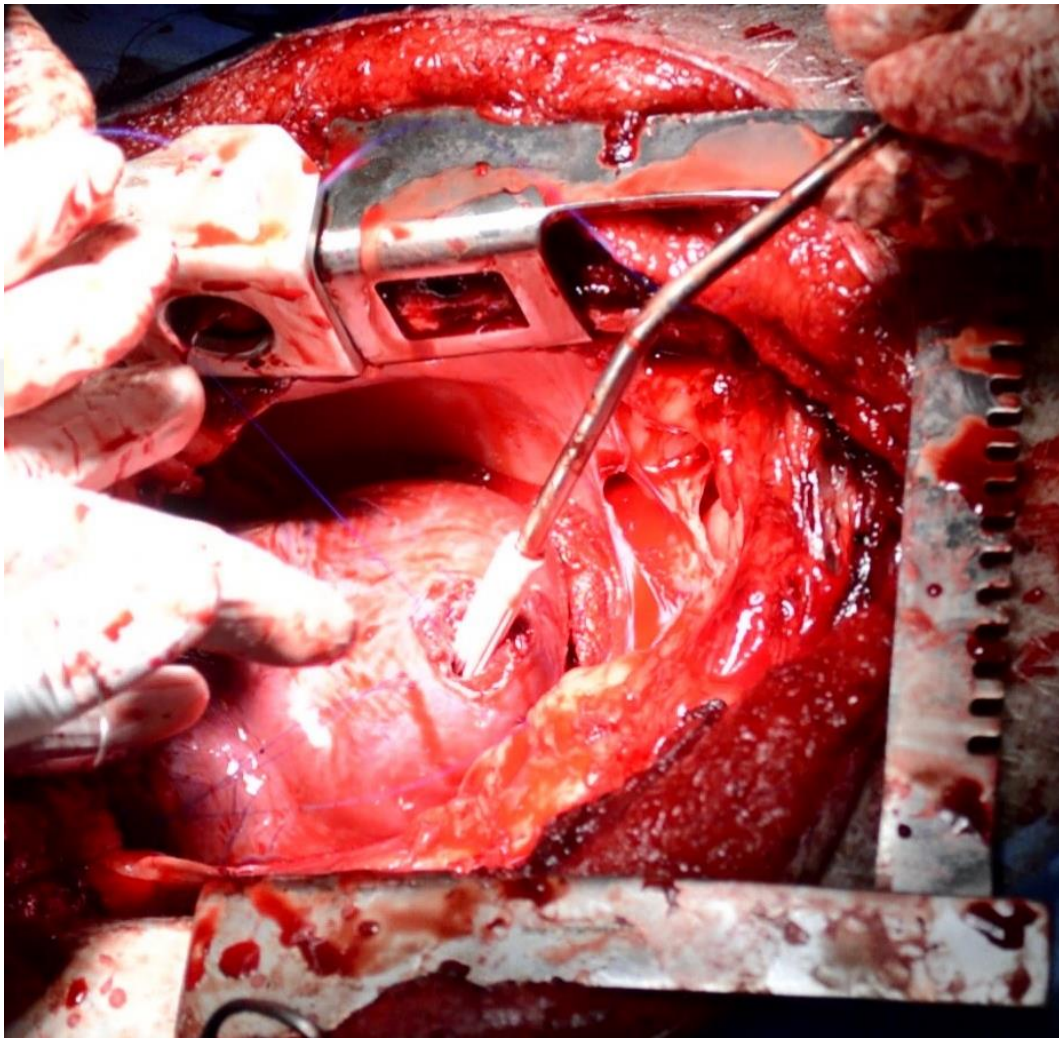


Figure 55 - The process of the removing the LV core.

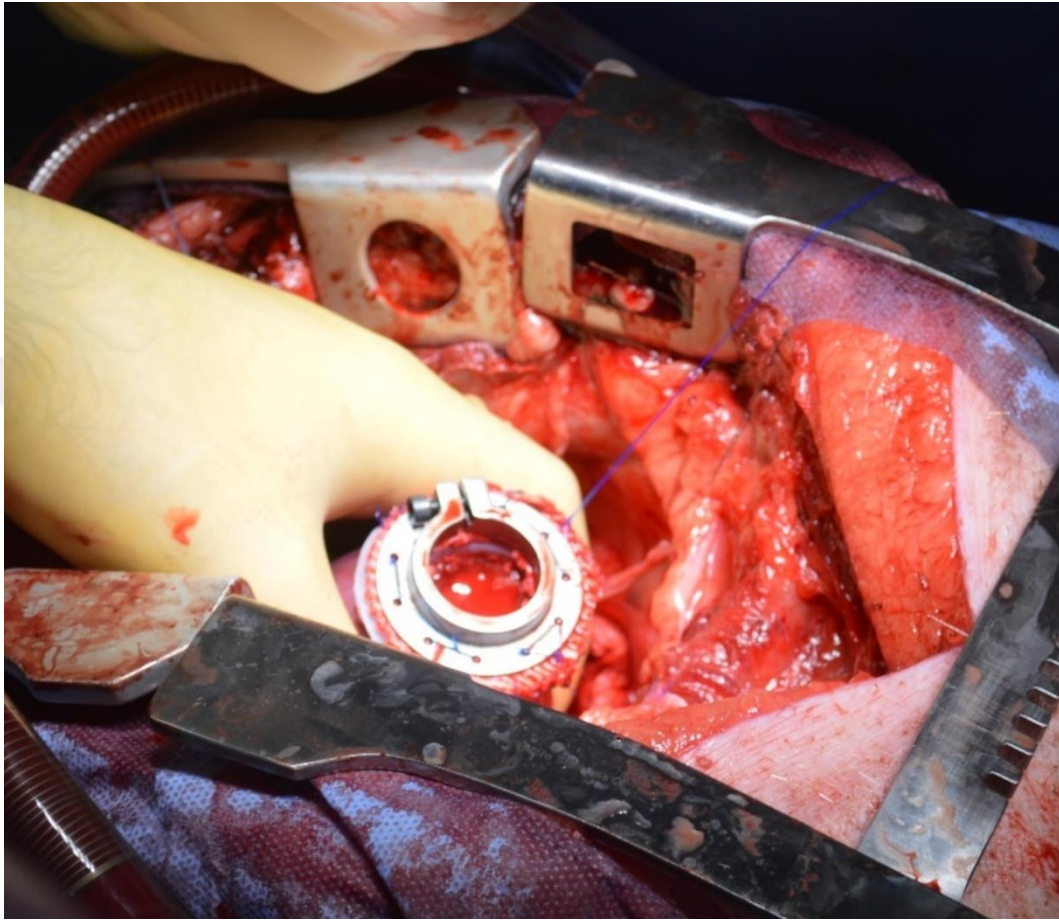


Figure 56 - The process of suturing the sewing ring.

The inlet port of the pump was then inserted into the cavity of the left ventricle, and the position was stabilized by the help of sewing-ring. Figure 57 demonstrates the pump implantation during the second in vivo experiment.

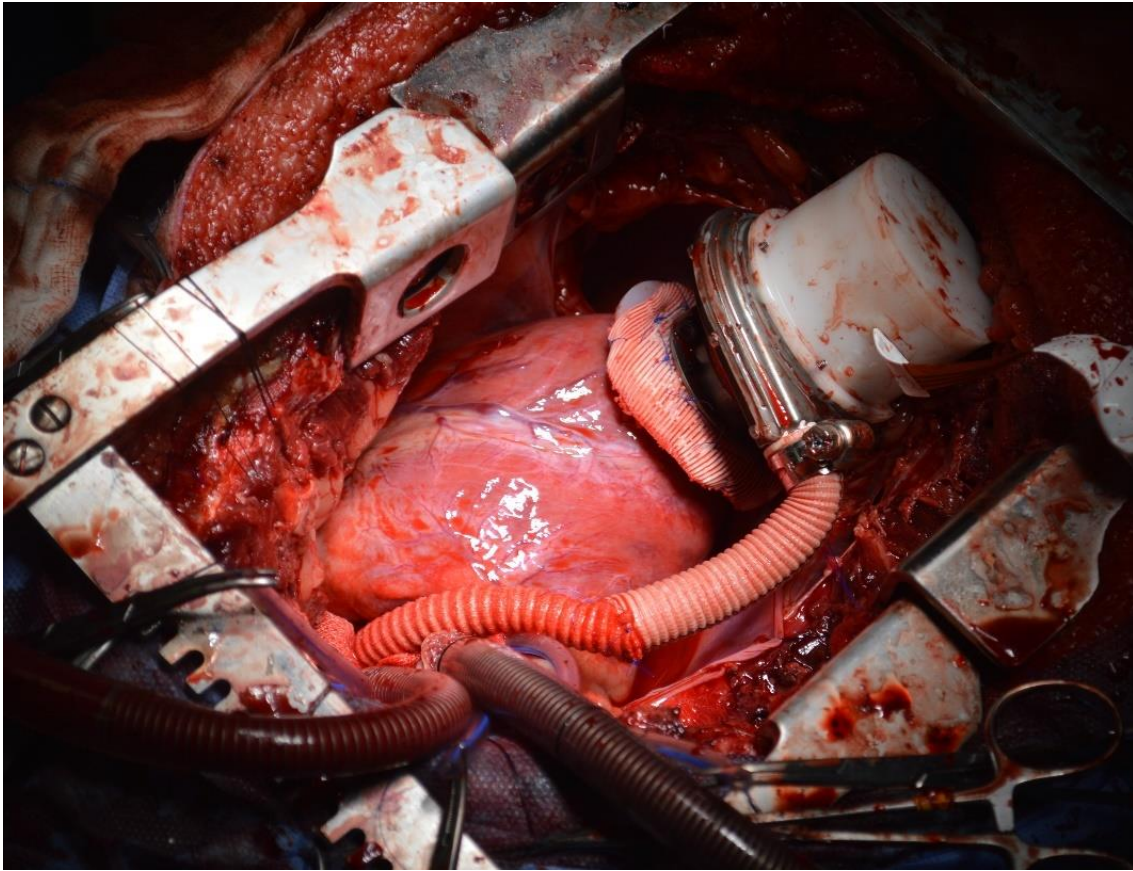


Figure 57 - Implantation of the pump in the second in vivo experiment.

The air inside of the pump was removed by a small-diameter needle injected into the outflow graft. The chest of the pig left open, and the driveline of the pump was then exteriorized near to the surgery table where the controller box and batteries were placed. A flow probe was positioned at the outflow graft to measure the flow rate. The pump was started at low rotation speeds around 1250 rpm and then gradually increased to 2000 rpm. The pump was targeted to provide a blood flow of 3 L/min to achieve maximum heart unloading. Blood volume of the body was

stabilized by providing continuous isotonic saline supply. Blood samples were collected from the outlet graft at the intervals of 30 minutes to analyze the blood gas analysis (pO₂, O₂ saturation, pCO₂, etc.) and measure the hematocrit, hemoglobin level. The status of heart was monitored with an electrocardiogram using the surface probe as shown in Figure 58. The GE Vivid T8 ultrasound system (General Electric Healthcare, Wauwatosa, WI, USA) was used to capture the dynamic data of moving the heart and assess the left ventricular ejection fraction using the probe.

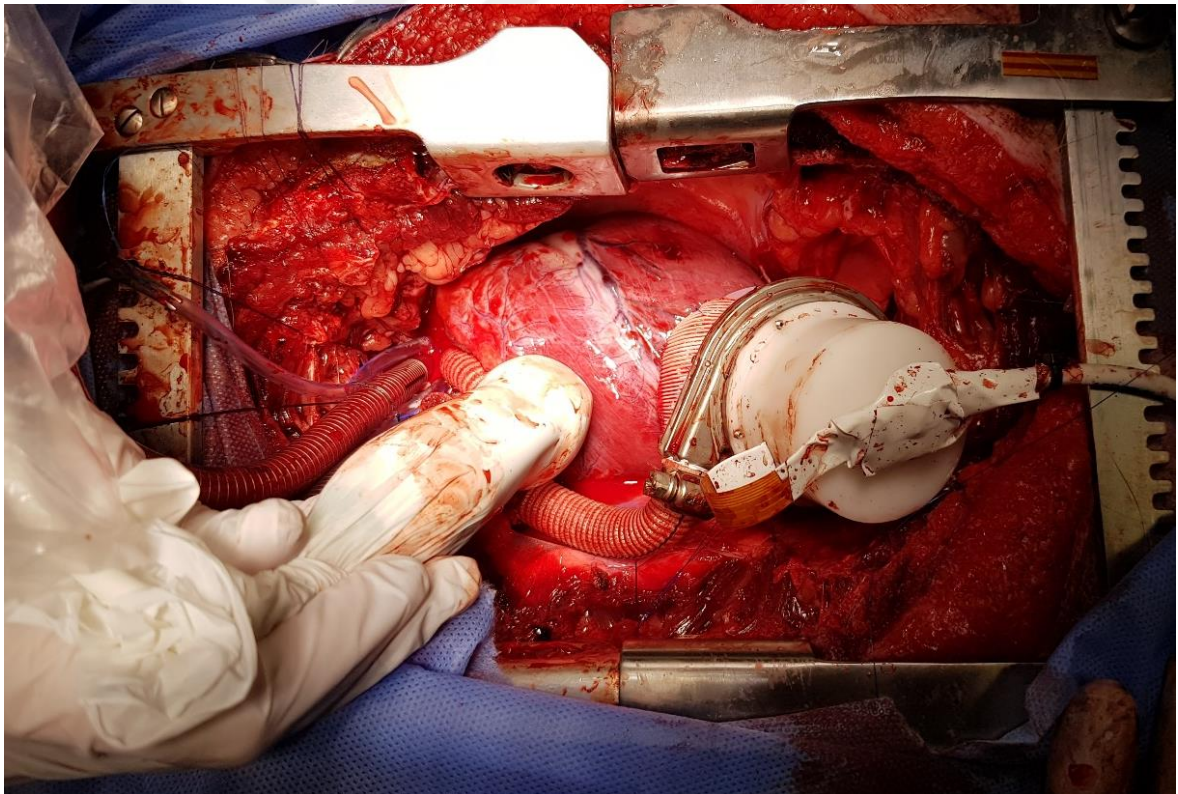


Figure 58 - Electrocardiogram using a surface probe.

6.3 Results

No device-related problems occurred during the experiments. For three animals, the test duration was ranged 3-5 hours. Flow averaged 2.5 ± 0.4 L/min at a power consumption of 8.4 ± 3.1 watts. The speed of impeller was varied between 1250 rpm and 3000 rpm. The physiological indices, including heart rate, respiratory rate, and body temperature were in the normal ranges during the operation.

Table 10 - Hematologic data before the surgery and post surgery.

	Presurgery	30 min	60 min	120 min	180 min	240 min	300 min
WBC (10^6 / μ L)	12.21 ± 6.74	5.37 ± 3.42	4.13 ± 2.42	2.53 ± 0.38	2.56 ± 0.18	2.43	2.41
RBC (10^6 / μ L)	5.44 ± 1.15	5.69 ± 1.28	5.82 ± 2.18	4.97 ± 1.16	4.38 ± 1.36	5.34	4.02
HGB (g/dL)	11.17 ± 2.78	11.7 ± 2.26	11.67 ± 4.03	9.93 ± 2.02	8.65 ± 2.47	10.4	7.9
HCT (%)	32.07 ± 4.8	37.5 ± 6.36	38.07 ± 12.92	33.3 ± 5.93	28.05 ± 8.13	33.8	26.4
MCV (fL)	64.23 ± 1.46	66.35 ± 3.75	65.93 ± 3.48	67.7 ± 4.81	64.35 ± 1.48	63.3	65.7
MCH (pg)	20.07 ± 0.83	20.65 ± 0.64	20.17 ± 0.91	20.07 ± 0.76	19.85 ± 0.49	19.5	19.7
MCHC (g/dL)	31.2 ± 0.61	31.15 ± 0.78	30.6 ± 0.26	29.73 ± 0.96	30.85 ± 0.07	30.8	29.9
PLT (10^3 / μ L)	101.67 ± 64.76	56.5 ± 9.19	42.33 ± 4.51	36 ± 3.61	21.5 ± 3.54	19	21
RDW-SD (fL)	38.07 ± 2.68	40.65 ± 0.07	40.33 ± 2.72	40.3 ± 2.4	37.75 ± 1.06	37	37.8
RDW-CV (%)	17.13 ± 1.37	17.8 ± 1.84	17.9 ± 2.52	16.63 ± 0.49	16.5 ± 0.28	16.3	16.1

where the parameters stand for; WBC: White Blood Cell (10^6 / μ L), RBC: Red Blood Cell (10^6 / μ L), HGB: Hemoglobin (g/dL), HCT: Hematocrit (%), MCV: Mean

Corpuscular Volume (fL), MCH: Mean Corpuscular Hemoglobin (pg), MCHC: Mean Corpuscular Hemoglobin Concentration (g/dL), PLT: Platelet Count ($10^3/\mu\text{L}$), RDW-SD : Red Cell Distribution Width Standard Dev. (fL), RDW-CV: Red Cell Distribution Width – Complete Volume (%).

The pig was sacrificed at the end of each experiment, and the examination of end-organs was performed. Table 10 illustrates the hematological data during the acute in vivo animal experiments. Biochemical values of before and after the operation are also summarized in Table 11.

Table 11 - Biochemical data before the surgery and post surgery.

	Presurgery	30 min	60 min	120 min	180 min	240 min	300 min
AST (U/L)	25.5 ± 26.2	216 ± 52.9	318 ± 41.6	278 ± 19.7	206	1338	-
ALKP (U/L)	29 ± 18.5	41 ± 10.2	50 ± 21.2	40 ± 18.2	74.5 ± 55.9	114	29
ALT (U/L)	26.7 ± 6	30 ± 1.7	37.7 ± 15.1	23 ± 14.7	17.5 ± 10.6	10	10
BUN (mg/dL)	6.7 ± 2.5	5 ± 2.5	7.3 ± 3.2	8.3 ± 5.1	18.5 ± 21.9	34	17
CREA (mg/dL)	1 ± 0.2	0.8 ± 0.2	1 ± 0.2	2.6 ± 2.8	6.1 ± 7.8	11.6	5.9
GGT (U/L)	40.7 ± 32.1	29 ± 8.3	28 ± 8.9	19 ± 16.6	16 ± 17	4	0
TBIL (mg/dL)	0.3 ± 0.3	0.6 ± 0.2	0.7 ± 0.3	1 ± 0.9	1.3 ± 0.8	1.9	0.1

where AST is aspartate aminotransferase, ALKP is alkaline phosphatase level, ALT is alanine aminotransferase, BUN is blood urea nitrogen, CREA is creatinine level,

LDH is lactate dehydrogenase, GGT is gamma-glutamyl transferase, and TBIL is total bilirubin level.

The decreases in the amount of red blood cells and the level of hematocrit were observed in all porcine models as expected. The hematocrit level was measured below the normal range, and the plasma free hemoglobin (pHb) levels indicated variations with respect to the experiment time (Figure 59).

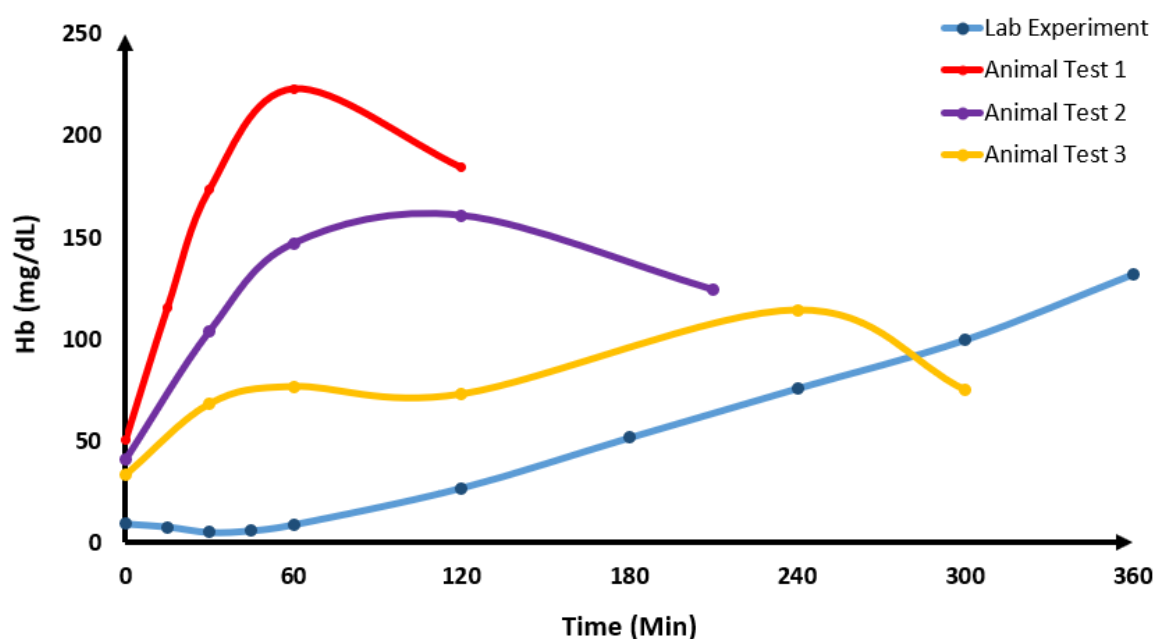


Figure 59 - Plasma free hemoglobin level of in vitro and in vivo experiments.

After the termination of each test, the pump was taken out and photographed to investigate the anatomical fit of inflow cannula in LV core (Figure 60). Blood flow channel was also demonstrated in Figure 61.

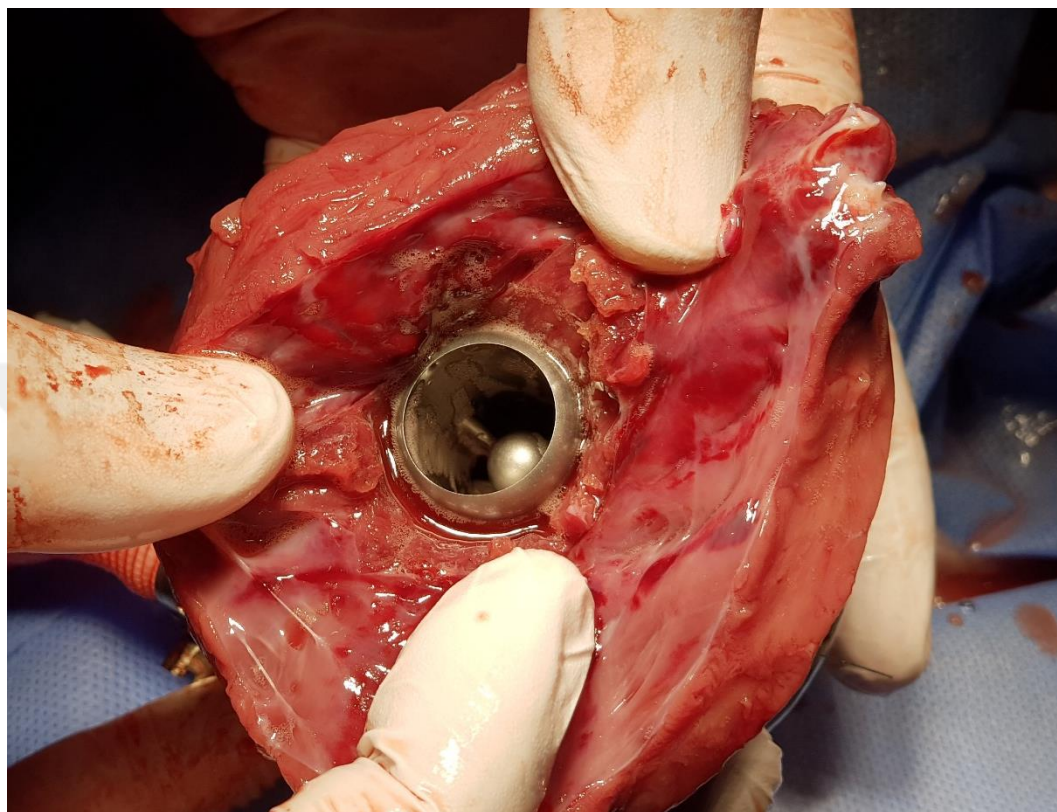


Figure 60 - Examination of inflow cannula position.

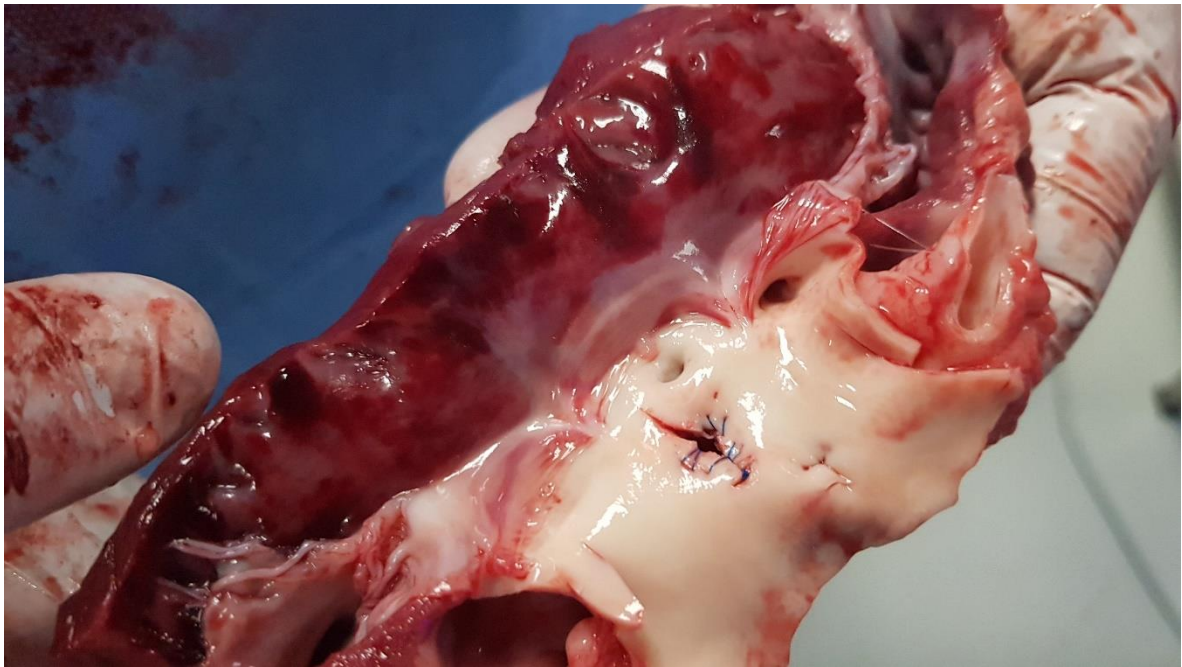


Figure 61 - The blood flow channel.

The inflow cannula was found to be well-located into the apex of the heart. Moreover, the examination of the disassembled device indicated no sign of thrombus formation on the blood contacting surface and bearings in all experiments. However, small tissue pieces were found during the examination of the second in vivo test. Disassembled pump geometry contained small tissue pieces which are evidently the residuals of LV core from the removing process. In general, there was no observation of thrombosis or residual tissue in the pump geometry and outflow graft except for the second in vivo experiment (Figure 62).



Figure 62 - The outflow graft after the first in vivo test.

6.4 Discussion

The short-term in vivo experiments of Istanbul Heart VAD (iHeart VAD) have been performed to evaluate the performance, hemocompatibility, anatomical fitting. In summary, the device demonstrated appropriate biocompatibility characteristics in the porcine model. The extent of hemolysis was considered in an acceptable range based on the results of this study.

In vivo tests were conducted in a porcine model with normal heart function. As these devices are developed for the heart failure patients, implanting a pump to the

normal functional heart can be considered as a limitation. The circulatory support should also be evaluated by developing a heart failure model.

The process of removing the LV core was found to be an important procedure considering that small tissue residuals were found inside of the device after the second experiment. The clean cutting process must be performed while opening the cavity on the left ventricle. Furthermore, the placement of the pump and tension of the outflow cannula have a significant effect on the performance of the pump. Any error in the placement of the pump would cause unnecessary workload on the heart and affects the pressure and flow rates eventually. Similarly, if any tension or bending occurs at the outflow graft, the flow could be interrupted/blocked, and the increase of the power usage can be observed.

In the selection of animals, the body weight, blood cell type or coagulation characteristic should be considered and planned before the surgery. Isotonic saline is used to maintain the blood volume of the pigs during the experiments. However, the hematocrit levels of the animals are negatively influenced by this method. In future studies, several units of blood of the animal should be obtained days before the surgery and must be stored for the usage in the surgery day to compensate the blood loss.

Overall, Istanbul Heart VAD (iHeart VAD) indicated satisfying performance. Nevertheless, the modification in size of the device should be considered in the future studies. Specifically, the motor case which is located under the pump casing

requires an optimization. A new custom motor will be designed as the next stage of development and integrated into the pump system. This would decrease the overall size of the pump and provide a more appropriate fit for the future studies.

6.5 Summary

In this chapter, the initial in vivo evaluation of Istanbul Heart VAD (iHeart VAD) was described. The objective of the chapter was to achieve a non-clinical evaluation of the final prototype regarding the biocompatibility, performance and anatomical fitting in a porcine model. The initial evaluation was achieved by performing surgeries on three pigs. Firstly, the details about the animal model and animal care were described. Later, a standard surgical procedure was established and introduced in the methods section. Overall, Istanbul Heart VAD (iHeart VAD) demonstrated promising results based on the circulatory support, anatomical fitting and blood-handling characteristics such as hemolysis/thrombus. In the discussion section, we have attempted to address the important factors which could potentially affect the results of the in vivo test and the limitations. Based on the findings of this initial in vivo evaluation, some design modifications in the motor casing of the prototype are recommended and should be considered for the further acute trials and long-term evaluation.

Chapter 7

CONCLUSION

This chapter describes the conclusion of this study by summarizing the development cycle of Istanbul Heart VAD (iHeart VAD). The encountered problems and suggestions for further improvements are also presented for future research.

7.1 Overview

The main objective of this thesis is to develop a novel LVAD which can be used for the treatment of heart failure patients. The design optimization of Istanbul Heart VAD (iHeart VAD) has been initially carried out by the performance evaluation using CFD and experimental testing. The comprehensive review of literature in this thesis provides information about the development cycle and the design consideration of LVADs. Figure 63 demonstrates the development cycle for Istanbul Heart VAD.

The impeller and volute geometry has been optimized and characterized computationally. The iterative design procedure utilized for the development of LVAD. A number of impeller/volute configurations were established. The CFD models were successfully generated to simulate the hydraulic output considering the pressure head, flow rate, velocity profile and the hydraulic efficiency. The blood damage potential was then analyzed to improve the hemocompatibility. Later, a

number of impeller/volute configurations were rapid prototyped to perform hydrodynamic experiments for the verification of computational results. This optimization process provided comparative information about the effect of impeller/volute geometry configurations on the performance of blood pump. The analysis of different impeller/volute configurations confirmed the final prototype of Istanbul Heart VAD (iHeart VAD), leading to a good hydraulic performance characteristic while minimizing the extent of hemolysis generation as described in Chapter 4.

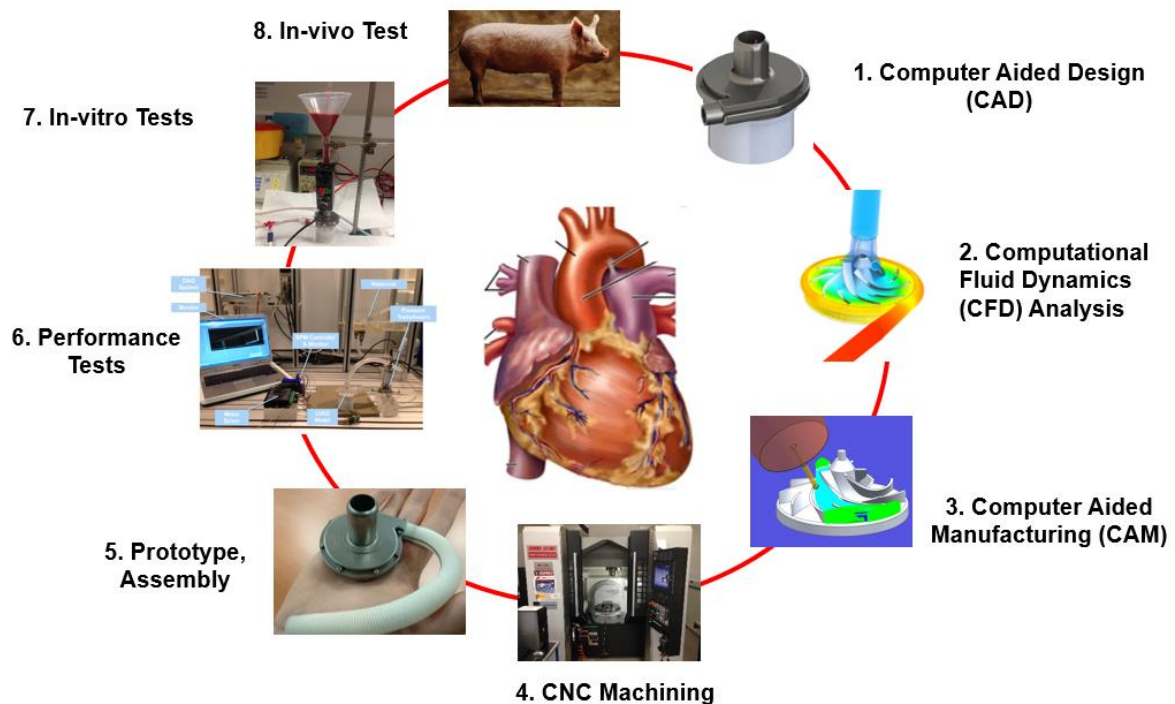


Figure 63 - Development cycle of Istanbul Heart VAD (iHeart VAD).

A hemolysis test loop has been designed and constructed in this study for the investigation of the final prototype of Istanbul Heart VAD (iHeart VAD). The prototype was manufactured using Ti-6Al-4V ELI material which is a widely used hemocompatible material and in vitro blood tests conducted according to ASTM F1841–97 standards. The in vitro test result demonstrates satisfying performance regarding the hemolysis index, *pHb* generation, hematocrit level, etc. in the range of clinically available LVADs.

Preliminary in vivo tests have been performed in a porcine model demonstrating the ability to produce promising results regarding the circulatory support, anatomical fitting and blood-handling characteristics. The study has also indicated a great importance that a rotary blood pump is implanted to the animal and in vivo evaluation is performed for the first time in the history of Turkey.

7.2 Future Work

In vitro evaluation of the final prototype of Istanbul Heart VAD (iHeart VAD) has provided data about the flow characteristics and a better understanding about the blood pump system. However, it would be beneficial to conduct a particle image velocimetry (PIV) testing to validate the flow characteristics and possible stagnation zones by manufacturing the prototype with a transparent housing.

Moreover, utilizing a cardiovascular mock loop which mimics the physiologic flows-pressures of a human cardiovascular system is recommended for testing the pump under realistic physiologic flow-pressure conditions. Mock circulation loop

would help to create the hemodynamics of normal and heart failure conditions, and it can reduce the number of animal tests to be conducted in the future.

The pump developed in this study could also be used as an extracorporeal circulatory support device (ECMO). The design can be enlarged to increase the flow capacity, and magnetic levitation concept can be integrated with a large motor and pump size. The prototype can be manufactured with low cost glass compositions like Thoratec CentriMag ECMO device. The findings of such a study may provide insights into the new motor design with magnetic levitation concept in Istanbul Heart VAD (iHeart VAD).

To provide a better anatomical fitting for living animal tests, the design of the final prototype must be modified to achieve more competitive miniature size and weight. The size of the motor casing can be reduced by designing a special embedded motor system instead of using a commercially available motor. In future studies, the modified pump prototype should be manufactured considering the international standards (CE) for sealing, connector, cable, surface treatment techniques for extensive animal tests.

The in vivo study presented in this thesis is considered as an initial evaluation of Istanbul Heart VAD (iHeart VAD) in a large animal model, and further acute in vivo evaluations need to be performed. In future, acute tests will be followed by the chronic in vivo experiments for long-term evaluation of the hemocompatibility and end-organ effects.

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