Development of Heart Turcica Centrifugal

(a Left Ventricular Assist Device)

for *in vitro* blood tests

by

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This is to certify that I have examined this copy of a master's thesis by

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ABSTRACT

Patients need heart transplantation in order to recover from heart related diseases but there is shortage of donor. Left ventricular assist devices (LVADs) are developed for patients that are in the late stages of cardiovascular diseases. Heart Turcica Centrifugal (HTC) is the first centrifugal LVAD that is being developed in Turkey. In the previous stages of the development, HTC was brought to the stage of blood tests in order to determine its hemolytic performance. This thesis covers the development process of HTC for *in vitro* blood tests. First prototype of HTC was manufactured of biocompatible Ti-6Al-4V ELI for the *in vitro* blood tests. However, the driver magnets on the bottom of the impeller were not biocompatible, so a solution had to be developed. The first approach was to coat these magnet surfaces with biocompatible coatings such as Diamond Like Carbon (DLC) coatings. Those coating failed to solve the problem. In order to solve the problem a design modification has been made. Impeller of HTC was manufactured from two components, which encapsulated driver magnets and prevented their blood contact. HTC could be subjected to *in vitro* blood testing for hemolytic performance. During *in vitro* blood test ASTM International standards F1830 and F1841 will be used. A test loop with proper equipment will be prepared and HTC will be connected to this setup for the *in vitro* blood testing. According to the ASTM F1841, Normalized Index of Hemolysis (*N.I.H.*) will be calculated in every hour for test duration of 6 hours.

ÖZET

İleri seviye kalp hastalıklarına sahip hastalarda acil olarak kalp nakli gerekmektedir, fakat organ bağışçı sayısının azlığı nedeniyle bu hastalara kalp nakli yapılamamaktadır. İleri seviye kalp hastalıklarına sahip ve nakil olamayan hastaları hayatta tutmak için sol karıncık destek üniteleri (LVAD) geliştirilmiştir. Heart Turcica Centrifugal (HTC LVAD) adıyla geliştirilen sistem Türkiye'de geliştirilen ilk sol karıncık destek ünitesi olacaktır. Bu proje kapsamında yapılan çalışmalarla HTC LVAD, hemolitik performansını saptamak üzere kan testleri aşamasına gelmiştir. Bu tez çalışması HTC LVAD sisteminin *in vitro* kan testlerine girebilmesi için geliştirilmesi ile ilgili çalışmaları kapsamaktadır. HTC LVAD'nin ilk prototipi biyo-uyumlu Ti-6Al-4V ELI malzemesinden üretilmiştir. Fakat kanatçıkların altında yer alan sürücü mıknatıslar biyouyumlu olmadığı için kan testleri için bir çözüm geliştirme gerekliliği doğmuştur. İlk aşamada kanatçığa gömülü şekilde bulunan bu mıknatısların yüzeyleri elmas benzeri karbon (DLC) ile kaplanması üzerine çalışılmıştır. Fakat bu kaplamalar başarısızlıkla sonuçlanmıştır. Bunun devamında sorunu çözmek için kanatçığın tasarımı değiştirilmeden yapısı üzerinde birkaç değişiklik yapılmıştır. Kanatçık tek parça yerine iki parçalı bir tasarımda üretilmiş ve yeni tasarımda mıknatıs yüzeylerinin kan ile temasları kesilmiştir. Bütün problemlerin çözüldüğü bu noktada HTC LVAD'nin son prototipi *in vitro* kan testlerine tabi tutulabilir haldedir. *In vitro* kan testleri sırasında uluslar arası ASTM International F1830 ve F1841 standartları kullanılmıştır. Bu standartlar ışığında bir deney düzeneği hazırlanacaktır ve 6 saatlik kan testi boyunca her saat başı kandan alınan örneklerle Normalize Edilmiş Hemoliz İndeksi (*N.I.H.*) ASTM International F1841'e göre hesaplanacaktır.

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NOMENCLATURE

N	Motor speed [rpm]
Q	Flow rate [L/min]
P_{diff}	Pressure difference [mm Hg]
σ	Shear Stress [Pa]
$\varnothing$	Diameter [mm]
R_a	Surface Roughness [μm]
a_p	depth of cut [mm]
a_e	width of cut [mm]
V_c	surface speed [m/min]
F	feedrate [mm/min]
f_z	feed per tooth [mm/tooth]
N.I.H.	Normalized Index of Hemolysis [g / 100L]

Chapter 1 - INTRODUCTION

Medical industry is one of the most developing in terms of economical scales. After 1990s, healthcare spending in the developed and developing countries have been increasing rapidly. Healthcare expenditures take a big percentage of most countries Gross Domestic Products (GDP). Millennium Research Group published a report about the health care expenditures in BRIC countries (Brazil, Russia, India and China). According to the report in 2009 those countries spent $500 billion on health related issues and medical technology market [1]. United States of America spent $2.5 trillion on healthcare in 2009 [2]. Even though countries spend such a huge amount of money in order to solve health issues and diseases, patients are still passing away. There are innovative studies, especially in nano technology sector and genetics area, which try to solve diseases even before they occur. However, those studies will be a cure for diseases in the long term. Nevertheless diseases, especially cardiovascular diseases, will still be a problem for the patients for the next few decades.

1.1. Statistics about Cardiovascular Diseases

World Health Organization (WHO) Global Health Observatory program follows the causes of death disease by disease. According to this program in 2009, 58.7 million people died because of diseases, and 29 percent (17 million) of these mortalities were because of cardiovascular diseases, which are the number one cause of death globally. Moreover the situation in Turkey is not any better either. Furthermore, as stated by the mortality and burden of disease estimates of WHO for Turkey; in 2009, 436,900 people died because of diseases and among those 236,800 Turkish citizens, which is 54 percent, died because of cardiovascular diseases. WHO also measures the possible years of healthy life lost because of diseases using the Disability-Adjusted Life Year

(DALY) scale. According to 2004 DALY data of WHO, 2,082,000 years of possible life was lost in Turkey.

Table 1.1 - List of abbreviations

Abbreviation	**Meaning**
BTR	Bridge-to-Recovery
BTT	Bridge-to-Transplantation
CAD	Computer Aided Design
CAM	Computer Aided Manufacturing
CE	Conformité Européenne (European Conformity in French)
DALY	Disability-Adjusted Life Year
FDA	Food and Drug Administration (US)
HTC	Heart Turcica Centrifugal
LVAD	Left VAD
MARC	Manufacturing and Automation Research Center at Koç University
MCS	Mechanical Circulatory System
RVAD	Right VAD
TAH	Total Artificial Heart
VAD	Ventricular Assist Device
WHO	World Health Organization

In Turkey 5000 people are waiting for heart transplantation operation [3]. Engineers and medical doctors are working together to either cure those patients or give their heart a chance to recover by the help of medical devices; such as pacemakers, stents, implantable cardioverter-defibrillator, and ventricular assist devices. Among

various choices ventricular assist devices are sometimes the only option for rescuing a patient's life with cardiovascular disease.

1.2. Mechanical Circulatory Support Systems

A ventricular assist device (VAD) is a blood pump specially designed to supply blood to the body of a patient with late stage cardiovascular diseases. The concept of using blood pumps first emerged in 1957 more than 50 years ago. In 1957, Kolff and Akutsu initiated the first total artificial heart (TAH) development program whereas in 1962, DeBakey and Liotta started first left ventricular assist device program [4]. The first clinical heart transplantation came after those two programs; in 1964, the first heart transplantation to a man was accomplished in the department of surgery in University of Mississippi Hospital [5]. In 1967, the first human-to-human heart transplantation was accomplished by Christiaan Barnard [6]. Even though the human-to-human heart transplantation is accomplished a couple of decades ago, patients with cardiovascular diseases could not always had heart transplantation, so they should be kept alive by artificial circulatory supports.

K. B. Chandran stated that there are two kinds of patients who need artificial circulatory support or in other words ventricular assist devices [7]. The first category is the patients who have a heart surgery because of valvular disorders, ventricular aneurysm, or coronary artery diseases. Heart of these patients could not recover immediately after surgery, so for a couple of weeks ventricular assist devices can be implemented in order to reduce the load of the heart. The second category of patients are the patients with advanced heart diseases such as late stage cardiomyopathy and need immediate heart transplantation [7]. However, because of the shortage of suitable donors and not all patients are candidates for heart transplantation, ventricular assist devices are usually implanted as a bridge to heart transplantation [7-8].

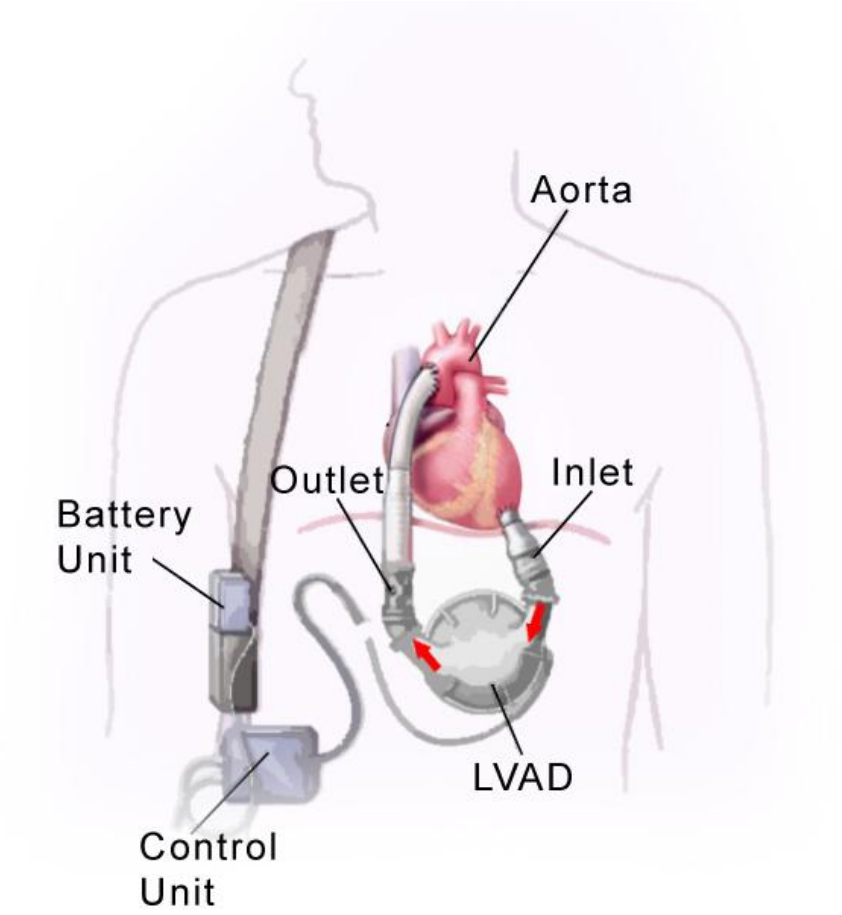

Figure 1.1 - An illustration of an LVAD system

Ventricular assist devices are categorized under three headings; right ventricular assist devices (RVADs) which are employed for pulmonary circulation support between the lungs and heart, left ventricular assist devices (LVADs, Figure 1.1) which are utilized for systemic circulation support between the heart and body through aorta, and if both of these devices are used at the same time than it is named as biventricular assist devices (BVADs). If the heart is taken out and a biventricular assist device was installed with minor changes to the patient, than this system is called a total artificial heart (TAH).

Furthermore, those are main categories but all of the ventricular assist devices are listed in generations according to their technology and size. First generation ventricular

assist devices are generally pulsatile blood pumps with huge sizes and cannot be implanted inside the body. Those devices generally used a pneumatic system that created pressure difference of a moving chamber to pump blood not continuously but in pulses. Those pulses pumped the blood at discrete times similar to the heart's beating method. Heartmate IP® and Novacor® systems were commercially available first generation VADs with weights over 1 kilograms [9-10]. Second generation ventricular assist devices are rotary blood pumps with impellers rotating to increase the pressure of blood which could be both axial flow rotary blood pumps and centrifugal rotary blood pumps. Second generation pumps are continuous blood pumps that are magnetically driven but have mechanical bearings. Unlike first generation pumps, second generation pumps do not use pulses to pump the blood; these pumps create continuous flow to the body. Jarvik 2000® and Heartmate II® are two examples of commercially available second generation pumps [11-12]. Third generation blood pumps are basically second generation blood pumps without mechanical bearings and under 300 grams of weight. Instead of mechanical bearings that support the rotating impeller, those pumps either use magnetic levitation bearings or hydrodynamics effect to hold the impeller in its suitable position. VentrAssist®, DuraHeart®, Berlin Heart Incor®, HeartMate III®, Heartware® etc. are third generation blood pumps [13-17].

1.3. Heart Turcica Centrifugal

Heart Turcica Centrifugal (HTC) as a long term left ventricular assist device is being developed since 2006 in Manufacturing and Automation Research Center (MARC) in Koç University. Heart Turcica Centrifugal is a second generation centrifugal rotary blood pump that is being developed as a bridge-to-transplantation (BTT) or as a bridge-to-recovery (BTR). HTC is designed as a second generation long term blood pump.

Yukihiko Nosé stated that researchers should pass three main phases in order for the development of a long term or permanent blood pump. Nosé listed those three phases as *phase 1 pump* (2 day), *phase 2 pump* (2 week) and *phase 3 pump* (long-term or permanent) [18-19]. As Ichikawa et al stated a 2 day pump could be used in patients who had a cardiopulmonary bypass surgery, where a 2 week pump could be used in patients who had postcardiotomy cardiac failures, need a pump for extracorporeal membrane oxygenation or percutaneous cardiopulmonary support, and long-term pumps should be used in patients as a bridge-to-transplantation or recovery [20]. In Figure 1.2 a representation of this classification and the usage areas can be seen.

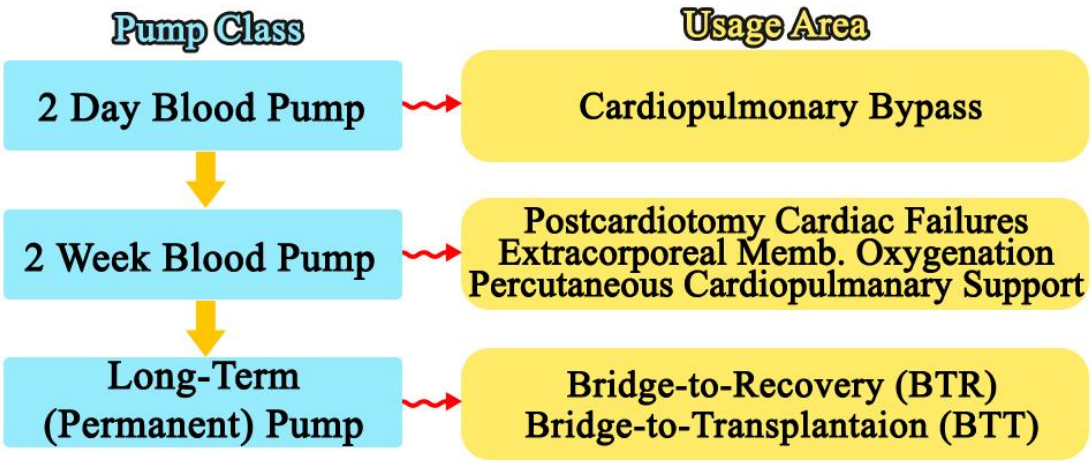

Figure 1.2 - Classification of Ventricular Assist Devices and Usage Areas

It took 10 years of research for a team of engineers and medical doctors to develop a long-term VAD (DeBakey LVAD) [4]. Moreover, the estimated cost of a third generation centrifugal pump is high [21]. In Turkey, a second generation LVAD system cost almost $100,000. An article directly focuses on the cost of using an LVAD for long term was published by Moskowitz et al who estimated the average cost of the first year of usage to be $222,500 [22]. In United States, the effective hospital cost per patient with LVAD without physicians cost is about $400,000 [23]. The overall market in United States for mechanical circulatory support devices has reached $23.1 billion

[24]. Such high costs push Turkish researchers to design a second generation pump which will be more cost effective and affordable for Turkish citizens.

Moreover, second generation pumps were available since late 1990s and they had enough time to prove themselves to be durable. Many of the commercially available second generation blood pumps have high percentage of survival rates; Peter Houghton was a patient that lived 7 years with a second generation Jarvik 2000® pump [25].

Koç University Manufacturing and Automation Research Center (MARC) researchers decided to develop a second generation pump named as Heart Turcica Centrifugal (HTC). Instead of an axial flow blood pump a centrifugal blood pump was chosen for development. The reason behind this decision was the fact that the axial flow pumps have high rotation speeds in the order of 10,000 rpm that causes high amount of mechanical wear, whereas centrifugal blood pumps have rotational speeds under 3,000 rpm which makes them more sustainable [26].

At MARC at Koç University, previous researchers have accomplished a remarkable job throughout the development stage of Heart Turcica Centrifugal [27-30]. There were too many design parameters; such as the diameter of the impeller, type of the impeller, impeller blade geometries, impeller blade heights, number of blades on the impeller, volute design, axial and radial gaps inside the pump, etc. In Figure 1.3, some of the design parameters are shown.

Gökhan Yıldız has done computational fluid analysis among various types of centrifugal blood pump designs in order to obtain the most significant factors that affect the performance of blood pumps [27]. Onur Demir continued the research by working on the designs that Gökhan made and determined important parameters such as the shape of the volute tongue, blade heights, etc. [28]. Çınar Ersanlı worked on experimental procedures and manufactured the first Ti-6Al-4V ELI (ASTM Grade 23) prototype pump for *in vitro* blood tests however there were some complications about

this design [29]. Finally Emre Bıyıklı utilized computational fluid dynamics tools and found out the remarkable features of the blood pumps that were listed in the literature. As a result of these earlier developments, final design of HTC LVAD came out. In Figure 1.4, the final design is shown [30].

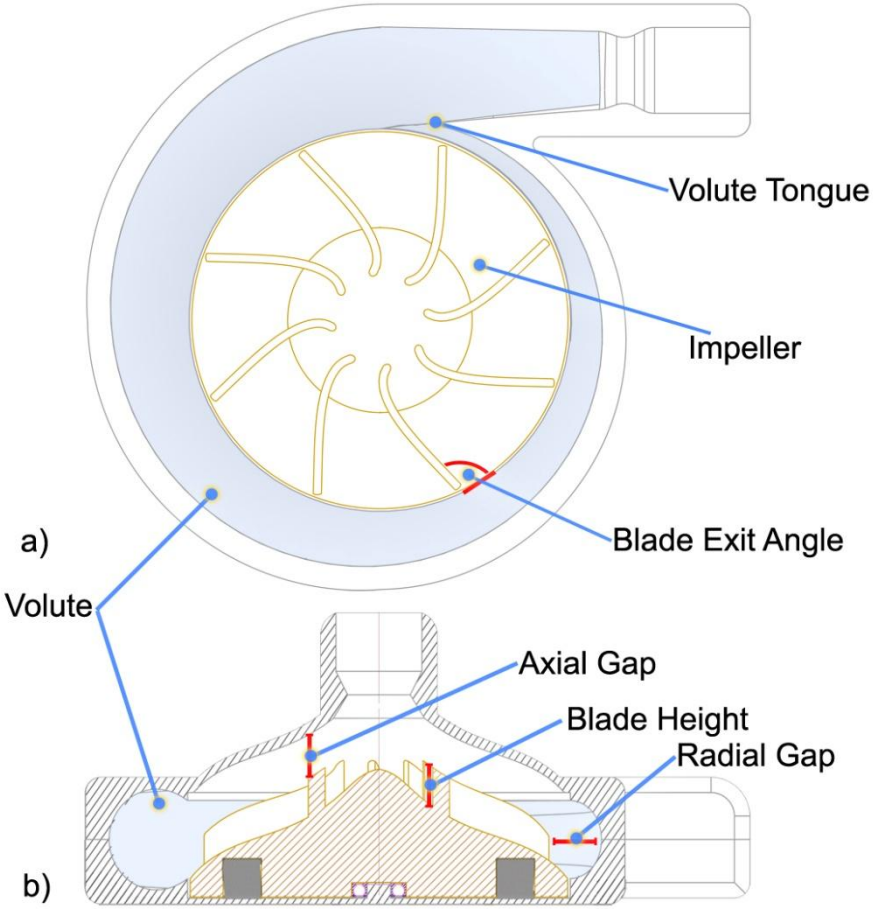

Figure 1.3 - Some of the Design Parameters for Ventricular Assist Devices; a) Top view of the device through its cross section, b) Cross sectional view of the device from the center of the impeller

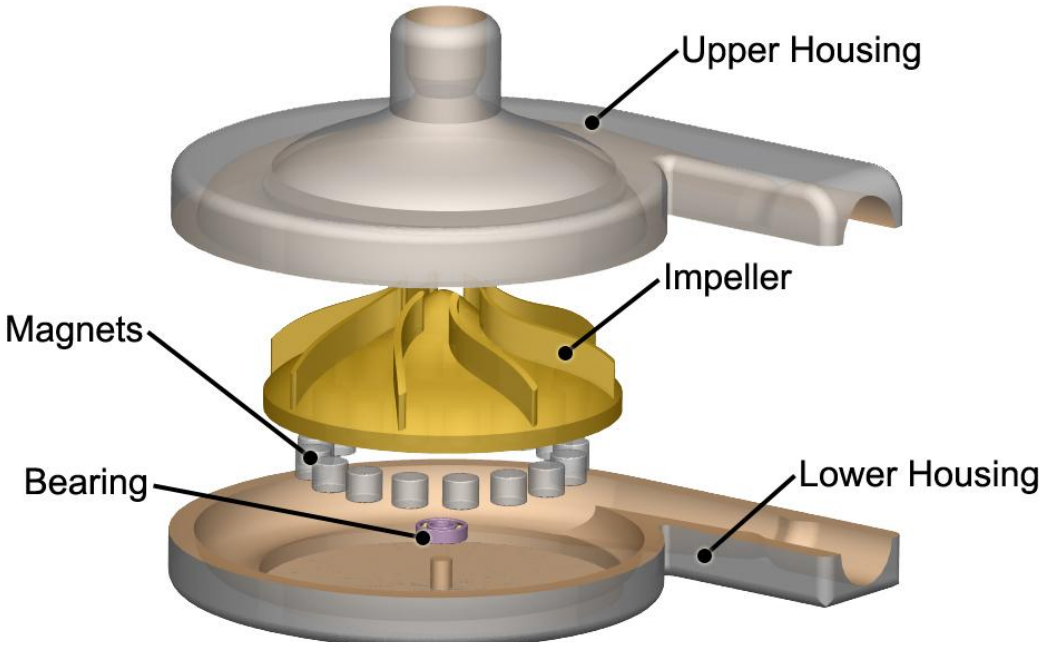

Figure 1.4 - Final Design of HTC

This research has focused on the development of the final design of Heart Turcica Centrifugal for *in vitro* blood tests. Throughout this thesis study, problems that occurred during the development of HTC for *in vitro* blood tests will be listed and the solutions for the problems and design modifications that were made will be explained in detail.

Chapter 2 covers the detailed review of the previous studies that were made in the literature. The up-to-date studies from the beginning of the usage of ventricular assist devices will be presented. Moreover, important aspects and the design procedure of blood pumps throughout the world will be explained in detail.

Chapter 3 will give information about the development stage of the final design of Heart Turcica Centrifugal for *in vitro* blood tests. The components that are being used in Heart Turcica Centrifugal will be listed; the problems about the previous Ti-6Al-4V ELI HTC blood pump will be explained. Methodology for solving those problems and the computer aided design (CAD) procedure will be stated in this chapter.

Chapter 4 will be discussing the manufacturing process of Heart Turcica Centrifugal which will be used in *in vitro* blood testing. A detailed procedure for the manufacturing of HTC LVAD will be presented from the beginning of computer aided manufacturing (CAM) programs, to intermediate post-control programs and the manufacturing of Ti-6Al-4V ELI in a Computer Numerical Control (CNC) turning and milling centers.

In Chapter 5, the procedure for *in vitro* blood testing of Heart Turcica Centrifugal according to the international standards of ASTM F1830 – 97 and ASTM F1841 – 97 will be explained.

In the final chapter, author will conclude the effort that this research has focused on and will be explaining the future work for this project.

Chapter 2 - LITERATURE REVIEW

This chapter will give a detailed description of the state of the art for ventricular assist devices. First, a brief history of the ventricular assist devices will be presented. Global statistics about cardiovascular diseases and death related to them will be given, as well as the situation in Turkey. Then the ventricular assist devices that are approved by the US Food and Drug Administration (FDA) or have a Conformité Européenne (CE) mark, for the usage in Europe, will be explained in detail.

In general the best option for patients with late stage cardiovascular diseases is the heart transplantation. There are tens of thousands of people waiting for heart transplantation however; only 3,500 heart transplant operations are performed worldwide because of the shortage of suitable donors and age limitations. There is need for ventricular assist devices in order to keep those patients alive [7-8, 31-33].

As a result of the shortage of donors, there has been a rush to develop better and better ventricular assist devices since 1960s, however as Yukihiko Nosé stated, with his tens of years of experience in developing ventricular assist devices, it is not an easy task [18]. For over 50 years researchers have been trying to design and manufacture ventricular assist devices. Ventricular assist devices could be used in three situations, as a Bridge-to-recovery (BTR) after a complicated heart surgery, as a Bridge-to-transplantation (BTR) where the heart could no longer keep the patient alive or as a destination therapy (DT) for the rest of their lives [6, 34].

2.1. History of Cardiovascular diseases and assist devices

The first cardiac surgery was accomplished by Ludwig Rehn, a German surgent, in 1896. Almost 60 years later, John Gibbon successfully used a mechanical circulatory

support system in an atrial septal defect surgery of an 18 year old girl in 1953 [35]. Later in 1964, Hardy et al accomplished the first heart transplant to a man [5]. In 1965, Spencer et al demonstrated the successful usage of DeBakey roller pumps to a postcardiotomy patient [36]. Moreover in 1967, the era of human-to-human heart transplantations began with the successful operation of Christiaan Barnard [6]. The first human-to-human heart transplantation in Turkey was just one year later; in 1968, Kemal Beyazıt has accomplished the first human-to-human heart transplantation in Turkey [37]. Cooley et al reported the first usage of a total artificial heart as a bridge-to-transplantation in 1969 [36]. In 1971, Micheal E. DeBakey reported the successful usage of LVADs in two patients with advanced cardiovascular problems, which both of them were able to recover by themselves completely [38]. In table 2.1, remarkable events for the cure of cardiovascular diseases are provided chronologically.

Table 2.1 - Historical events in the area of cardiovascular diseases [5-6, 35-38]

Person	**Subject**	**Date**
Ludwig Rehn	First cardiac surgery	1896
John Gibbon	First usage of Mechanical Circulatory Support	1953
J. D. Hardy et al	First heart transplant in man	1964
F. C. Spencer et al	Successful usage of pumps	1965
Christiaan Barnard	First human-to-human heart transplant	1967
Kemal Beyazıt	First human-to-human heart transplant in Turkey	1968
D. A. Cooley et al	First usage of TAH as a bridge-to-transplantation	1969
Micheal E. DeBakey	Successful usage of LVADs	1971
J. C. Norman et al	First usage of LVAD as a bridge-to-transplantation	1978
W.C. DeVries et al	Usage of a TAH for a patient to support 112 days	1984

2.2. Situation of Heart Diseases Globally

The first human-to-human heart transplantation in 1967 has started a new era to cure the patients with advanced cardiovascular diseases; however the shortage of donor hearts became apparent soon. As stated earlier by the World Health Organization (WHO) statistics, 17 million people die just because of cardiovascular diseases every year and many of them need immediate heart transplantation. However, according to Reiner Körfer, approximately 3,500 heart transplants were accomplished globally each year [33]. In Turkey the situation is not different either; there are approximately 30 heart transplant operations each year, whereas there are 5,000 people in need of a heart transplantation [3]. Since the chance of having a heart transplantation is low; the patients need alternative methods for living a healthy life, whether with ventricular assist devices till having heart transplantation or having a ventricular assist device as an artificial organ till the rest of their life as in the case of Peter Houghton. Peter Houghton was the first person who lived seven years with an LVAD outside the hospital and continued a normal life. [25].

In table 2.2**,** statistical data about cardiovascular diseases is given.

Table 2.2 - Statistical Data about cardiovascular diseases

Data	**Country**	**Source**
17 million deaths because of cardiovascular diseases	Global	WHO
236,800 people die because of cardiovascular diseases	Turkey	WHO
5,000 people need heart transplantation per year	Turkey	[3]
3,500 heart transplant operations per year	Global	[33]
Approximately 30 heart transplant operations per year	Turkey	[3]
$23.1 billion average market size for MCS in US	US	[24]

2.3. Cause of Diseases in Ventricles

As mentioned before, the only way for patients with advanced cardiac failures are the usage of ventricular assist devices. Among such patients most need a left ventricular assist device [4]. The right ventricle pumps the blood to the lungs by pulmonary circulation. On the other hand, left ventricle pumps the blood even the farthest point of the body like the fingertips by the systemic circulation. The left ventricle is a very strong pump that creates a systolic blood pressure of 120 mm Hg which is an optimal condition for a healthy human [39]. The usage of LVADs is higher because the effects of cardiovascular diseases in the left ventricle of the heart become apparent earlier, since its work load is much higher.

Fibrosis is one of the most critical cardiovascular diseases; it is related with abnormalities in cardiac muscle cells. The cardiac muscle cells degenerate and turn into cells that cannot contract. As a result of this, heart start to enlarge and there can be changes in its shape, moreover the heart cannot pump blood with enough pressure. In Figure 2.1, optical microscopy images of a patient's heart tissue with fibrosis can be seen. Black marks show the areas with fibrosis. As can be seen from the figure, degenerated cells in the fibrosis areas have a significant ratio in comparison to healthy tissues. As the ratio of the fibrosis areas in the left ventricle increases, the ability of the left ventricle to pump the blood to the aorta with enough pressure decreases. If the fibrosis level passes a threshold value than the patient is faced with heart attacks or other serious cardiac problems.

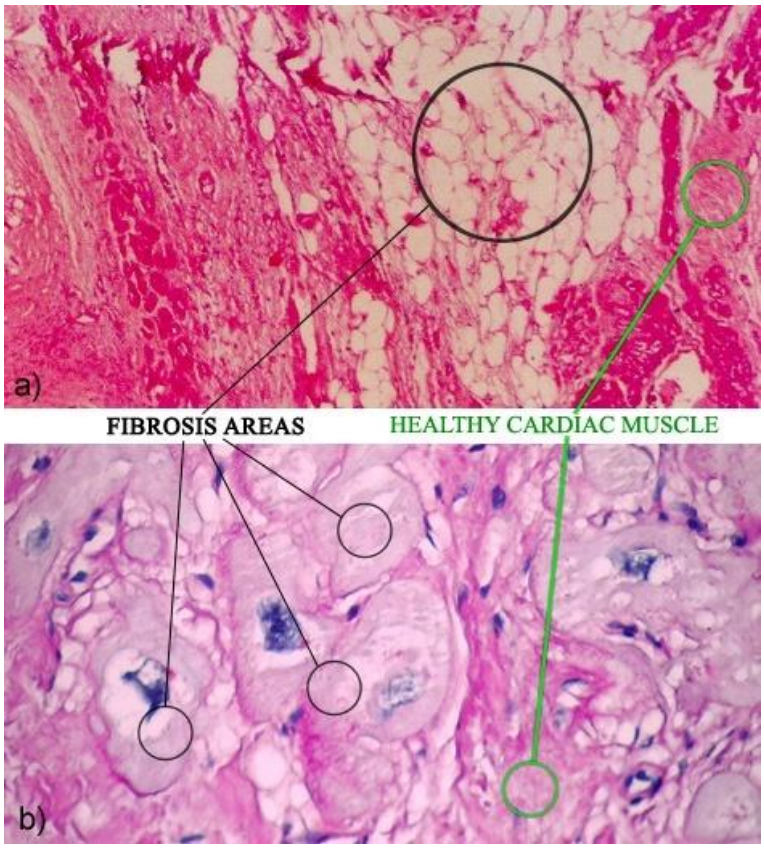

Figure 2.1 - Fibrosis in heart muscle Magnification a) 40x b) 100x (Printed with the permission of Süha Küçükaksu)

2.4. Left Ventricular Assist Devices (LVADs)

In relation with the left ventricular problems, LVAD practices are a lot higher than the RVAD practices. In 1971, DeBakey published an article about two successful usages of left ventricular assist devices (LVADs) and their importance [38]. The first case was a young girl with long-standing rheumatic heart disease for whom an LVAD was used until the fourth postoperative day. The second case was a woman with serious aortic insufficiency where doctors used an LVAD until the 10^{th} postoperative day. These were the first clinical uses of LVADs and both of the patients recovered completely. DeBakey indicated the potential of LVADs as a curing element in cardiovascular diseases to be considerable [38].

After the success of DeBakey and the first human-to-human heart transplant in 1967, Mechanical Circulatory Support (MCS) systems, especially LVADs, gained attention. In 1972, a committee to study the role of LVADs as long term mechanical circulatory support devices was formed by National Heart and Lung Institute in United States. Moreover, published a "Report on Left Ventricular Assist Device", in which the committee pointed out the potential usage of LVADs as a recovery element for patients [40]. After this report, National Heart, Lung and Blood Institute (NHLBI) in US started to support an LVAD program initiated in 1975. Between 1975 and 1980, 13 patients were supported in four medical centers with LVADs and one of the patients gave satisfying results. The patient was supported on an LVAD for 105 hours and 16 months later the patient was healthy without any cardiac symptoms [41]. The results obtained from this research were worthy of attention so in 1977, NHLBI requested suggestions from researchers around US for "Development of electrical energy converters to power and control left heart assist devices" [40]. Finally in 1978, the first usage of an LVAD was used on a patient as a bridge-to-transplantation in Texas Heart Institute [40].

The research continued during 1980s. LVADs started prove themselves as a bridge-to-transplantation and sometimes to a complete recovery; however, there were some complications about the first working designs (First generation LVADs). As stated before, the first generation LVADs are pulsatile assist devices where there is a pneumatic system that sends and draws pressurized air in a pumping chamber. However, those systems create an excess of air between pneumatic parts and moving parts. In order to solve this problem researchers sent the excess of air to an implantable and flexible air bag called the compliance chamber, and then this excess of air was sent outside of the body through a ventilation [40]. Even though the excess of air is a problem, it is not that important since it can be solved with a compliance chamber and ventilation through a channel on the skin. But the concern of blood clotting on the blood contacting surfaces inside pump was much more important. DeBakey pointed out this problem in the early 1970s, however in the mid 1970s researchers started to publish

surface treatments methods that make the surfaces both biocompatible and hemocompatible. Hemocompatibility is the compatibility of the surfaces that are in direct contact with the blood. In 1974, Chawla et al reported that a surface was modified with radiation grafting of heparin, results showed that after 60 minutes there were no sign of blood clotting on the surface [42]. As the research continued, better and better nonthrombogenic surfaces with no sign of blood clotting were developed. Not only surface treated materials are nonthrombogenic, but also newly developed materials are nonthrombogenic too. Among those a titanium alloy, Ti-6Al-4V, proved itself as completely heamocompatible material, the heamolysis rates of this alloy is almost zero [43].

Apart from those studies, in 1986, Texas Heart Institute initiated clinical trials for the first generation Thoratec HeartMate IP® (implantable pneumatic) LVAD. After 8 years of modifications, in 1994, finally Thoratec HeartMate IP® was approved by the US Food and Drug Administration (FDA) for marketing [9]. HeartMate IP is a pulsatile LVAD that pumps the blood with an implantable pusher-plate blood pump made of titanium alloy which is pneumatically driven through an external drive console. The pusher-plate section consists of blood and air chambers, which is positioned in the upper left abdominal quadrant inside the body [44]. After the success of HeartMate IP, researchers also created a modified version of HeartMate IP named as HeartMate VE®. HeartMate VE works on the same principle as HeartMate IP, with a similar pusher-plate section implanted inside the body however, this model uses electrical actuation to push the pusher-plate instead of a pneumatic system as in HeartMate IP. Both of these models are called the first generation pumps, therefore they are named as HeartMate I. In 2001, HeartMate I has already been used in 2,300 patients globally [45]. Subsequent to the good cardiovascular support of HeartMate I, Thoratec Company developed a second model, HeartMate II®, which is a second generation pump. HeartMate II is an axial flow rotary blood pump with mechanical bearings. In 2003, the FDA approval for clinical trials of HeartMate II was given, meanwhile in 2005 CE mark was granted for

HeartMate II which gives opportunity for all patients around Europe to use HeartMate II as a bridge-to-transplantation [6, 46]. Development of Jarvik 2000® was started in 1988 and around 2000 the first clinical trials were begun, and in 2003, FDA gave permission for the patients to be discharged from the hospital to wait for heart transplant at their home [6]. At the end of 2000s, there were many commercially available LVADs. As of 2009, based on the data obtained from Thoratec Corporation, there are 14,215 patients implanted just with Thoratec Corporation's ventricular assist devices around the world (HeartMate IP:1,317 patients, HeartMate VE: 4694 patients, HeartMate II: 3,276 patients, others: 4928 patients). Currently the total number of VADs implanted to patients is estimated to be over 25,000 globally.

Chapter 3 - DEVELOPMENT OF HEART TURCICA CENTRIFUGAL FOR *IN VITRO* BLOOD TESTING

This chapter will cover the details about the design modifications and development stage of Heart Turcica Centrifugal for *in vitro* blood testing. First of all, the up-to-date studies of HTC before this research will be explained with the short summary of the final model that will be tested for *in vitro* blood testing. Next, the components of HTC that is used in the system will be explained; driver magnets, housing, bearing, material, etc. Driver mechanism and bearing mechanism will be presented, and its components will be explained. Then, the first *in vitro* blood testing prototype will be explained and the problems it encountered will be listed. Finally, the modified prototype for *in vitro* blood testing will be discussed in detail.

3.1. Human Heart

A normal human heart weights about 300 grams and beats at 72 beats per minute and for a life span of 70 years it beats approximately 2.65 billion times. In Figure 3.1 an illustration of a human heart can be seen.

By pulmonary circulation the right ventricle pumps the low-oxygen blood to the lungs. In the alveoli of the lungs blood is oxygenated and this oxygen-rich blood goes into left ventricle passing through left atrium. Then left ventricle pumps the blood to body through aorta by systemic circulation. LVADs are used in order to achieve the goal of reducing the work-load of left ventricle, in systemic circulation. An LVAD is placed inside the body and the inlet channel of the LVAD is connected to the left ventricle and the outlet channel of the LVAD is connected to the aorta. This procedure enables the LVAD to suck blood from left ventricle and pump it to the aorta at a certain

pressure. The illustration in Figure 3.1 also represents the placement of an LVAD from left ventricle to the aorta.

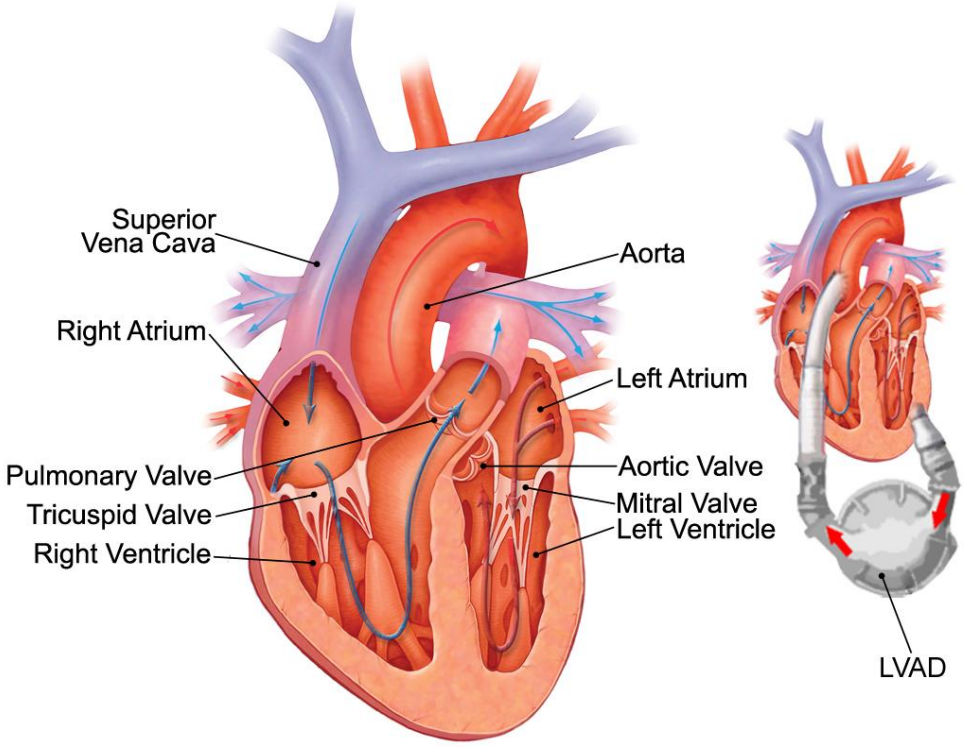

Figure 3.1 - An illustration of Human Heart, and Placement of an LVAD

3.2. Determination of the Final Model

Researchers at MARC were working on Heart Turcica Centrifugal project for the last couple of years in order to create a blood pump that will at least perform as a support device to heart. Throughout the research, the endless effort of the researchers at MARC was the main element that this research has reached to the level of *in vitro* blood testing in this short period of time. Gökhan Yıldız, Onur Demir, Çınar Ersanlı, Emre Bıyıklı and I worked on this project respectively and as a result many left ventricular assist device models were created.

The left ventricular assist device models were created after determining design parameters. The first step was to transfer this geometry into a solid computer aided design (CAD) model in computer environment with the help of Unigraphics program. After the design geometry was turned into a model in the computer environment, fluid geometries were prepared. In order to predict the performance of the model detailed computational fluid dynamics (CFD) analyses with ANSYS were performed using the fluid geometries created. Streamlines, pressure distribution, shear stresses inside the pump, etc were estimated from those CFD analyses. The models that satisfied the necessary performance expectations were than manufactured from acrylic glass in the machining centers located at MARC. The manufacturing process will be discussed in detail in the following chapters. The models that were manufactured were tested in a test setup specially design for determining the performance of the pump.

The test setup consists of a servo motor that drives the motor at a certain rotational speed which is controlled by a servo motor driver and suitable power supplies. There is a reservoir which contains a liquid with viscosity value analogous to that of blood. Two pressure sensors; one in front of the inlet of the pump and one after the outlet of the pump are placed into the setup. Those sensors are used for calculating the pressure difference that the pump produces. Test setup can be seen in Figure 3.3. The reservoir is placed in a certain height that will create a preload pressure of 15 mm Hg on the pressure sensors. This 15 mm Hg was determined from the Left Ventricular End-Diastolic Pressure (LVEDP) average obtained from literature [47-48]. LVEDP is the pressure of the left ventricle at the end of the pumping cycle. In Figure 3.2 a Wiggers diagram can be seen where the end of the left ventricular line corresponds to the LVEDP. Wiggers diagram represents the pressure changes during one beat of the heart. The diagram shows that left ventricle of the heart create approximately a maximum pressure of 120 mm Hg and a minimum pressure of 15mm Hg in every beat.

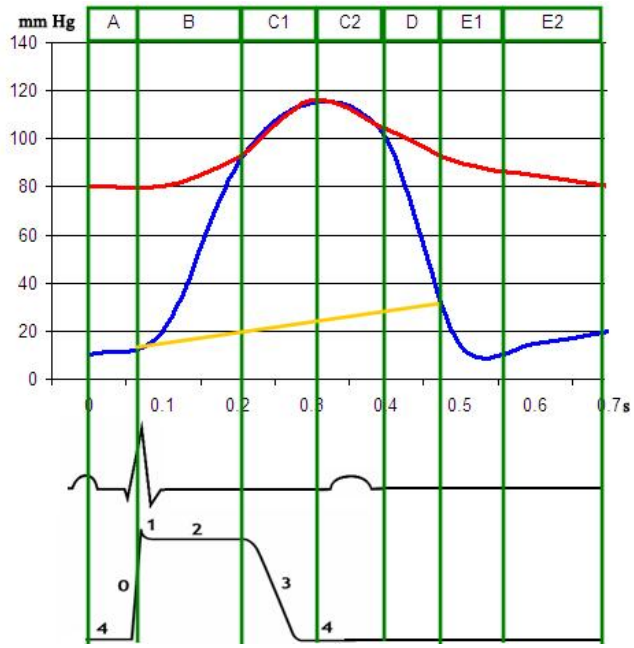

Figure 3.2 - Wiggers Diagram (Red = aortic pressure, Blue = left ventricular pressure, Yellow = left atrial pressure)

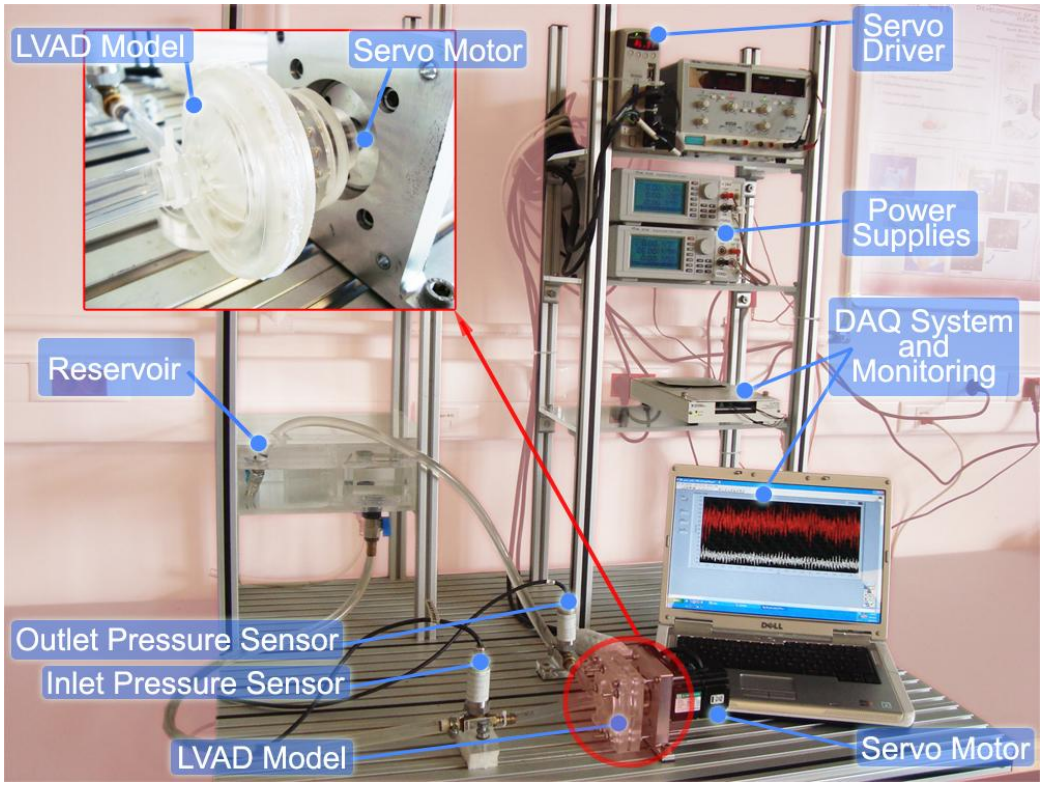

Figure 3.3 - Test Setup

In order to determine the performance of a certain design, suitable power is supplied to the servo motor and a servo driver controls the rotational motor speed, *N (rpm)*. The motor speed is increased gradually and the pressure difference is adjusted by an adjusting knob at the outlet line of the pump. Data for the flow rate, *Q (L/min)*, at pressure difference, P_{diff} *(mm Hg)*, is taken and performance curves (*Q* versus P_{diff}) are plotted for certain motor speed; 2000 rpm, 2250 rpm, 2500 rpm, 2750 rpm, and 3000 rpm. In Figure 3.15, performance chart for the final prototype can be seen.

As mentioned earlier there were many designs that satisfied the necessary performance expectations. All of these designs were manufactured and tested in the experimental setup in MARC. Performance curves from these experiments were used to determine to optimum model. In order to determine the most suitable model, the performance of the pump in the MARC experiment setup was the first elimination factor. Designs that gave out the finest performances were chosen, and then their computational fluid dynamics analyses were analyzed one more time. CFD analyses were used to determine the flow behavior and shear stress, σ, value in the pump. The streamlines and velocity vectors obtained from CFD analyses, which were used to determine the pumps with a steady and linear flow. Moreover, shear stress values were also examined since a shear stress value over 120 Pa was critical for red blood cells, which starts to tear them [30]. As a result of all of this elimination procedure, researchers at MARC came out with a final design. In Figure 1.4, the CAD drawing of the final design can be seen. The final design has 8 blades on its impeller, with a constant blade height. The diameter of the final design is 48.3 mm.

3.3. Final Design of HTC

As soon as the final design was determined by the researchers at MARC, manufacturing the model from a suitable material in order test it within the *in vitro* blood testing was the main focus.

There are many different materials that can be used in medical applications. For a material to be used as a medical material, it should be biocompatible. The Oxford Dictionary of Biochemistry and Molecular Biology describe biocompatibility as "*compatible with life; having no injurious effect on living organisms*" [49]. However, this description does not cover the whole idea behind biocompatibility. Biocompatibility is determined in accordance with the material, and its usage area. For example, there are biocompatible steels that were used in implants however; blood contacting medical devices like LVADs cannot be made of steel because it is not hemocompatible. Hemocompatibility is the compatibility of a material within direct contact with the blood. Just by itself, biocompatibility is not enough for a material to be used in ventricular assist devices.

Since all biocompatible materials are not suitable for the final model of HTC; a suitable material both biocompatible and hemocompatible is found from the literature. Ti-6Al-4V is a titanium alloy that is widely used in medical applications. This titanium alloy, Ti-6Al-4V, is also used in aerospace industry and in engine components. It contains 6% Aluminum and 4% Vanadium with little amounts of other components. There are two commonly known grades of Ti-6Al-4V in the market, Ti-6Al-4V ASTM Grade 5 and Ti-6Al-4V ASTM Grade 23 also known as Ti-6Al-4V ELI (Extra Low Interstitials). Ti-6Al-4V Grade 5 received some attention as a metallic biomaterial, with its biocompatibility and good corrosion resistance [7]. However, Ti-6Al-4V ELI Grade 23 with reduced amounts impurities of oxygen, iron, nitrogen and carbon is known to be the first registered titanium alloy as a biomaterial according to the ASTM standard F136 [50-52]. Ti-6Al-4V ELI Grade 23 with its reduced impurities performs a better ductility and it has a better fracture toughness.

As stated earlier, a material listed as a biomaterial does not mean that it can be used directly as a ventricular assist device however, Ti-6Al-4V also listed as an excellent hemocompatible material in the literature. Dion et al performed in vitro

hemocompatibility test of Ti-6Al-4V and the results demonstrated that the hemolysis rates were almost zero, which proved that Ti-6Al-4V was a suitable material that could be used in Heart Turcica Centrifugal [43].

In conclusion, Ti-6Al-4V ELI Grade 23 was chosen to be the material for HTC in *in vitro* blood tests. Based on the results obtained of prior to this research a Heart Turcica Centrifugal prototype was manufactured from Ti-6Al-4V ELI Grade 23 in MARC.

In Figure 3.4, the first prototype made of Ti-6Al-4V ELI can be seen.

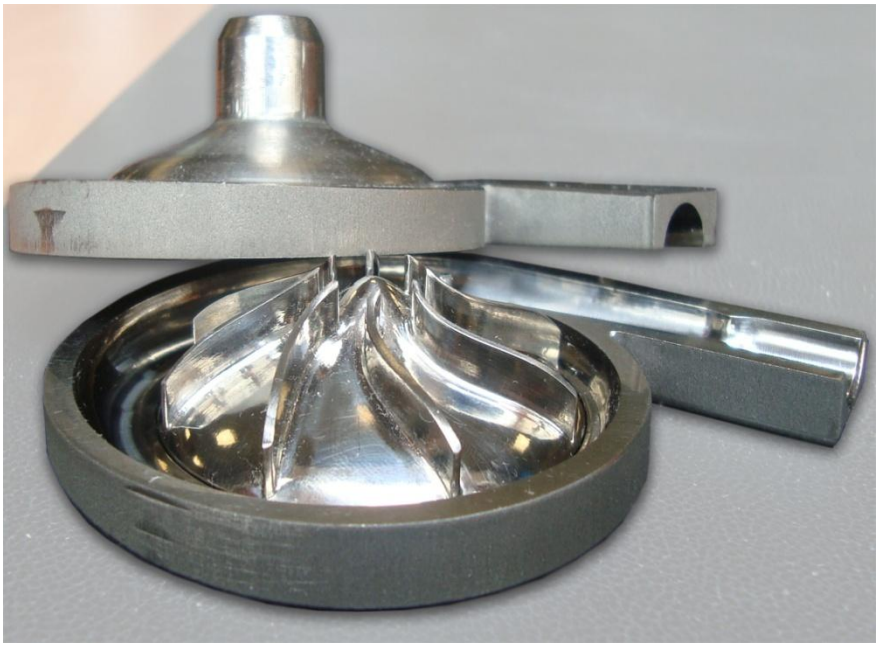

Figure 3.4 - First prototype of HTC made of Ti-6Al-4V for in vitro blood tests

The first prototype was very promising; however, there was a need to solve two problems. The first problem was the mechanical bearing, and the second problem was the driver neodymium magnets.

3.4. Problems about the First Ti-6Al-4V prototype

The mechanical bearings that were used during the performance testing in MARC were made of steel. But the steel was neither biocompatible nor hemocompatible. There were many biocompatible bearings. Bearings in small sizes that are suitable for use in Heart Turcica Centrifugal are found to be ceramic bearings. There are many ceramic bearings in the market. There are hybrid bearings with steel rings and ceramic ball inside and there are full ceramic bearings that all of the components are made of ceramics.

As stated in literature, Al_2O_3 ceramic bearings were used in some ventricular assist devices and they performed well [53]. As a result Al_2O_3 full ceramic bearing was chosen to be used in Heart Turcica Centrifugal. In Figure 3.5, the Al_2O_3 full ceramic bearing that was used in HTC for *in vitro* blood testing can be seen. The outer diameter of the Al_2O_3 used is 7 mm whereas the inner diameter is 3 mm. The height of the bearing is 2 mm.

Figure 3.5 - Al_2O_3 Full Ceramic Bearing used in HTC final model

The first problem of non-hemocompatible bearings was solved by the use of full ceramic Al_2O_3 bearings.

The second problem with the final prototype was the driver magnets. The impeller is rotated by neodymium magnets that are placed under the impeller. Those neodymium magnets are coupled with the neodymium magnets on the motor shaft. When the motor rotates the magnetic coupling that those magnets made, rotates the impeller. In Figure 3.6, an illustration for this magnetic drive can be seen.

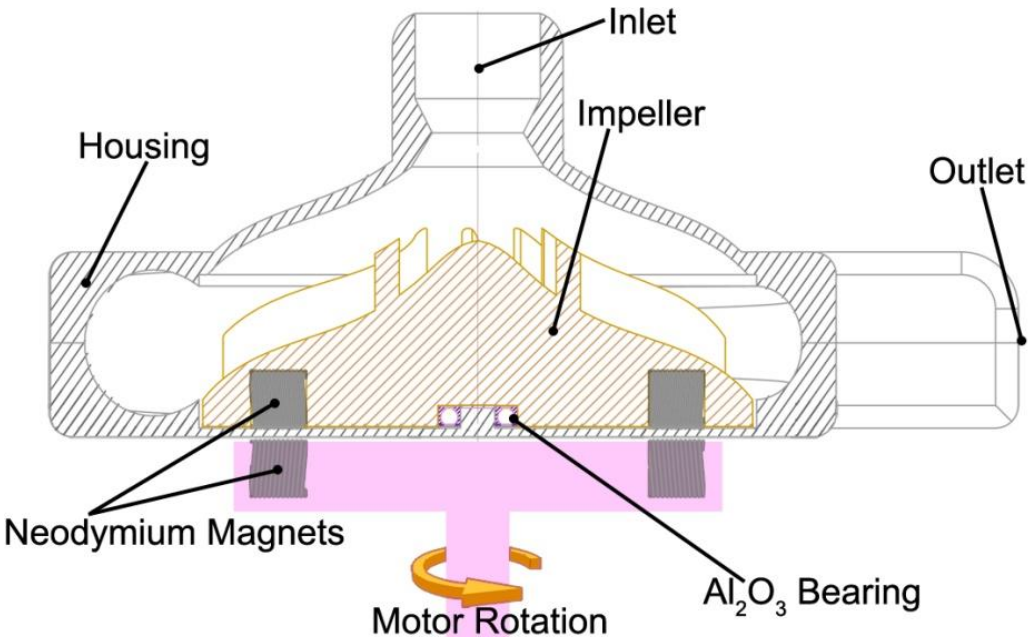

Figure 3.6 - Cross Sectional view of the final design of HTC

Making a magnetic coupling is a hard process since the impeller rotates at speeds up to 3000 rpm. In order for the magnets to be coupled at these speeds, they must be very strong. As in literature, Neodymium-Iron-Boron (NdFeB), neodymium magnets are known to be the most powerful magnets, in their magnetic properties per volume at present [54]. As a result of that, this type of neodymium magnets is utilized in Heart Turcica Centrifugal. In Figure 3.7, a neodymium magnet that is used in HTC can be seen.

Figure 3.7 - An example of Neodymium Magnet used in HTC (Height = 4 mm, Diameter = 4 mm)

Neodymium magnets have the highest amount of magnetic force per volume, but their curie temperature is low. Curie temperature is the temperature where the magnet completely loses its magnetic properties. Alnico magnets and samarium-cobalt magnets have curie temperatures higher than 700 ˚C. Neodymium magnets have lower curie temperatures (310-400 ˚C) in comparison to alnico and samarium-cobalt magnets. However, alnico or samarium-cobalt magnets could not be used instead of neodymium magnets because their magnetic energy per volume is less than neodymium magnets.

Neodymium magnets are known to be the strongest rare earth magnets, and sixteen of them were placed on the bottom section of the impeller of the final design. In Figure 3.8, the placement of those magnets can be seen.

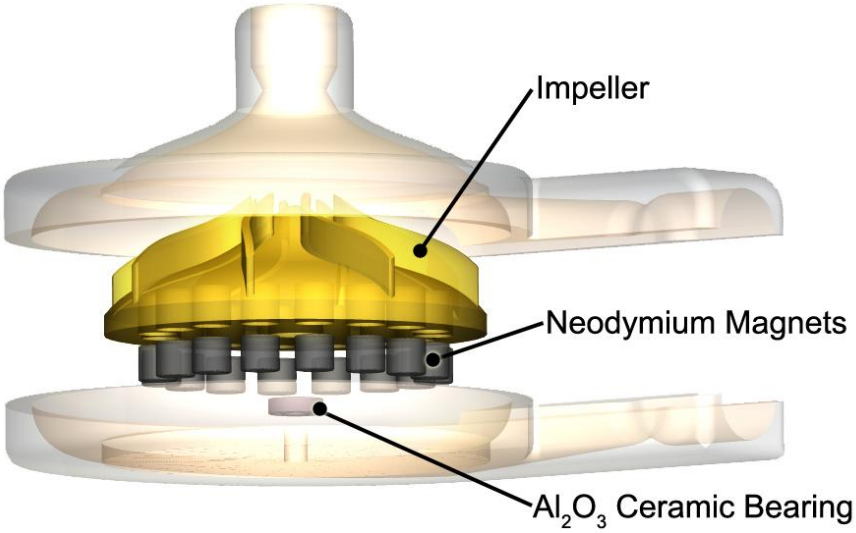

Figure 3.8 - Placement of neodymium magnets in the impeller

In order to have the strongest magnetic coupling the magnetic poles of two adjacent neodymium magnets have to be opposite. The magnetic poles are N-S-N-S-…., as a result of this sequencing the sixteen magnets on the impeller easily couples with the sixteen neodymium magnets of the motor shaft.

During the performance test there was no problem with the magnets, since there was no blood in the system. However, the situation in *in vitro* blood tests are different; even though the material (Ti-6Al-4V ELI) used is biocompatible, the neodymium magnets are not biocompatible. In Figure 3.9, the bottom side of the impeller is shown, and one can understand that after the magnets are placed into the sixteen holes opened for neodymium magnets, one side of the magnets will be in direct contact with the blood since the whole impeller will completely be in the blood.

Figure 3.9 – Bottom side of the impeller where the neodymium magnets are placed

In order to solve this problem, the magnets must be coated with a hemocompatible material. The first thinking was to coat the magnets first and then put them into the impeller bottom side, however, this was not appropriate because the holes on the bottom side of the impeller were manufactured to make an interference fit with the cylindrical magnets. If the magnets are coated with a suitable material and then placed into the holes, the coating will get destructed while tight interference fitting. As a

result, the coating of the magnets should be done after placing the magnets on the bottom side of the impeller.

The holes on the bottom side of the impeller for the neodymium magnets are designed for a tight interference fitting. The fitting is chosen to be an ‘m6’ class tight interference fit. Tight interference fit is chosen because the impeller will rotate at high rotational speed up to 3000 rpm.

The first Ti-6Al-4V ELI prototype was manufactured according to this ‘m6’ class of tight interference fit, however the estimated coatings cannot be directly tried on the impeller of the first prototype. This is because if the coating does not work properly, manufacturing a new impeller from Ti-6Al-4V ELI is time consuming as well as Ti-6Al-4V ELI is an expensive material.

In order to prevent this situation happening 10 mm x 10 mm x 10 mm sample cubes, that can be seen in Figure 3.10, of Ti-6Al-4V ELI were manufactured, then according to ‘m6’ tight interference fitting conditions, a hole in each sample was drilled. After this, neodymium magnets are tightly fitted into those holes. The sample at that situation in not ready though. The Ti-6Al-4V ELI surface, with the magnet inside, is polished and grinded till it has a surface roughness, R_a, of 0.2 μm. The polishing and grinding operation, as well as the 0.2 μm surface roughness, R_a, value will be discussed in the following chapters in detail.

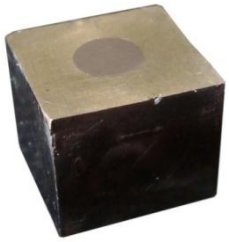

Figure 3.10 - A polished Ti-6Al-4V ELI Sample with a Neodymium Magnet in it

3.5. Trials for Diamond Like Carbon (DLC) Coating

The first choice of coating to be tried is the diamond like carbon (DLC) coating. DLC coatings are a group of materials that have at least some 'sp^3' diamond bonds and reflect properties similar to natural diamond [55]. DLC coatings are known to be strong and have excellent corrosion resistance. DLC coatings are widely used in medical applications since their superior tribological properties and good mechanical properties are followed by good biocompatibility as well as hemocompatibility [55-57]. Even though, the hemocompatibility of DLC coatings are very good, the coating process is a hard issue to deal with. There are many coating methods in order to coat a surface with DLC.

DLC coating techniques can be listed as; filtered cathodic vacuum arc (FCVA), ion beam deposition, ion plating, radio frequency plasma enhanced chemical vapor deposition, plasma immersion ion implantation and deposition (PIIID), ion beam sputtering, pulsed laser deposition, mass selected ion beam deposition and magnetron sputtering, etc [56].

Among these DLC coating techniques many of them are not suitable for coating of neodymium. The materials with magnetic properties become paramagnetic over a certain temperature. This temperature is called the Curie temperature. Most of the DLC coating methods require high temperatures more than 300 ˚C and high voltages created in the plasma. On the other hand, neodymium magnets have curie temperatures around 300 ˚C. Even though, Curie temperatures of neodymium magnets are approximately 300 ˚C, they start to lose their magnetism at a lower temperature and when temperature of the magnets reaches to the Curie temperature they become completely paramagnetic. In order to determine the temperature, that the neodymium magnets start to lose their magnetic properties, magnets were placed in an electric oven and temperature was increased gradually. At predetermined temperatures the oven was opened and the

magnetic properties of the magnets were measured by a Gaussmeter and the values were compared with the values before the heating process has begun. The results showed that the magnets lost most of their magnetism after 150 ˚C.

This lead to the conclusion that DLC coating methods, such as electron beam techniques or cathodic arc techniques, could not be used in the coating of neodymium magnets since they require very high temperatures to operate [58]. Methods like hybrid plasma assisted chemical vapor deposition (PACVD) techniques can be used since they have lower deposition temperatures of diamond like carbon (DLC) coatings in the temperature ranges between 100-150 ˚C [59-60]. In Figure 3.11, an illustration of PACVD can be seen. The necessity of using low deposition temperatures under 150 ˚C leads to the usage of techniques like PACVD to coat the neodymium magnets with DLC.

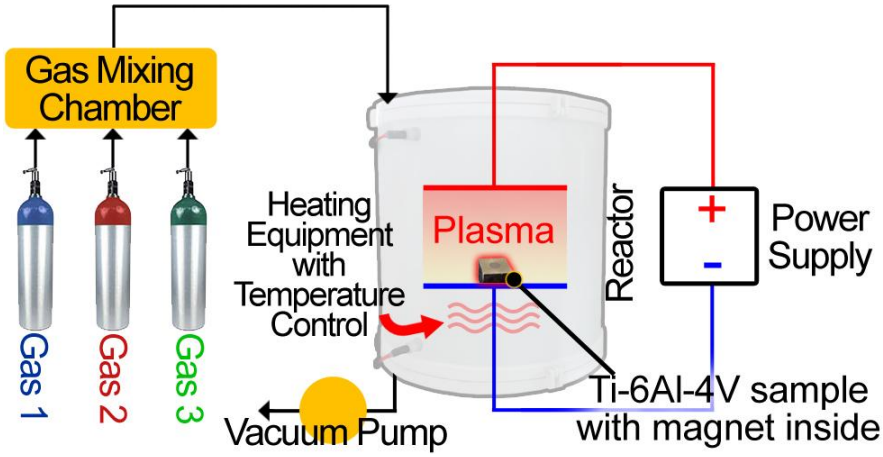

Figure 3.11 - An illustration of PACVD process

In PACVD process, suitable gases are sent into a gas mixing chamber where the gases are mixed in a suitable ratio and adjusted to necessary pressure. Then the gases are transferred to a vacuum chamber that is heated to a predetermined temperature. In this chamber a power supply provide voltage to the electrodes and the suitable gas atoms are directed on to the substrate surface; in our case on to the Ti-6Al-4V samples. As a result of this process a coating on top of the surface can be formed.

However, even though the Ti-6Al-4V ELI surfaces are coated well with the PACVD process, the surface of the neodymium magnets cannot be coated with DLC. The reason behind the failure of DLC coating on neodymium magnets is the magnetism of neodymium parts. The magnetism of neodymium parts push the atoms of carbon during the PACVD process, so they cannot form a DLC coating on top of the neodymium magnets. As a result, coating of the magnets with DLC cannot be achieved with the method that is used.

3.6. Solution for final model of HTC to get into in vitro blood test

Since the idea of using coatings have failed, another point of view was necessary to solve the problems. The problem of the final model is the driver magnets that will be in direct contact with blood. So the first idea was the use of coatings to cut this contact with the blood. However, the coatings have failed, but still there is a need to cut the contact of magnets with blood. So this thesis proposed a solution, by a major design modification. Up to this point, all of the impellers were made of a single raw material. However, the final modification that this manuscript is suggesting does not require any coating in order to cut the contact of magnets with the blood. In order to solve this problem, impeller was designed of two pieces. In order to cut the contact of magnets with the blood an additional surface of Ti-6Al-4V ELI must be placed on the bottom surface of the impeller, however it is a hard issue to deal with. The extra material that would cover the bottom side of the impeller and blood contacting surfaces of the magnets must be thin, because as the material at the bottom side of the impeller get thicker, magnets on the impeller get away from the driver magnets on the shaft. If the distance, between driver magnets and the magnets on the impeller, exceeds a critical level; the impeller cannot be rotated. In order to rotate the impeller safely, the anticipated thickness of the extra Ti-6Al-4V ELI thickness is 300 μm at most.

As a result, 300 µm thick plate of Ti-6Al-4V ELI was planned to be used, however the method for placing a 300 µm thick plate is a complicated issue. First problem is that a 300 µm thick plate could not be placed easily on the bottom side of the impeller because a plate as thin as 300 µm will bend. Even if it does not bend, a hole must be drilled in the center of this plate for the placement of Al_2O_3 bearing. As a result the attachment of a thin plate of Ti-6Al-4V ELI is not possible, because of the bearing hole, this thin plate will eventually fail.

Another approach must be employed; as a result the design of the impeller is changed, without changing the blade geometries and total height. In Figure 3.12, the solid CAD model of the final design of the impeller can be seen.

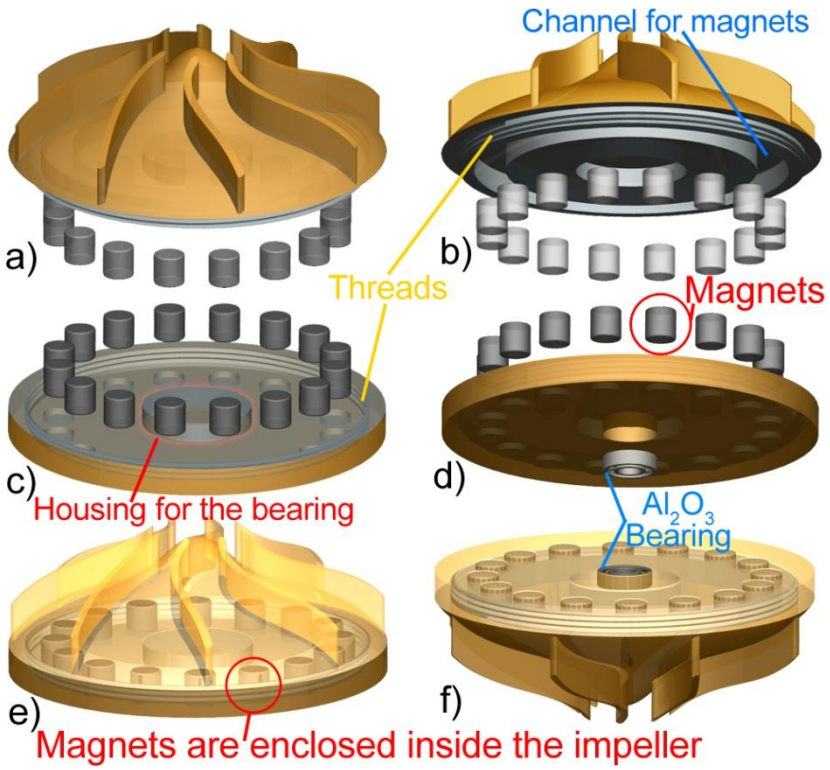

Figure 3.12 - The New Design of the Impeller; a) top side of upper element, b) bottom side of upper element, c) top side of lower element, d) bottom side lower element, e) top view of the impeller mounted, f) bottom view of the impeller mounted

The new design of the impeller is composed of two components; the upper component of the design (Figure 3.12 a and b) is the element where the blades will be machined, the lower component of the design (Figure 3.12 c and d) is the element which will be used as the blockage of contact between the magnets and the blood. Since a thin plate with a thickness of 300 μm would not have enough strength, the bottom side of the impeller is designed to be 1000 μm, however the thickness is decreased to 300 μm on the sections where the magnets will be placed (Figure 3.12c). At these sections holes with a diameter of 4 mm (diameter of the magnets = 4 mm) and 0.7 mm of depth are drilled. These holes also form a template for the magnets to be placed.

Another function of the lower element of the impeller is the threads on the inner side of the impeller. These threads on the inner side of the lower element connect to the threads on the outside of the upper element. During this connection process, while the magnets are also inside the holes of the lower part, magnets locate themselves into the channel that is opened on the upper element of the impeller. In Figure 3.12b this channel can be seen.

The upper and lower elements of the impeller are mounted together with the following process. First the magnets are placed into the sections on the lower element, then in order to keep them stand still, driver magnets are located on the bottom side of the impeller. At this point the upper element of the impeller is placed on top of the lower element carefully. While the beginnings of the threads both at the upper and lower elements meet, the upper part is rotated gently till the mirror surfaces on the upper and lower parts touched to each other. However before screwing the upper and lower elements a suitable polymer will be applied to the threads in order to make it leak proof.

Subsequent to connecting upper and lower elements the impeller is ready (Figure 3.12 e and f). Following this, Al_2O_3 bearing is tightly fitted into the hole (Figure 3.12d)

that was opened inside the bearing housing (Figure 3.12c) during the manufacturing process.

In Figure 3.13, solid CAD model of the final design including housings can be seen.

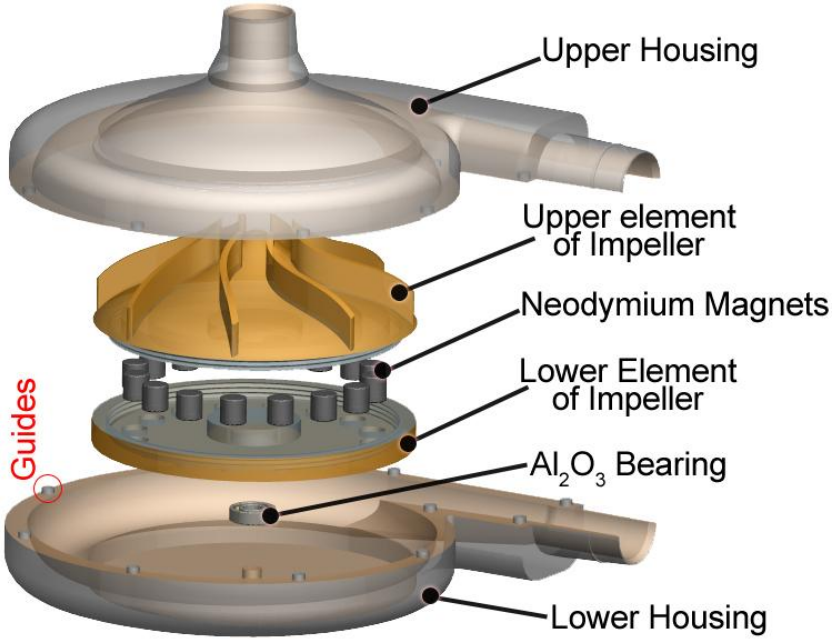

Figure 3.13 - Solid CAD model of the Final Design

After designing the impeller, the housing of the final model was modified with minor changes. First change is the guides added to the housings; these guides will ensure that the upper and lower housings fitted perfectly. The other design change is the addition of tubing connections; in the model prior to this one, the tubing connections required an additional element however for this final design the tubing that will be used in the *in vitro* blood test will be connected to the HTC LVAD directly.

The design is updated without changing the fluid passing geometry inside the HTC LVAD; no change has been made on the volute. Moreover, the overall height of the impeller is kept the same as before. Yet the final design still needed to be tested before manufacturing it from Ti-6Al-4V ELI. As a result, a prototype was manufactured from

acrylic glass. The acrylic glass model can be seen in Figure 3.14. Not only it was manufactured but also a performance test with blood analogous fluid has been made. In Figure 3.15, results for the performance test can be seen.

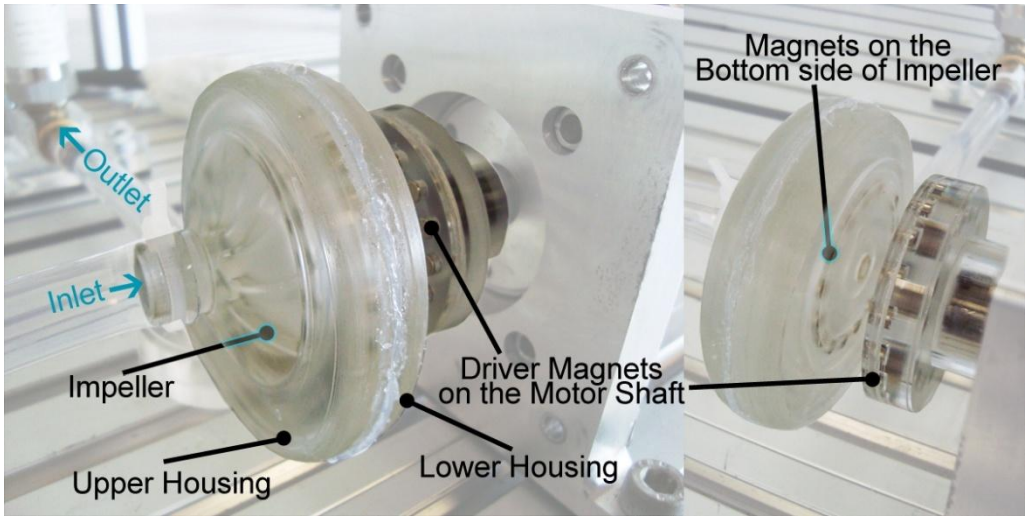

Figure 3.14 - Prototype of Final Design made of Acrylic Glass

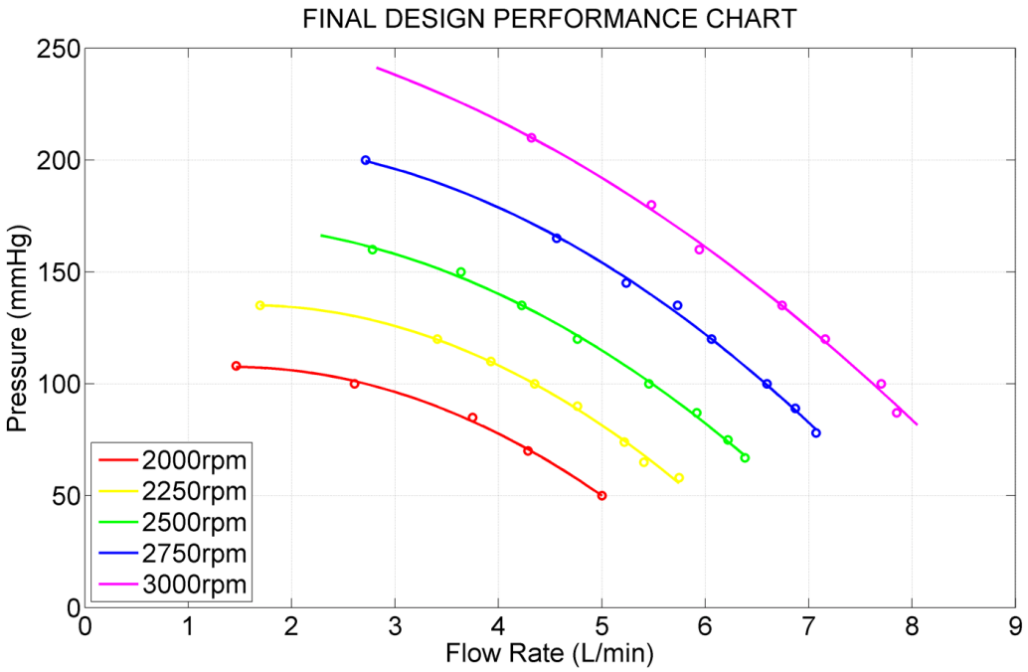

Figure 3.15 - Performance Chart for Final Design (Flow Rate vs. Pressure)

The results of the performance test show that this model can supply blood to the body with enough pressure and flow rate. Not only it can create a pressure difference of 200 mm Hg but also it can supply blood to the body with a flow rate of approximately 8 L/min if necessary. The pump also achieves the 5 L/min flow rate versus a pressure head of 100 mm Hg at 2350 rpm, which is a satisfying rotational speed in comparison to the pumps in literature where the pumps in the literature reach the 5 L/min flow rate versus a 100 mm Hg pressure head around a rotational speed of 2000 rpm [26, 61-62].

Chapter 4 - MANUFACTURING PROCESS OF HEART TURCICA CENTRIFUGAL FOR *IN VITRO* BLOOD TESTS

The final design of the HTC has performed well in the tests and as a result the manufacturing process of this model has begun. The first thing to determine in the manufacturing process is the selection of the materials and preparation of them. In the case of HTC the material is chosen to be Ti-6Al-4V ELI (Astm Grade 23) since the hemocompatible properties of this material makes it a perfect choice [43]. Moreover, its strength is a good advantage of Ti-6Al-4V ELI, however machining titanium alloys is a complicated process. Titanium alloys are known with their high strength to density ratio, moreover with their biocompatibility. Nevertheless the difficulty of machining these alloys is an important issue to deal with [63]. As a result of those, cutting parameters must be chosen carefully.

In a machining operation there are many parameters to adjust, but among those most important parameters are depth of cut, a_p [mm], width of cut, a_e [mm], surface speed, V_c [m/min], feed rate, F [mm/min], feed per tooth, f_z [mm/tooth], etc. Determination of these parameters is a process that must be done step by step.

The first step of determining these parameters is to choose the suitable tools to manufacture your part; at this very first step the only consideration is the ability of the cutting tools to cut the material; for example if the model to be manufactured has a slot with a width of 12 mm, it is sure that this model cannot be manufactured with a cutting tool which has a diameter of 16 mm. As a result the user must choose the cutting tools carefully, so that the cutting tools can enter all the slots, holes, closed areas, etc. The next assessment is to decide the machining operations to be accomplished; generally those operations are roughing, semi-finishing and finishing operations. However,

according to the complexity of the model to be manufactured additional operations such as super-finishing or additional roughing operations may be necessary.

At this step of the process, cutting tools and operations according to the choice of tools were organized. Subsequent to this step, depth of cut, a_p and width of cut, a_e must be chosen according to the properties of cutting tool. Following to this cutting speed, V_c and feedrate, F must be defined according to the limitation of the tool manufacturer and the properties of the material that was going to be manufactured.

Finally, after determination of all these steps, a computer aided manufacturing (CAM) module should be employed to prepare the G-codes (also called NC codes) of the tool paths and parameters chosen. G-codes are the programming language that is read by a computer numerical control (CNC) machining center. G-codes contain information about the tool paths that the cutting tool will follow. Tool paths are points in the Cartesian coordinate system, and the CNC controller take these point data from the g-code and it moves between two cutter locations by a liner or circular path. G-codes also include information about feedrate values as well as spindle speed. An example g-code can be seen in Figure 4.1.

In order to create a G-code a CAM module should be used, in order to prepare the necessary G-codes, Unigraphics NX6 CAM module was used, since the solid CAD models were also prepared in this program. In Figure 4.2, one can see the operations build in the CAM module of the Unigraphics NX6. Figure 4.2b shows the roughing operation with an end-mill cutting tool, following to that in Figure 4.2c an end-mill with a smaller diameter is used to machine the surface more precisely. Finally a ball-end mill is used in order to give the final shape to the workpiece (Figure 4.2d). Once those operations are completed, the workpiece is ready to be used. However, if the surface roughness is an important case; then the surface must be further polished with suitable polishing equipment. The polishing operation of Heart Turcica Centrifugal will be mentioned in the following sections.

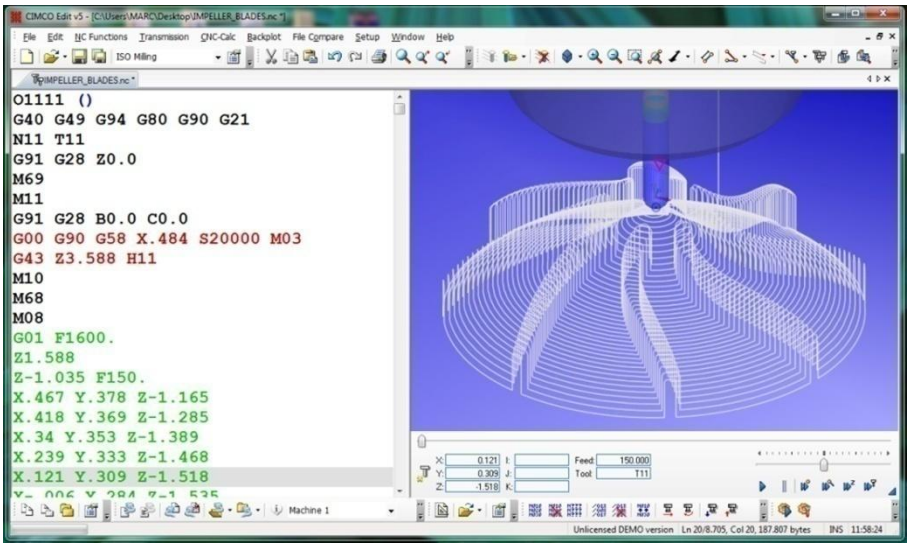

Figure 4.1 - A portion of a G-code and representation of tool path

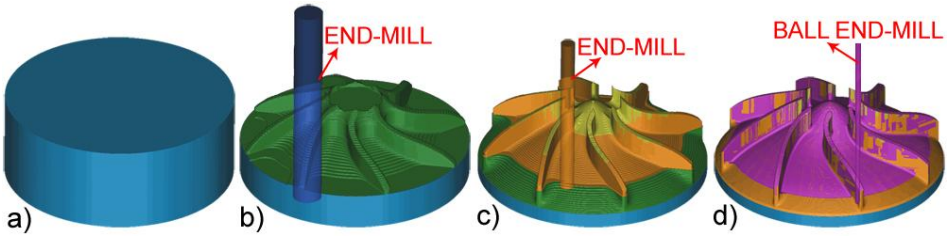

Figure 4.2 - Machining Operations of the impeller; a) Workpiece before operations, b) Roughing, c) Semi-finishing, d) Finishing

Figure 4.3 - Some of the cutting tools used in manufacturing

4.1. Machining

There were many machining operations, which were prepared in order machine 4 Ti-6Al-4V ELI parts (Upper Housing, Lower Housing, Upper component of the Impeller, Lower component of the Impeller) and 2 acrylic glass parts which will hold the upper and lower housing together in their place during the *in vitro* blood test.

There were 49 machining operations (NC codes) from roughing operation to super-finishing operations. The cutting speeds of the operations vary between 45 m/min to 135 m/min; moreover feedrates were between 40 mm/min to 250 mm/min. The estimated machining time of the operations is approximately 105 hours.

The machining center used is Mori Seiki NMV5000 DCG 5 axis machining center that was located in MARC (Figure 4.5). This machining center has a spindle that can achieve the rotation speed of 20,000 rpm as well the ability of using coolant fluid enables to material to be machined faster and safer; since the temperature of the machining area is controlled by the coolant.

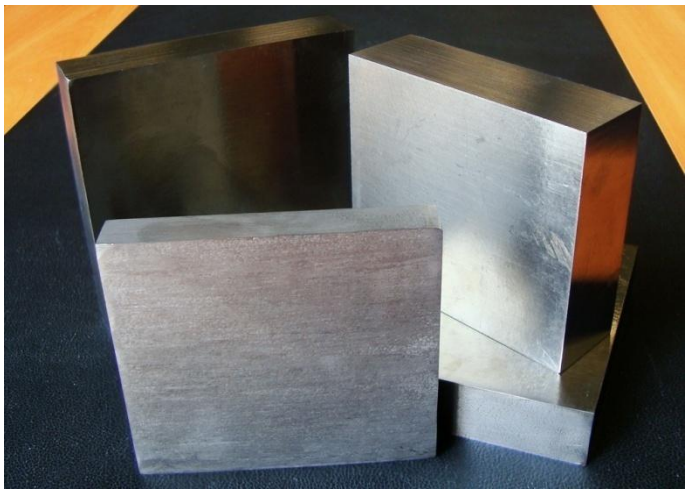

Figure 4.4 - Ti-6Al-4V ELI Grade 23 Raw Materials before machining

The raw materials seen in Figure 4.4 were placed onto the table of the machining center. The workpieces to be machined were fixed to the table with suitable fixture

elements. Majority of the machining operations were performed in the Mori Seiki NMV5000 DCG 5 axis machining center. In this machine milling operations were performed. But in order to machine the threads on the upper and lower components of the impeller, a Majak Nexus 150 lathe was used.

Figure 4.5 - Mori Seiki NMV5000 DCG 5 axis machining center

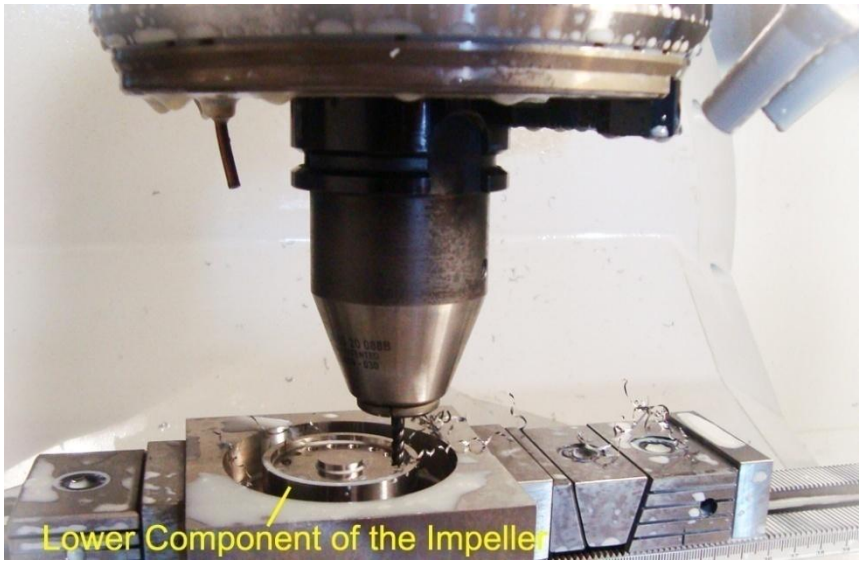

Figure 4.6 - Lower Component of the Impeller during machining

Workpieces were then machined with the operations created by the Unigraphics NX6 CAD and CAM module.

After, the machining operations, even though the final shapes of the parts were obtained. The surface of the parts, especially the blood contacting surfaces of the parts must have a better surface roughness value. For blood contacting surfaces, the surfaces must be smooth and have at a maximum surface roughness value, R_a, of 0.2 μm.

4.2. Polishing

The maximum surface roughness value, R_a, of 0.2 μm was determined by the researchers by many investigations [26, 64]. If the surface roughness value of the blood contacting surfaces exceeds this critical level, then the hemolysis rates increases which means the breakdown of red blood cells increases, which results in the release of hemoglobin into the surrounding fluid. In order to prevent this from happening, blood contacting surfaces were polished and grinded by equipment that can be seen in Figure 4.7.

Figure 4.7 - Rotary polishing equipment with various head and polishing stones that were used

Polishing stones were used to get rid of the scratches on the surface and then by the help of a hand type polishing equipment with a rotary head, which uses spiral stones, various rotary polishing heads with diamond pastes, were used to reduce the surface roughness value of the blood contacting surface of the final Ti-6Al-4V ELI prototype. The polishing procedure is a step by step process; in which one has to accomplish all the steps in order have a good surface quality. The polishing starts with polishing stones with grain sizes such as 120, then a polishing stone with a finer grain size such as 320 must be used. After the polishing stones, polishing with diamond paste with the rotary hand piece must be performed. The use of diamond paste procedure is almost the same with polishing stones. First diamond paste with a rough grain size such as 25 μm was used on the surface, than finer grain sized diamond paste such as a diamond paste with 3 μm grain size is used by the suitable rotary polish heads. After following all of these steps, with lots of polishing hours a surface roughness value, R_a, under 0.04 μm was achieved.

Figure 4.8 - Final Prototype that will be tested in *in vitro* blood tests

In Figure 4.8, machined workpieces after the machining operations and polishing procedure can be seen. This final prototype was ready to be used in *in vitro* blood tests.

In the following chapter details about the *in vitro* blood testing procedure and the results of those tests will be discussed.

Chapter 5 - *IN VITRO* BLOOD TESTING PROCEDURE AND RESULTS

A left ventricular assist device is a medical equipment that is designed to be used in humans. However since the life of a human cannot be ventured by direct trials of the machinery inside the body, another method must be employed. As a result, in order to test the functionality and performance of a newly designed LVAD, a suitable testing procedure must be used. The testing procedure in according to the testing environment is separated into two groups; *in vitro* testing and *in vivo* testing. The Latin translation of *in vitro* is meaning "*within the glass*"; as a result *in vitro* tests are performed out of living organisms but in a control environment. On the other hand *in vivo* means "*within the living*" in Latin; therefore *in vivo* testing takes place in living organisms or living environment; animal testing and clinical trials of devices fall into this group. Commonly, in order for a device to be tested in clinical trials, it has to perform well in *in vitro* tests. As a result for a blood pump to pass to the level of animal testing and clinical trials, it should perform well in *in vitro* blood testing.

In order to form a common application of *in vitro* blood testing for continuous flow blood pumps between the studies; in 1997, the international standard organization, "ASTM International" has published two international standards. The first standard was about the selection of blood and the procedure to take the blood out of the body, which is the ASTM International Standard F 1830 – 97 [65]. Following that standard the same institution also published another standard, ASTM International Standard F1841 – 97, that gives information about the *in vitro* blood testing procedure with all of its aspects [66]. Both of these standards were reapproved in 2005, since they are arranged well in order to evaluate hemolytic performance of blood pumps.

5.1. Selection of Blood for *in vitro* Evaluation of Ventricular Assist Devices

In order to test the hemolytic performance of a ventricular assist device, the blood must be chosen carefully, since it is the most important component in the *in vitro* blood testing of the HTC LVAD. ASTM International F 1830 – 97 gave detailed instructions for the blood source, the method for it to be collected and storing procedure before the in vitro blood test [65].

The first issue in the test is selection of the blood. International standard recommends the use of fresh bovine or porcine blood. The donor animals should have no signs of diseases and their body temperatures should be normal. Moreover, the hemological profiles of the animals are supposed to be at acceptable levels and the blood should be used *in vitro* blood testing in the first 48 hours. On the other hand fresh human blood is also recommended. If fresh human blood is used, the usage of blood *in vitro* blood testing should be done in the first 24 hours. If the collected bloods are not used immediately, it should be refrigerated at 2 to 8 ˚C, until the usage. However, the standard strongly suggests the usage of bovine blood since healthy cattle are not affected by drawing several units of blood from them.

The collection of blood is also explained in detail in the international standard, a large bore needle (14 G or larger) must be used when collecting the blood sample and the blood should be drawn into a blood bag with anticoagulants. Cirrate phosphate dextrose adenine (CPDA-1) is one example for anticoagulants that can be used. If CPDA-1 will be used as an anticoagulant, then 63 mL of this solution must be added for 450 mL of blood sample. Total volume of the blood with anticoagulants should be 450 ± 45 mL.

During the transportation of the blood, the blood should be refrigerated between 2 to 8 ˚C, and before using it *in vitro* blood test, it must be warmed to 37 ± 1 ˚C with water bath.

5.2. Evaluation of Hemolysis in Continuous Flow Blood Pumps

Hemolytic performance of a ventricular assist device should be tested according to the international standard, ASTM International F 1841 – 97 [66]. The international standard explains the method to estimate the hemolytic performance of a continuous flow ventricular assist device in detail.

In order to determine the hemolytic performance of a continuous flow ventricular assist device, some measurements must be made to the blood used in order to see the effect of blood pump on the blood damage. The international standard especially suggests the calculation of two equations which are; Normalized Index of Hemolysis (*N.I.H.*) and Modified Index of Hemolysis (*M.I.H.*). These values can be calculated according to the following two equations listed in the standard;

$$N.I.H.g\ /\ 100l = \Delta freeHb \times V \times \frac{100 - Ht}{100} \times \frac{100}{Q \times T} \qquad (1)$$

$$M.I.H. = \Delta freeHb_{mg} \times V \times \frac{100 - Ht}{100} \times \frac{10^6}{Q \times T \times Hb} \qquad (2)$$

Here in these formulas;

- *V* is the circuit volume [L],
- *Q* is the flow rate [L/min],
- *T* is the sampling time interval [min],
- *Ht* is the percentage hematocrit [%],

- Hb is the total hemoglobin concentration at the beginning of the test [mg/L],
- $\Delta freeHb$ is the increase in the concentration of plasma free hemoglobin over the sampling time interval [g/L],
- $\Delta freeHb_{mg}$ is the increase in the concentration of plasma free hemoglobin over the sampling time interval [mg/L].

Along these calculations, *M.I.H.* is recommended in order to reflect the degree of hemolysis rate generated by the blood pump. However, in literature generally *N.I.H.* levels were given in order to compare HTC LVAD with the pumps in literature, both of these values will be calculated.

The test setup is a simple blood circulating loop shown in Figure 5.1. In order to begin test, polyvinyl chloride tubing with a total of 2 m length and 9.5 mm inner diameter must be connected to the inlet and outlet of the blood pump and the two other ends must be connected to the blood reservoir which has a sampling port. The temperature of the blood circulating must be controlled during the test and a flowmeter after the outlet of the pump should be used in order to follow the flow rate. Pressure sensors before and after the blood pump must be used in order to arrange the pressure level necessary during the test. The pressure head difference of the pump should be adjusted by a clamp that is placed after the outlet of the pump and before the flowmeter.

The testing procedure begins with the selection of blood which is explained in the previous heading. After collecting the blood from a suitable source, free plasma hemoglobin should be controlled. If the plasma free hemoglobin of the sample blood is more than 20 mg/dL, then it should not be used. When a suitable blood sample is collected before transferring it to the test loop through the reservoir, test loop should be filled with phosphate buffered saline which should be circulated in the loop for about

20 min. After 20 min this solution should be drained, and then the blood should be transferred into the reservoir bag. Air collected inside the reservoir bag must be removed through the sampling port on the reservoir.

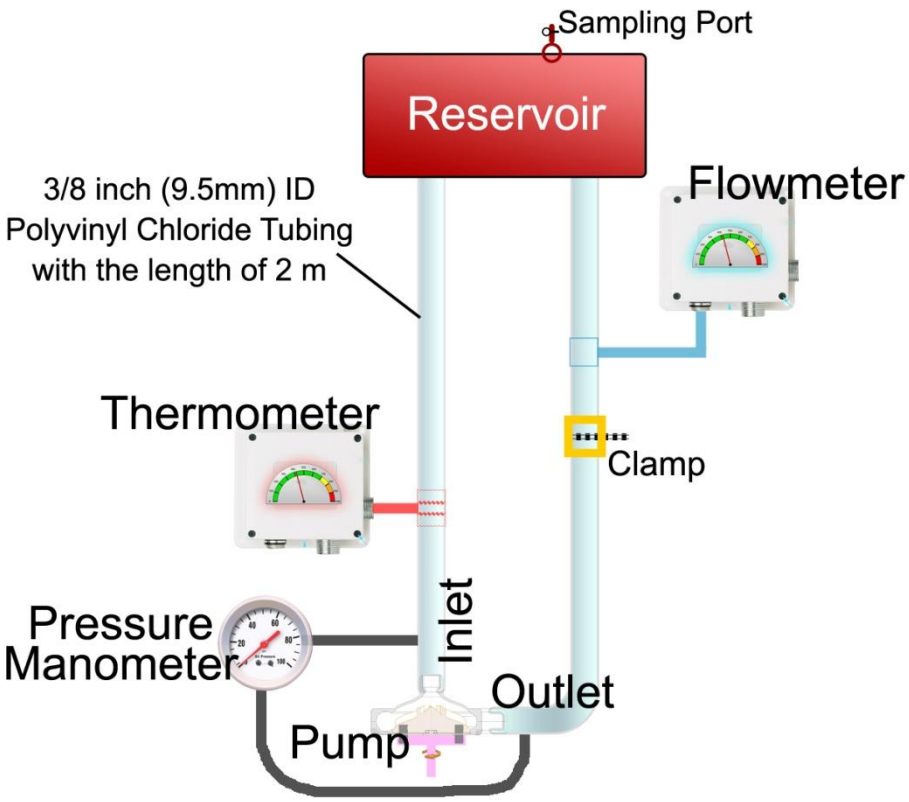

Figure 5.1 - Test Loop for Hemolysis Test

After accomplishing all of these steps, pump should be adjusted to rotate to a flow rate of 5 ± 0.25 L/min where it creates a pressure head difference of 100 ± 3 mm Hg in order to simulate left heart assist application. During the test the blood temperature should be kept in 37 ± 1 ˚C by a water bath.

Subsequent to the start of the test, the "*time zero measurements*" should be taken after circulating the blood for about 5 min inside the loop to ensure a complete mixing. After taking the first blood sample for test duration of 6 hours, at every hour a blood sample of 1 mL should be taken through the sampling port. Sample blood is then used to calculate the *N.I.H.* and *M.I.H.* values.

There were several studies about centrifugal blood pumps in literature, and some of these devices were achieved to the level of *in vitro* blood testing. Moreover, those studies were performed *in vitro* blood test and publish their results in the literature. From the results of other studies, a hemolytic performance comparison of HTC LVAD with the pumps in literature and clinically available pumps can be made.

In literature, *Normalized index of Hemolysis* values varies between 0.0001 to 0.0096 g/100L [67-70]. However, the clinically available centrifugal blood pumps have *N.I.H.* values under 0.003 g/100L [67]. Therefore, in order HTC to be a clinically available centrifugal blood pump, the *N.I.H.* values obtained from in vitro blood test should be close to those values.

Chapter 6 - CONCLUSION & FUTURE WORK

6.1. Conclusion

Ventricular assist devices are life savers since there are lots of patients with advanced cardiovascular diseases, but there are not enough donors for heart transplantation. Those patients require mechanical circulatory support systems, such as LVADs. However there are many patients who cannot afford these support devices because of the expensive implantation price of these devices.

During this thesis study, many major and minor changes were performed in order to take the HTC LVAD project to the level of *in vitro* blood tests. Finally, the final prototype pump was manufactured of bio and hemocompatible grade Ti-6Al-4V ELI and which will be used in the *in vitro* blood tests.

After several years of development and manufacturing period, HTC LVAD will offer those patients a hope as a Bridge-to-transplantation, as a Bridge-to-recovery or as a destination therapy. The final design with its simplistic model offers an optimum solution among the left ventricular assist devices.

6.2. Future Work

The project's main motivation was its critical function. The device developed is directly a life saver, which can be used in patients with advanced cardiovascular diseases. Since, the final objective of HTC LVAD is implantation of this device into humans, the project should continue. However the results of *in vitro* blood tests must be carefully examined. If the results are found to be well, then *in vivo* animal testing

should begin. Animal testing can be done with the same prototype that was used in *in vitro* blood tests.

If the *in vivo* animal testing gives out satisfying results, then clinical trials with human volunteers should be planned. However, prior to the human clinical trials HTC LVAD must be updated by a team of engineers and medical doctors. In order for HTC LVAD to be used in humans wall thicknesses should be reduced, inlet-outlet channels should be re-designed according to the human conditions, if it is possible the overall size could be reduced without changing the design parameters obtained in past by HTC LVAD project.

Last of all, the further development of HTC LVAD should be made for it to become first Turkish LVAD, but its price should be kept at minimum for it to become a hope for the patients.

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