In Vitro Blood Tests of New Heart Turcica Centrifugal as the Artificial Heart Pump System

by

Suat CÖMERT

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

Suat CÖMERT

and have found that it is complete and satisfactory in all respects,

and that any and all revisions required by the final

examining committee have been made.

Committee Members:

Prof. Dr. İsmail Lazoğlu (Advisor)

Prof. Dr. Süha Küçükaksu

Assoc. Prof. Dr. Erdem Alaca

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ABSTRACT

Heart failures are the most common diseases causing deaths globally. According to the report of International Society for Heart and Lung Transplantation, there are approximately 50,000 patients all around the world who are candidates for heart transplant and only about 5,000 heart transplantations can be performed each year in the world. According to the data announced by Turkish Ministry of Health, about 300 patients were registered in the waiting list for heart transplantation and only 63 heart transplantations were performed in 2013. Whereas, the unregistered number of patients waiting for heart transplantation in Turkey are estimated around 3,000 by the cardiovascular surgeons. Therefore, artificial heart pump and support systems become the only solution for these patients. Ventricular Assist Devices (VADs) play a vital role in the survival of these patients, however imported heart pumps are not affordable for every heart patient due to their high prices. Consequently, research on the development of VADs is of vital importance.

This research is a part of developing New Heart Turcica Centrifugal (NHTC) as the first implantable left ventricular assist device (LVAD) produced in Turkey. It covers in vitro blood tests performed with the aim of evaluating the hemolytic performance of the developed LVAD and investigates the effects of different bearing designs on hemolysis. Five prototypes with different bearings were designed and manufactured for the blood tests under various conditions. The tests were conducted in a small scale test loop which was built in order to minimize the amount of blood to be used. Normalized index of hemolysis (*N.I.H.*) was calculated for these tests according to American Society for Testing and Materials (ASTM) F 1841-97 standards. The final prototype of this study showed excellent performance by achieving *N.I.H.* values of 0.002 g/100L where blood pumps are considered antitraumatic as long as their *N.I.H.* values remain under 0.01 g/100L.

ÖZET

Günümüzde sık rastlanan ileri seviye kalp hastalıkları dünya çapındaki hastalığa bağlı ölümlerin nedenleri arasında başı çekmektedir. Uluslar arası Kalp ve Akciğer Nakli Derneği'nin yayınladığı rapora göre, yaklaşık olarak dünyada 50.000 hasta kalp nakli beklemektedir. Buna karşın dünya genelinde yılda ortalama 5.000 kalp nakli gerçekleşmektedir. T.C. Sağlık Bakanlığı'nın verilerine göre 2013 yılında Türkiye'de 298 hasta kalp nakli bekleme listesine kaydedilmiş ve aynı yıl içerisinde 63 kalp nakli ameliyatı gerçekleştirilmiştir. Bunun haricinde kayıtlı olmayan ve kalp nakline ihtiyaç duyan hasta sayısının 3.000 civarında olduğu tahmin edilmektedir. Hal böyleyken mekanik dolaşım destek sistemleri bu hastalar için tek çözüm olarak öne çıkmaktadır. Karıncık destek cihazları bu hastaların hayatta kalması için hayati bir öneme sahiptir. Buna karşın yurtdışından ithal edilen bu sistemlerin maliyeti her bütçe tarafından karşılanamayacak ölçüde yüksektir. Buradan yola çıkarak karıncık destek sistemleri üzerine yapılan araştırmaların kritik öneme sahip olduğu sonucuna varılabilir.

Bu çalışmada Türkiye'deki ilk vücut içerisine yerleştirilebilir sol karıncık destek cihazı olan Yeni Heart Turcica Centrifugal (NHTC)'ın geliştirilmesi amaçlanmıştır. Çalışma ana hatlarıyla, geliştirilen cihazın hemolitik performansını değerlendirmek amacıyla yapılan laboratuvar ortamındaki kan testlerini ve farklı yataklama tasarımlarının bu performansa olan etkilerinin incelenmesini içermektedir. Farklı yataklama tasarımlarına sahip olan dört farklı prototip üretilmiş ve bu prototiplerle sekiz kan testi gerçekleştirilmiştir. Testler donörlerden alınacak olan kan miktarını minimize etmek amacıyla küçük ölçekli bir deney düzeneği kullanılarak yapılmıştır. Bu testlerden beşi için normalize edilmiş hemoliz indexi ASTM F 1841-97 standartlarına göre hesaplanmıştır. Üretilen son prototip hemoliz ve sağlamlık anlamında tatmin edici sonuçlar göstermiş ve uluslar arası standartlara uygun büyük ölçekli testler için cesaret vermiştir.

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This thesis is dedicated to the memory of deceased Prof. Dr. Oğuz Kerim Başkurt.

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NOMENCLATURE

R_a	Surface Roughness [μm]
N.I.H.	Normalized Index of Hemolysis [g / 100L]
V	Circuit volume [L]
Q	Flow rate [L/min]
T	Sampling time interval [min]
Ht	Hematocrit percentage [%]
Hb	Total hemoglobin concentration before the test [mg/L]
$\Delta freeHb$	increase in the free plasma hemoglobin concentration over the sampling time interval [g/L]
$\Delta freeHb_{mg}$	increase in the free plasma hemoglobin concentration over the sampling time interval [mg/L]

Chapter 1 - INTRODUCTION

Congestive heart failure is one of the most frequent diseases all around the world. It occurs when the heart loses its functionality to pump sufficient blood through the body to meet the demands of the metabolism [1]. According to a report published by World Health Organization (WHO) Global Health Observatory program in 2011, cardiovascular diseases take place on the top with one third of the mortalities caused by diseases in the world [2]. The picture in Turkey is even worse according to Turkish Statistical Institute. Deaths due to cardiovascular diseases constitute 38% percent of deaths resulting from diseases in Turkey. Nevertheless roughly 3,000 people are hoping for heart transplantation in order to clutch onto the life. However, only about 70 heart transplantation operations are performed in Turkey per year on average due to insufficient number of donors [4]. In these circumstances, mechanical circulatory assist systems become prominent as life savers.

Mechanical circulatory support systems are developed for the purpose of keeping patients alive until a suitable donor can be found for transplantation. These systems can be analyzed in two primary categories: Ventricular Assist Devices (VADs) and Total Artificial Hearts (TAHs). Ventricular assist devices are split into three categories in themselves. Right ventricular assist devices (RVADs) are developed to pump the blood taken from right ventricle of the heart to the lungs for pulmonary circulation. Left ventricular assist devices (LVADs) pumps the blood taken from left ventricle to the aorta and helps systemic circulation. When both of these devices are utilized together, the system is named as biventricular assist device (BVAD). If the heart of a patient cannot do its function at all, the heart is totally taken out and total artificial heart (TAH) is implanted to the patient in order to take on the task of the heart.

This study is a part of developing first implantable left ventricular assist system in Turkey, New Heart Turcica Centrifugal (NHTC). Left ventricular assist devices (Figure 1.1) are most commonly used mechanical circulatory support systems. The LVAD system consists of a pump, control and power units. The pump can be either inside the body (incorporeal) or outside the body (extracorporeal). The power and control units are generally located outside the body. The patients usually carry these units underarm or around their waists attached to the belt.

Figure 1.1 An illustration of an LVAD system [5]

LVADs are utilized for prolonging surviving period of the patients until finding a donor for transplantation. This is called bridge-to-transplantation. Another long term usage area of the LVADs is bridge-to-recovery. In this case, LVAD helps the heart to improve its cardiac function and even after removal of the LVAD, heart transplantation is no more needed. Another usage of LVAD is destination therapy where LVAD is used as permanent support in patients who are not candidates for heart transplantation. While LVADs have such a vital importance, their high costs prevent them to be a hope for low-incomers. The cost of a LVAD system in Turkey is about €80,000. This fact is another source of motivation for this study, since NHTC is aimed to be a hope for some patients who need such solutions.

Throughout the evolution of blood pump development, several types of pumps came up such as pulsatile blood pumps, continuous centrifugal pumps and continuous axial pumps were studied and compared [6]. Comparing to the others, continuous centrifugal pumps have aroused more interest for their three main advantages such as high durability [7], high efficiency [8] and less vulnerability to the failures [6].

Blood pumps are also divided into three groups in themselves considering their technological features [9]. First generation pumps are generally pulsatile devices with large sizes and based on pneumatic actuation through a moving chamber and valves. These devices are extracorporeal. In second and third generation blood pumps, continuous blood flow is provided based on increasing the blood pressure by means of a rotation of an impeller. The only difference between second and third generation blood pumps is the bearing method. In second generation pumps mechanical bearings are employed through a shaft or magnetic coupling, where rotation of the impeller is supported by magnetically levitated or hydrodynamic bearings.

Researchers in Manufacturing and Automation Research Center (MARC) at Koç University have been working on the development of NHTC, first implantable left ventricular assist system in Turkey. NHTC is under development as a second generation centrifugal blood pump for long term usage. There are some reasons for deciding on a second generation centrifugal pump. First of all, the second generation pumps have proven themselves to be durable since late 90s and have examples of long survival periods. Secondly, the second generation pumps can be developed with low costs which will enable more people to afford them. The reason for preferring centrifugal pump concept to axial pump concept is the fact that axial pumps operate at very high rotational speed which results in excessive wear on the pump components. Centrifugal pumps are able to operate at relatively lower rotational speeds, therefore they are less vulnerable to mechanical wear which makes them more durable [10].

Over the years, researchers at MARC have made important contributions on this project [11-15]. In order to come up with an optimum design, they worked on many parameters.

The research on this project started with computational fluid dynamics analysis for different pump designs which were done by Gökhan Yıldız [11]. Onur Demir worked on determining and investigating the effects of decisive design parameters [12]. Çınar Ersanlı extended the research by working on experimental procedures and first prototype for *in vitro* blood tests was manufactured by him, however this design had some deficiencies [13]. Emre Bıyıklı conducted a research on exploring new design features by performing CFD analysis on the pumps available in the literature [14]. Finally, Fatih Şenbabaoğlu concentrated on the manufacturing of the final design for in vitro experiments which resulted from earlier developments [15].

This study mainly focuses on *in vitro* hemolysis tests with developed pump and effects of different bearing designs on hemolysis. Other issues such as pump material type, surface roughness, blood preparation and testing procedures will also be discussed.

Chapter 2 gives detailed information about state of the art in the development of left ventricular assist devices. It covers a literature review about historical background of mechanical circulatory support systems, fundamentals of LVAD development and up-to-date studies in the literature.

In Chapter 3, the steps throughout the development stage of NHTC for *in vitro* blood tests will be discussed. The deficiencies of previous designs will be listed and proposed solutions to overcome those challenges will be presented. Besides these, different bearing designs utilized for different prototypes and tests will be introduced.

Chapter 4 provides information about manufacturing the final design of this study of Ti-6Al-4V to be utilized in *in vitro* experiments based on international standards. Computer aided manufacturing concepts, machining processes in CNC machining centers and polishing procedures will be explained in detail.

In Chapter 5, *in vitro* blood testing procedure according to international standards will be presented. Following that conducted *in vitro* blood experiments, corresponding results and findings will be demonstrated.

In the final chapter, Chapter 6, conclusions will be drawn from the gained experiences in this research and the future work will be summarized.

Chapter 2 - LITERATURE REVIEW

2.1. Statistics about Cardiovascular Diseases

Cardiovascular diseases are the most frequent diseases and number one cause of deaths worldwide. In 2011, roughly 17 million people died in the world due to cardiovascular diseases which constitutes more than one third of the mortalities caused by diseases [16]. This rate is even much higher in Turkey which corresponds to 38 %. According to a report published by Turkish Statistical Institute in 2013, 142,000 Turkish citizens died in 2012 because of cardiovascular diseases where the number of deaths caused by diseases was 375,000 [94, 95]. The number of the patients who were waiting for an immediate heart transplantation reached 50,000 by the year 2007 [17]. However, only about 5,000 heart transplantations can be performed per year globally [17]. Approximately 3,000 people in Turkey are waiting for heart transplantation, however only about 70 operations can be performed per year on average due to the shortage in the number of suitable donors [4]. Therefore mechanical circulatory support systems are the only solution for these patients. Table 2.1 represents the situation in the world and Turkey.

Chandran declared that mechanical circulatory support systems can be utilized for two types of patients [20]. First one is the group of patients which cannot recover after a heart surgery and in order to decrease the load of the heart artificial circulatory support systems are implemented for a couple of weeks as bridge to recovery. Second group refers to the patients who have end-stage heart diseases and need immediate heart transplantation. These systems are implemented to these patients as bridge to transplantation. Three aspects of using an artificial organ for replacing or supporting a living structure should be taken into account: (i) response of the immune system (ii)

adaptation ability to new conditions and (iii) interrelationship of organisms and functions [21].

Table 2.1 Statistics about cardiovascular diseases

Data	Country	Source
17 million deaths because of cardiovascular diseases in 2011	Global	[16]
142,000 people died because of cardiovascular diseases in 2012	Turkey	[94]
50,000 people need heart transplantation by the year 2007	Global	[17]
5,000 heart transplant operations per year	Global	[17]
3,000 people need heart transplantation	Turkey	Dr. Küçükaksu
Approximately 70 heart transplant operations per year	Turkey	[4]

2.2. Physiology of the Human Heart and Causes of Ventricular Diseases

A normal human heart which has a weight of approximately 300 grams, beats 100,000 times in a day on average. It will contract about 3 billion times for 80 years of lifetime with the assumption of taking no rest or break [22]. The structure of a human heart is demonstrated in Figure 2.1.

Right ventricle of the heart is responsible for carrying the low-oxygen blood to the lungs. Blood returns back to the left ventricle, after being oxygenated in the alveoli of the lungs. This circulation is called pulmonary circulation [22]. The oxygenated blood is pumped to the body by left ventricle through aorta which comprises systemic circulation. Left ventricle of the heart functions as a strong pump which can create a systolic pressure of 120 mm Hg in healthy conditions [23]. In some cases, cardiac muscle cells lose their strength and they cannot contract properly anymore. This is the result of a disease which

is called fibrosis. As a result of this fact, the heart starts to expand and its pumping function weakens significantly. If the fibrosis spreads on the big portions of the areas on the heart, the patient becomes vulnerable to heart attacks. In Figure 2.2, an illustration of a fibrosis by taking an optical microscope image is presented, which shows a portion of an unhealthy heart tissue of a patient.

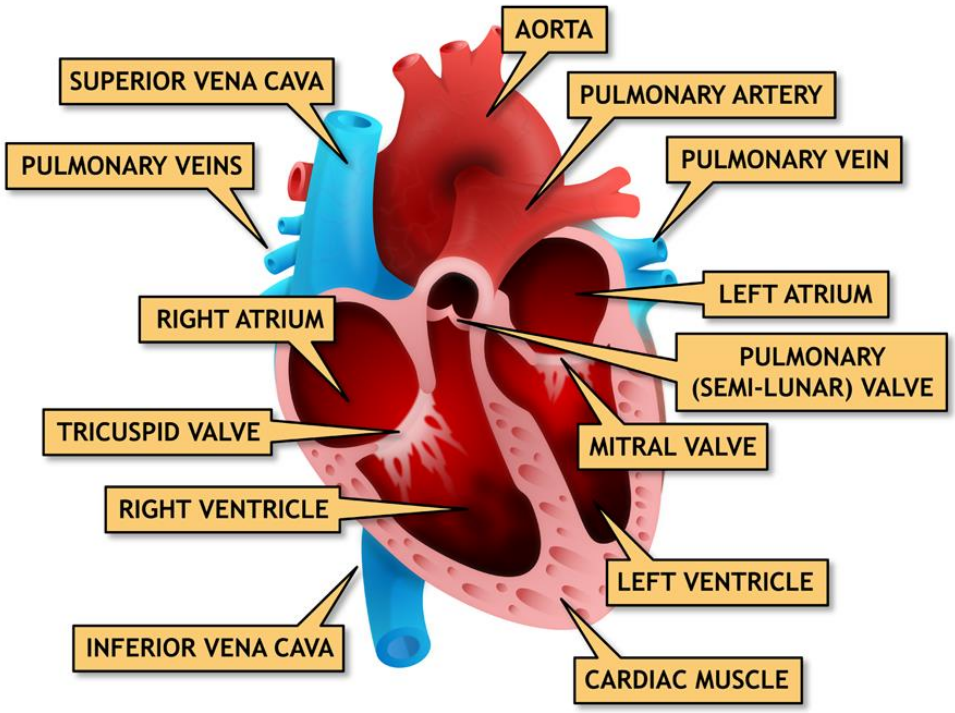

Figure 2.1 Representation of the human heart [24]

Left ventricle failures are more common comparing to the right ones, since they are more prone to the abnormalities in the cardiac muscle cells due to their relatively higher work load. In order to reduce its burden, LVADs are employed. LVAD is generally placed in abdominal cavity and its inlet is attached to the left ventricle where the outlet is connected to the aorta. In this way the blood sucked from the left ventricle can be transferred to the aorta at a certain pressure. Figure 2.2 represents the placement of the LVAD.

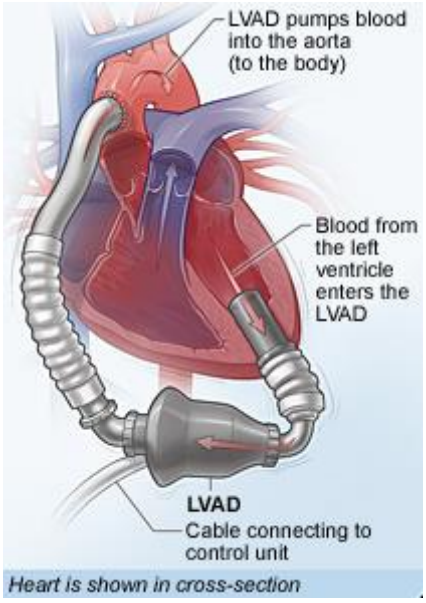

Figure 2.2 Placement of LVAD in the human body [25]

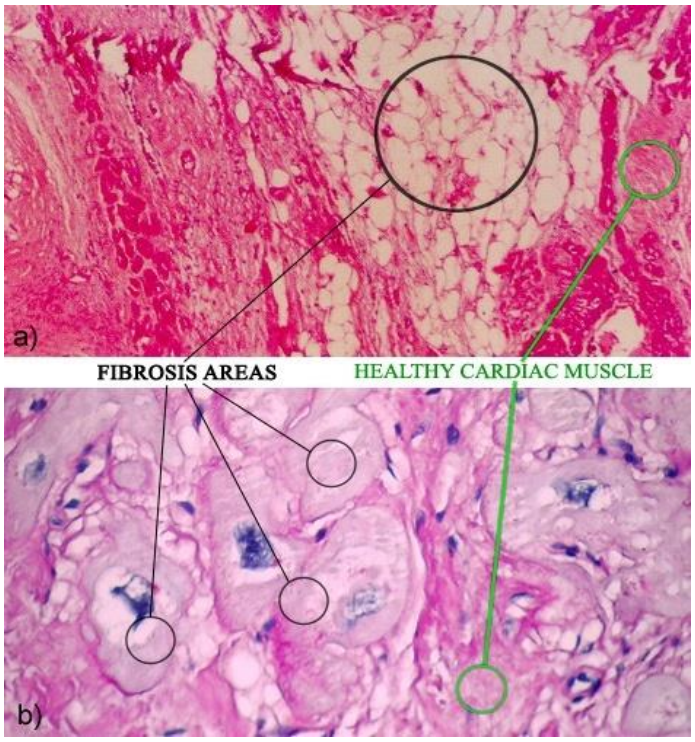

Figure 2.3 Fibrosis on a heart tissue magnification; a) 40X b) 100X (checked with Dr. Küçükaksu)

2.3. Milestones for the Treatment of Heart Diseases

The first usage of mechanical circulatory devices dates back to 1953 when John Gibbon applied a cardiopulmonary bypass to an 18 year old girl 57 years later than first successful cardiac surgery by Ludwig Rehn in 1896 [26]. The first heart transplantation to a man was accomplished by Hardy et al in 1964 [27]. In 1966, DeBakey roller pump was used for postcardiotomy support for ten days [28]. A few years later in 1967, Christiaan Barnard accomplished the first human-to-human heart transplantation [29]. The first human-to-human heart transplantation in Turkey was just accomplished one year later in 1968 by Kemal Beyazıt [30]. In 1969, the first total artificial heart (TAH) implantation was performed by Cooley et al in Texas [31].

In 1971, Dr. DeBakey reported first successful usage of LVAD in two patients with advanced heart diseases who were later on able to recover themselves completely [32]. Dr. DeBakey pointed out that LVADs could be used in the curing of the cardiovascular diseases. In 1972, a report on LVADs was published by a committee which was structured by National Heart and Lung Institute in the United States in order to study the role of LVADs as long term mechanical circulatory support systems [33]. Following this report which encouraged the usage of LVADs as recovery elements, a program was initiated by National Heart, Lung and Blood Institute (NHLBI) in which 13 patients were supported with LVADs in four medical centers. One of the patients who was supported for 105 hours by LVAD gave promising results such that the patients recovered completely after 16 months [34]. As a result of these progresses, studies on the "Development of electrical energy converters to power and control left heart assist devices" were started by NHLBI [33]. As a result of these developments, first usage of LVAD as bridge to transplantation was accomplished in Texas Heart Institute [33].

In 1979, first biventricular bypass by using two rotary blood pumps was reported [35, 36].

2.4. Historical Background of Ventricular Assist Devices

The idea of blood pumps arouse in 1950s. Dr. Wesolowski made a research on the role of the pulse in the maintenance of normal physiology in the systemic circulation during heart-lung bypass in 1955 [37]. First total artificial heart (TAH) development program was started by Kolff and Akutsu in 1957 [31]. The earliest article about continuous flow blood pumps was published by Saxton and Andrews in 1960 [38]. DeBakey and Liotta initiated the first LVAD development program in 1962 [31]. Rafferty et al developed a continuous flow blood pump in 1968 which had quite low hemolysis rates [39]. A year later, Dorman et al introduced a velocity head pump with an index of hemolysis less than 0.01 g/100L and presented their results in animals [40]. In 1974, Bernstein et al accomplished running a continuous flow pump in a calf for 24 hours and plasma free hemoglobin amount was below 21mg% [41]. However blood clotting was observed and there was a decrease in the number of platelets. Moreover plasma free hemoglobin exceeded 300mg% in the end due to the seal failure. Golding et al performed some clinical trials with Medtronic pump in 1979 and observed good hemodynamic support of patients with PFH of 39% for 24 h [42]. The same group initiated some experiments on calves in 1980 and survival period of 34 days was achieved by a nonpulsatile perfusion with centrifugal pumps [43]. In 1988, Wampler et al used an axial flow blood pump supporting five patients for the duration of from 26 to 113 hours [44]. Although the pump was operating between 25,000 and 35,000 rpm, no thrombosis, vascular injury or infection was observed except for transient hemolysis. Monties and Mesana came up with a rotary blood pump in 1990 which was based on Wankel engine principle [45]. In the same year, Akamatsu et al developed a pump with magnetically suspended impeller [46]. This pump kept a sheep alive for two years. Nose et al developed a pump in 1991, known as Baylor Gyro pump, which proved itself to be first to be used in human for long periods of time and modified version of it is still commercially available and used in cardiopulmonary bypass [47].

Until 1990s, utilization of the first generation pumps was common in the world. These are pulsatile pumps based on a pneumatic system and are for extracorporeal use for the duration of from 2 days up to two weeks. CardioWest TAH, Thoratec biventricular assist devices, TCI HeartMate I VAD and Novacor VAD are examples of first generation pumps [48].

The clinical trials of HeartMate I were initiated in 1986 by Texas Heart Institute. HeartMate I is a pneumatically driven first generation pulsatile LVAD which has an implantable pusher plate made of a titanium alloy. This pusher plate is structured by air and blood chambers to be placed upper left abdominal quadrant of the body [49]. This pump became commercially available in 1994 by the approval of US Food and Drug Administration (FDA) after 8 years of research [50]. Due to the success of HeartMate IP, a modified version of it, HeartMate VE was developed. Both of the pumps are known as HeartMate I and work using the same principle except for the fact that HeartMate VE is actuated electrically where HeartMate IP is pneumatically driven. It was reported in 2001 that HeartMate I has served to approximately 2,300 people all over the world [51].

In the last two decades, interest for continuous flow blood pumps has increased. These pumps comprise second and third generation pumps. Second generation pumps distinguish from third generation pumps with contact bearings where both type of pumps are magnetically driven. The earliest example of second generation blood pumps is known as Hemadyne Medtronic which was developed by Dr. Bernstein and Dr. Blackshear in 1965 [52]. The performance of the pump was assessed for 24 hours in calves and hemolysis and thrombosis rates were quite low. Since then second generation blood pumps have developed to correct the deficiencies of first generation pumps with remarkable contributions of DeBakey, Gibbons and Kantrowitz [6]. MicroMed DeBakey VAD, Jarvik 2000 and HeartMate II are the examples of second generation pumps [48].

Jarvik 2000 is a left ventricular assist device which can be a good example for second generation pumps. Research on the development of Jarvik 2000 was initiated in 1988 and first clinical trial on it was conducted in 2000 [29]. In 2003, it was implanted in two patients as a bridge to transplantation support, and after 49 days both of the patients were discharged home from the hospital by the approval of FDA without any problems [53, 54]. Peter Houghton was a patient who lived a normal life for 7 years with Jarvik 2000 [55, 56].

Considering the success of HeartMate I, Thoratec Company raised the bar by developing the second generation version of it, HeartMate II. It was created as an axial flow pump and its technology was based on the utilization of contact bearings. Permission for clinical trials and CE mark was awarded to HeartMate II in 2003 and in 2005 respectively so that it could be available for the patients all around Europe as a bridge to transplantation device [29, 57].

In the early 2000s, as a result of new advances in blood pump technologies, third generation pumps have become prominent. They differ from second generation pumps with their magnetically levitated non-contact bearings. Their features and clinical outputs were examined by Hoshi et al [9]. According to this study, developing a third generation pump is much more arduous comparing to second generation pumps. Examples of third generation pumps are VentrAssist, DuraHeart, Berlin Heart Incor, HeartMate III and HeartWare [58-62].

Fourth generation pumps have been developed to function as not only a LVAD, but also a RVAD [63]. These pumps can be converted to each type without any difficulties. Beside all these advances, research on percutaneous cables has been conducted in order to transmit the energy through the skin [64].

2.5. Key Points about Development of Ventricular Assist Devices

Nose and Ichikawa defined three phases throughout the development of blood pumps [65]. At the end of first phase, phase-1-pump (two-days-pump) comes up which could be used in cardiopulmonary bypass. Phase-2-pump (two-weeks-pump) could be used in patients who need postcardiotomy support where phase-3-pump (2 years pump) could be used as a long term pump for bridge to recovery or transplantation. Table 2.2 represents the development phases of blood pumps.

Table 2.2 Development phases of blood pumps [65]

PUMP CLASS	USAGE AREA
Two-Days-Pump (Phase-1-Pump)	Cardiopulmonary Bypass
Two-Weeks-Pump (Phase-2-Pump)	Postcardiotomy Cardiac Failures Extracorporeal Membrane Oxygenation Percutaneous Cardiopulmonary Support
Two-Years-Pump (Phase-3-Pump)	Bridge-to-Recovery (BTR) Bridge-to-Transplantation (BTT)

Y. Nose declared based on his decades of experiences that developing a ventricular assist device is not a simple work [66]. DeBakey and his group worked for 10 years in order to develop DeBakey LVAD [31]. Researchers all around the world have been working on developing VADs for more than 50 years, however the number of clinically available VADs is limited.

There are two phenomena which play crucial roles in the development stage of VADs. The first one is hemolysis which could be explained as the red blood cell damage caused by exposure to the excessive shear stresses within the pumping chamber. Hemolysis becomes evident when the hemoglobin in red blood cells is released into the surrounding plasma. Most crucial parameter which is directly associated with hemolysis is the surface roughness of the blood contacting surfaces. Surface roughness value (R_a) of the blood contacting surfaces should not exceed 0.2 μm in order to come up with anti-traumatic and anti-thrombogenic surfaces [66]. Takami et al supported this argument by comparing surface roughness values from 5 μm to 0.006 μm in cardiopulmonary bypass conditions and concluded that maximum surface roughness of 0.2 μm should be achieved for ventricular assist devices [67]. In order the evaluate hemolysis in the blood pumps, ASTM defined an index (*N.I.H.*) which constitutes a common method for researchers [68]. The details about the calculation of Normalized Index of Hemolysis (*N.I.H.*) will be given in Chapter 5. Generally, blood pumps are considered antitraumatic, as long as their *N.I.H* is kept under 0.01 g/100L at 100 mm Hg head pressure [66]. This value is considered as a benchmark for the development of VADs.

Other concern for the development of VADs is thrombosis or i.e. blood clotting. Although this issue was indicated by Dr. DeBakey in the early 1970s, it took a few years for researchers to report about surface modification methods in order to come up with nonthrombogenic surfaces. Chawlaa et al conducted a research in 1974 on the treatment of a surface with radiation grafting of heparin which resulted in success of preventing blood clotting after 60 minutes [69].

Hemocompatibility can be described as the compatibility of the blood contacting surfaces with the blood. In order for VADs to be hemocompatible, they should be both antitraumatic and antithrombogenic. Beside the surface modification techniques, hemocompatibility should be provided by the material itself as well. For example, Ti-

6Al-4V proved itself to be hemocompatible regarding to its antithrombogenicity and good hemolytic performance [70].

Chapter 3 - DEVELOPMENT STAGE OF NHTC FOR *IN VITRO* BLOOD TESTS

In this chapter, details about the design development of NHTC will be presented. Firstly, outputs of previous studies will be explained. Design details such as components of the pump, coupling and driving system, material types etc. will be mentioned. Then deficiencies of previous designs will be listed. Later, proposed solutions to these problems will be covered. Finally, design modifications according to *in vitro* blood tests' results will be presented in detail.

3.1. Previous Research and Existing Model

In previous studies, first step was to create 3-D CAD model of the pump after deciding on design parameters. Researchers at MARC came up with different centrifugal pump models by means of Siemens NX software. In order to predict the performance of these models, computational fluid dynamics (CFD) analysis were performed in the environment of ANSYS software. Pressure distributions and related shear stresses were analyzed carefully. The designs with satisfying results were chosen to be manufactured. Manufacturing processes will be explained in the following chapter in detail. After manufacturing process, performances of the prototypes were tested in a recirculating setup.

Main components of this setup are the driving system for transmitting the motor torque to the impeller and pressure sensors in order to measure the pressure difference across the pump. Circuit is completed with a reservoir and 3/8 inch PVC tubing. The setup can be seen in Figure 3.1.

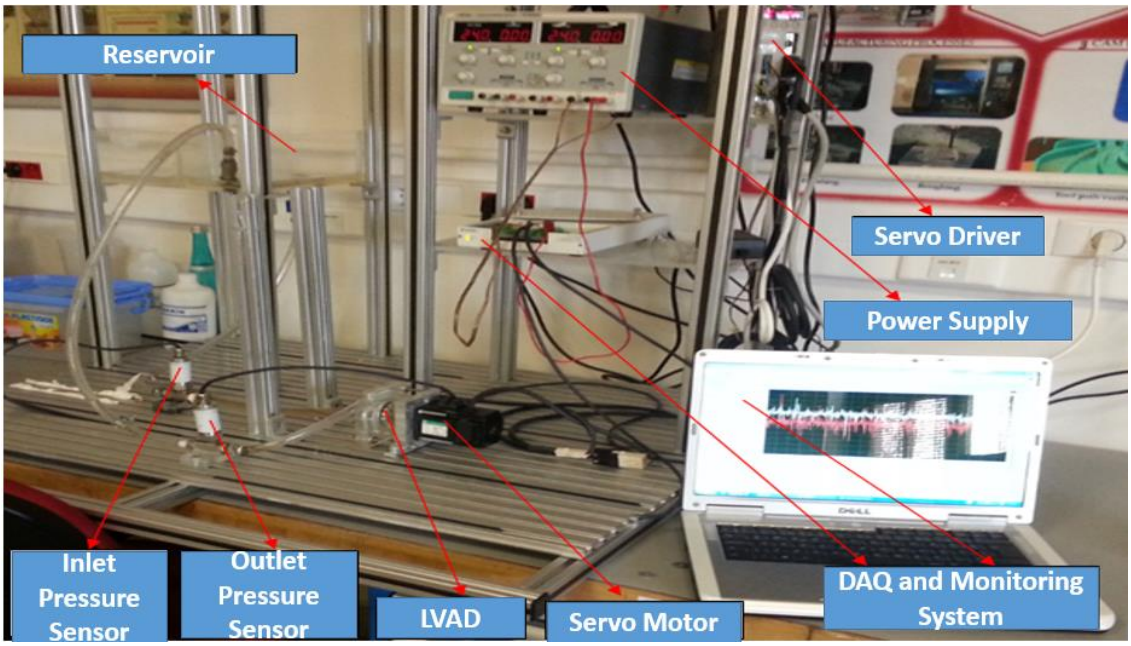

Figure 3.1 - Performance Test Setup

Driving system consists of an AC servomotor which is controlled by servo driver and power units. When the motor rotates at a certain rotational speed, moment is transmitted to the impeller through the magnetic coupling between motor shaft and magnets embedded in the impeller. Pressure difference between inlet and outlet pressure sensors is monitored by means of a data acquisition system. In order to mimic the blood viscosity, the circuit is filled with blood mimicking fluid which is composed of %40 glycerin and %60 water mixture. The reservoir is held at a certain height for simulating Left Ventricular End Diastolic Pressure (LVEDP) according to Wiggers diagram which can be seen in Figure 3.2. LVEDP corresponds to the pressure of the left ventricle at the end of the pumping cycle [71, 72]. Wiggers diagram shows the pressure change in one heartbeat. It can be inferred from the diagram that left ventricle creates a minimum pressure of 15 mmHg and maximum pressure of 120 mmHg in each heartbeat. Therefore the height of the reservoir is set to create 15mmHg preload pressure.

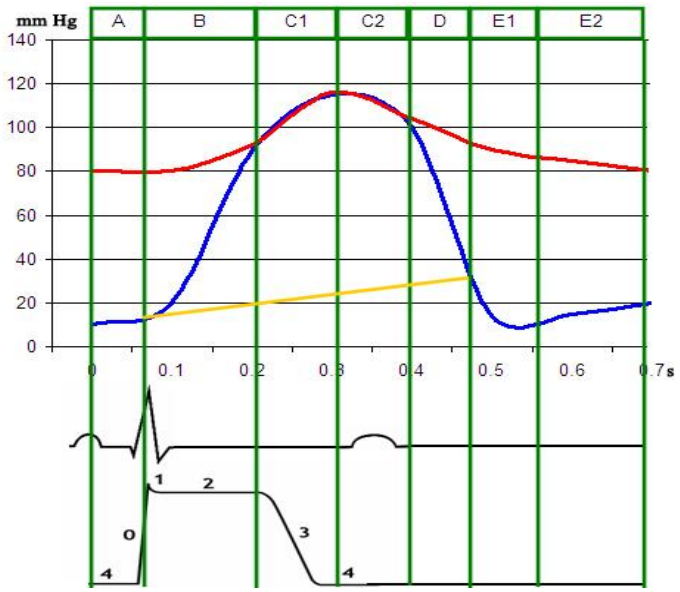

Figure 3.2 - Wiggers Diagram (Red = aortic pressure, Blue = left ventricular pressure, Yellow = left atrial pressure) [71, 72]

Among many designs, a final prototype came up based upon two selection criteria. First, the flow performance which is characterized by pressure difference across the pump and flow rate. Secondly, the maximum stress values created by the pump which are critical for red blood cells. Therefore 120 Pa was decided to be a threshold while evaluating CFD results [14]. This final design consists of three main parts: top housing, bottom housing and impeller. The pump dimensions are 81 x 87 x 35 mm (without cannulas). The impeller is 48 mm in diameter and 18 mm in height with 8 curved blades. The priming volume of the pump is 35 ml. The performance chart of this final design can be seen in Figures 3.3.

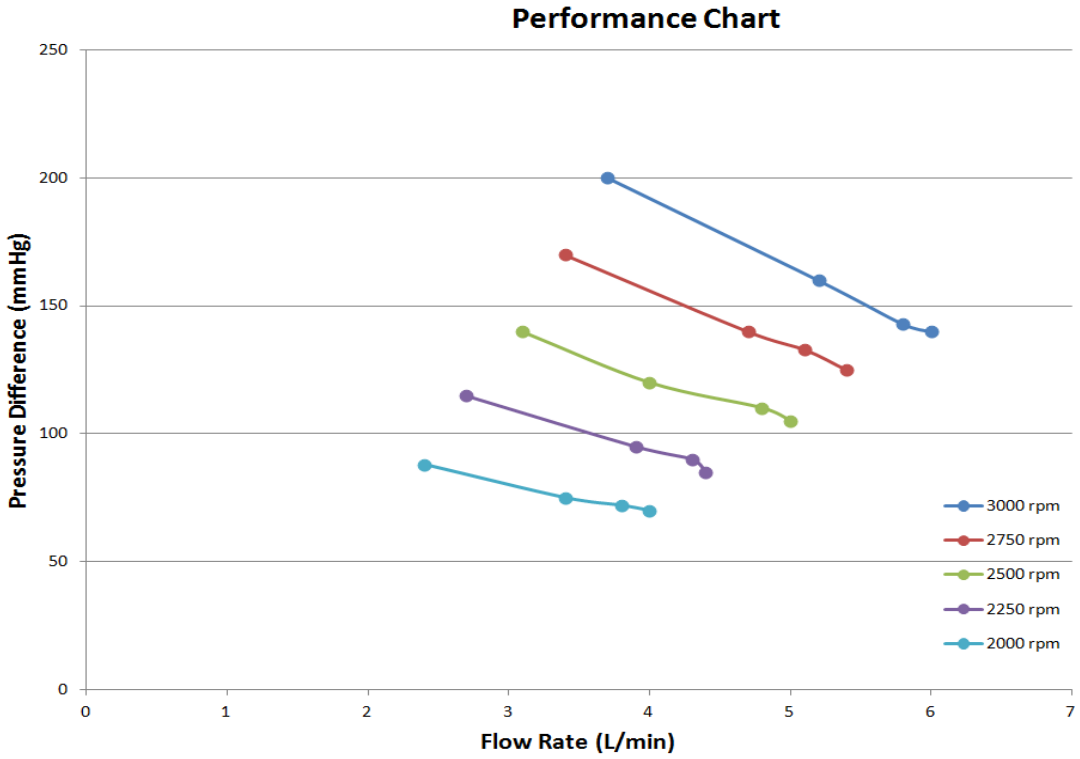

Figure 3.3 - Performance Chart for Final Design (Flow Rate vs. Pressure)

3.2. Problems about Previous Design and Proposed Solutions

In the previous design, upper and lower housings of the pump were assembled to each other by pin and hole method. This resulted in a leaking problem during the operation of the pump. In order to solve this problem, utilization of an O-ring made from biomaterial "polytetrafluoroethylene (PTFE)" was envisaged. Design of the upper and lower housings were modified in a way that O-ring acts as a barrier around the pump and housings are assembled by using bolts and nuts. Thus leaking problem was fixed.

Other problem with this design was that magnetic force between the magnets was not sufficient for a robust coupling. Due to this fact, slipping between the motor and

impeller was occurring during the performance tests. In this design, just 16 neodymium magnets with 4 mm diameter and 4 mm height were used with certain amount of spaces in between. In order to strengthen the force, number and volume of the magnets were increased, since the generated magnetic force is dependent on the volume of the magnets. 12 neodymium magnets with 8 mm. diameter and 4 mm. height were adopted to the system and the slipping problem was resolved.

This design showed satisfying CFD results and good performance with acrylic glass prototype. However for the blood experiments, it had to be manufactured from a material which is both biocompatible and hemocompatible. Hemocompatibility means the compatibility of a material with the blood. Ti-6Al-4-V is a widely used hemocompatible material in medical industry. It is a titanium alloy which contains 6% aluminum, 4% vanadium and small amount of other materials. Consequently, it was chosen for manufacturing, since it proved itself to be a perfect hemocompatible material in the literature. Ti-6Al-4-V prototype was manufactured in the machining centers of MARC for *in vitro* blood tests. The prototype can be seen in Figure 3.4.

Figure 3.4 – Final Ti-6Al-4V prototype of previous study

First blood test attempt with this prototype was unsuccessful and had to be terminated after couple of minutes. The reason for this was the breakdown of the ceramic bearing. First inference of the failure was based on excessive loads acting on the bearing due to high density of alloy. In order to overcome this problem, first solution offer was changing the material of the pump. This is the starting point of endless efforts to come up with a model which shows satisfying hemolytic performance. These efforts also constitute a significant portion of the outline of this study and will be covered in detail in the following chapters.

3.3. Design Evolution of NHTC

3.3.1. Prototype A (Test 1)

After fixing problems like leaking and magnetic coupling, the next challenge was increasing the durability of the pump. The malfunction of the ceramic bearing was firstly based on the weight difference between titanium and acrylic glass impeller prototypes. Because the acrylic glass pump prototype was performing smoothly. Based on this fact, the utilization of another biomaterial "Ultra high molecular weight polyethylene (UHMWPE)" came up. Its density is almost one fifth of Ti-6Al-4V and helps saving from weight of the prototype The first prototype of this study was manufactured from UHMWPE and will be named in this thesis as Prototype A.

The first *in vitro* blood test of this study (Test 1) was conducted with Prototype A. Test procedures and results will be explained in the following chapters. The experiment had to be terminated after 75 minutes again due to the breakdown of the ceramic bearing. After this finding, it was concluded that single ceramic bearing was not capable of carrying unbalanced loads acting on it during the operation. Thus the emphasis was laid on bearing designs and the studies were carried out mainly focusing on different bearing models.

3.3.2. Prototype B (Test 2 and Test 3)

In order to overcome instabilities in the rotation of the impeller, double pivot bearing method was proposed. Prototype B is the first example of these trials and characterized with two cylindrical shafts 3 mm. in diameter at the top and bottom of the impeller.

In the stage of manufacturing, acrylic glass was preferred as a material instead of UHMWPE. This is because UHMWPE is not very suitable for polishing and makes it difficult to come up with smooth surfaces. Acrylic glass is not known as a hemocompatible material, however it was assumed that it would enable assessing *in vitro* hemolytic performance of the pump design for the short term. It is also a convenient material for manufacturing and polishing. Second blood test (Test 2) was performed with this prototype. However, the polishing procedure was not adopted before Test 2 in order to see the effect of polishing by comparing with Test 3. Test 3 was kind of repetition of Test 2 with the same design. The only difference was the surface treatment of the pump components.

3.3.3. Prototype C (Test 4)

Prototype C is distinguished from Prototype B by the replacement of cylindrical shaft with a semispherical shaft 6mm. in diameter at the bottom of the impeller. The reason for this change is the breaking of the lower shaft and considerable amount of hemolysis during Test 2 and Test 3. Prototype C was utilized in Test 4.

3.3.4. Prototype D (Test 5, Test 6 and Test 7)

Test 4 was another unsuccessful trial in terms of durability and hemolysis. It was concluded after these tests that durability and hemocompatibility of the pump cannot be established, as long as friction is present in the system. Despite all the discredit of ceramic bearing acquired in several tests, implementation of double pivot ceramic bearings was worth a try. Because constraining the impeller from both top and bottom sides could allow a smooth rotation which also enables bearings to be exposed to more balanced loads. Additionally, mechanical damages caused by friction could be reduced to minimum with the help of bearings. In the light of these ideas, the final design of this study, Prototype D came up.

Other prominent detail about this design is the integration of sweepers to the design. Their function is to prevent blood stagnation in the clearance region between the base of the lower housing and bottom face of the impeller.

This prototype was manufactured of acrylic glass and tested in Test 5, Test 6 and Test 7. According to the results, this design finally met the expectations in terms of durability and hemocompatibility performance. Prototype D was operated in Test 5 and Test 6 for 6 and 12 hours respectively. Test 7 was performed at 3,000 rpm for 6 hours. There was no mechanical damage in the pump system after the tests and hemolysis levels were in an acceptable range comparing to clinically available pumps.

3.3.5. Prototype E (Test 8)

Test 5, Test 6 and Test 7 were kind of proof of concept which shows that there were very little amount of hemolysis caused by the design of the pump system. However, the experiments had to be extended and repeated with a new prototype which is manufactured of a hemocompatible material. This is because this pump is developed for long term usage and acrylic glass cannot meet this requirement. Therefore Prototype E was manufactured using Ti-6Al-4V and Test 8 was performed with this prototype. Details about this final prototype will be discussed in the next chapter.

Chapter 4 - MANUFACTURING PROCESS OF NHTC FOR *IN VITRO* BLOOD TESTS

After the design of the pump was finalized according to preliminary blood test results, the next step was the manufacturing of this design from a hemocompatible material. Due to its advantages such as good hemocompatibility and high strength to density ratio, Ti-6Al-4V ELI was chosen for manufacturing. On the other hand it is a difficult material to machine. Therefore machining strategies should be planned carefully.

The first step before manufacturing is to decide on the type and size of the cutting tools which will be used in the machining operations. Firstly, there are some limitations on the selection of the tools due to geometry of the parts to be machined. Secondly, material properties and restrictions based on tool manufacturers are determinative issues. Figure 4.1 shows some of the tools which were used during machining operations.

Figure 4.1 – Some of the cutting tools used in machining operations [15]

In machining operations, most important parameters are “depth of cut [mm]” and federate [mm/min] in terms of safety and speed of the production. When deciding on these parameters, material type and tool properties should be taken into consideration.

For machining operations, Computer Aided Manufacturing (CAM) modules are the tools which make this process easier. As CAD module of Siemens NX was used in the design stage, CAM module of this software was employed for the manufacturing as well. In this module, machining toolpaths and regarding G-Codes were generated. These G-codes should be generated for each machining operation. These operations generally include roughing, semi-finishing and finishing processes. Roughing is the process where the highest amount of material is removed from the workpiece by using relatively large diameter tools. On the other hand, finishing is a process where the workpiece is brought to its final shape. These operations are illustrated in Figure 4.2.

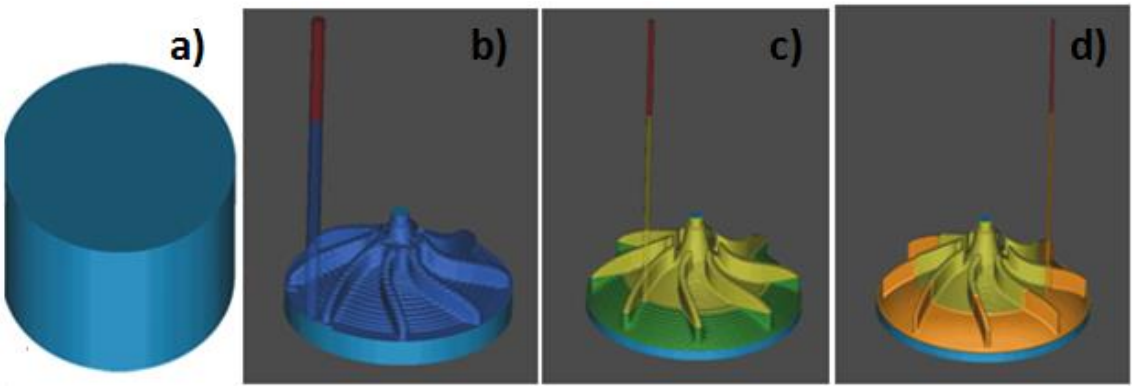

Figure 4.2 – Sample machining operations: a)workpiece b)roughing c)semi-finishing d)finishing

Machining operations are performed in computer numerical control (CNC) machining centers. CNC machining center gets the information from the user in the G-code format which is generated through the postprocessing of the machining operations created in the CAM software. G-code contains the information about the cutter locations which the tool is going to follow in sequence. A certain portion of G-code and a sample toolpath is demonstrated in Figure 4.3.

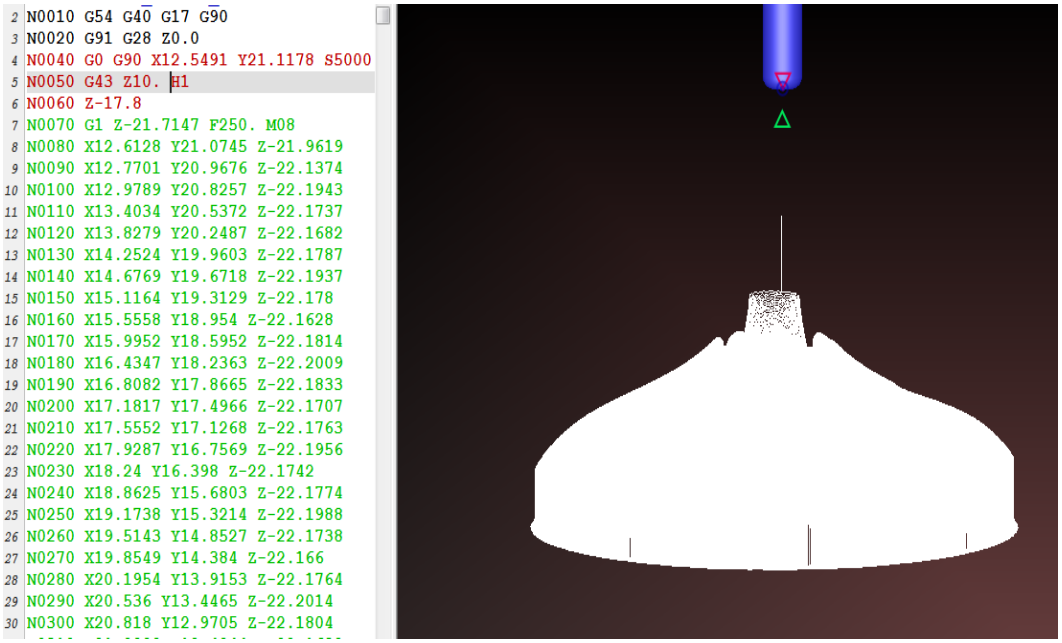

Figure 4.3 – Sample G-code portion and toolpath representation

After machining operations are finished, parts are ready for use in general, since CNC machine tools are able to work in a micron level accuracy. However, in some applications like in this case, further surface modification techniques might be needed. This is because surface roughness is a very important parameter in terms of hemolysis and plays a crucial role in blood pump development. Therefore polishing techniques were applied to the machined parts by means of specific polishing equipments. Polishing procedure will be discussed in the following sections in detail.

4.1. Machining

Since pump consists of upper housing, lower housing, upper and lower component of impeller, four parts had to be manufactured in the machine tools. All of these components were manufactured of Ti-6Al-4V. For upper and lower housings square shaped (100x100 mm); for impeller cylindrical shaped (dia. 50 mm) Ti-6Al-4V blocks were used.

Manufacturing process contains 31 milling operations which have machining time of approximately 100 hours. These operations were performed in Mazak FJV-200 UHS 3-Axis Vertical Machining Center in MARC which can be seen in Figure 4.4. Spindle system of this machine is able to rotate at 25,000 rpm and the machine is able to move in micron level accuracy.

Figure 4.4 – Mazak FJV-200 UHS 3-Axis Vertical Machining Center

After the machining operations created in NX CAM module were performed, final shapes of the parts were obtained. Nevertheless the surface quality obtained at the milling operation is not sufficient to pass on blood experiments. Because blood contacting surfaces must have maximum surface roughness value, R_a of 0.2 µm in order not to exceed the shear stress threshold after which blood cells will get damaged. Therefore, polishing procedure comes into the picture.

4.2. Polishing

In many studies, it was concluded that surface roughness value ($R_{a)}$ of blood contacting faces should be maximum 0.2 µm to prevent breakdown of the blood cells. In case of exceeding this threshold, blood cells will be more vulnerable against hemolysis.

Therefore, polishing techniques were implemented to machined parts by using special polishing equipments.

First of all, polishing stones with various grain sizes were utilized in order to get rid of feedmarks left from milling operations. Since these stones leave some scratches on the surface, abrasive metal brushes were used with the hand-type rotary head. Following that abrasive sandpapers were implemented starting with coarsest up to finest grit sizes. Finally, in order to come up with a smooth surface finish, last step is implementation of the diamond by means of the rotary head.

After all these efforts, parts were subjected to surface roughness measurement by using Mitutoyo Surftest SJ-301. Desired surface quality was achieved for all components and the parts were ready for assembly and then for *in vitro* blood tests.

In order to verify the results obtained with acrylic glass prototype in the blood tests, Test 8 was conducted with the prototype manufactured of biocompatible material Ti-6Al-4V and this prototype will be named as Protoype E in this thesis.

Chapter 5 - *IN VITRO* BLOOD TESTS AND RESULTS

Medical devices such as left ventricular assist devices, are developed to be implanted inside human body. Naturally, trials of these products cannot be performed directly on humans. Therefore other methods should be followed for testing of these devices. Generally, these methods are classified in two categories; *in vitro* and *in vivo* testing. In Latin language, *in vitro* means "*within the glass*" where *in vivo* means "*within the living*". In other words, *in vitro* tests indicate the tests performed in a controlled laboratory environment but out of the living organism. On the other hand, *in vivo* tests point out the tests performed within living organisms which includes animal experiments and clinical trials. In order for a medical device to pass on *in vivo* tests and clinical trials, it should perform well in *in vitro* experiments.

ASTM International, the international standard organization published two standards in 1997 in order to structure a common benchmark for the assessment of continuous flow blood pumps. One of them, ASTM International Standard F 1830 – 97, is about selection of blood and the other one, ASTM International Standard F1841 –97, is about the *in vitro* blood testing procedure for evaluation of blood pumps.

5.1. Selection Procedure of Blood for in vitro Evaluation of Blood Pumps

Since blood is the most crucial factor when evaluating hemolytic performance of ventricular assist device, it must be chosen and prepared carefully. ASTM International F 1830 – 97 contains detailed information about selection, collecting and storing procedures of blood before *in vitro* experiments [73].

First thing stated in the international standard is selection of blood. For an *in vitro test*, it is recommended to use fresh bovine, porcine or human blood. The donor animals

should have normal body temperature and not show any sign of disease. Bovine or porcine blood should be used within 48 hours including the transportation time. Human blood should be used within 24 hours after harvesting the blood. In case of not using the collected blood within 2 hours after harvesting, it should be refrigerated at 2 to 8 ˚C until testing.

According to the standard, blood should be collected by means of a large bore needle (14 G or larger) and drawn into a blood bag containing anticoagulants such as Citrate Phosphate Dextrose Adenine, CPDA-1, (63 ml for 450 ml of blood) or heparin sulfate (2,000 to 3,000 USP for 500 ml of blood). Including anticoagulants, blood should have a volume of 450 ± 45 ml. Right before the test, blood should be warmed up to 37 ± 1 ˚C through water bath.

5.2. In Vitro Evaluation Procedure of Continuous Blood Pumps

ASTM International Standard F1841 –97 describes the steps to be followed for assessing continuous flow blood pumps [68]. In this standard, preparation of test setup, testing procedure and evaluation of the results are explained in detail.

Test setup includes polyvinylchloride tubing with 9.5 mm inner diameter and 2 m in length. Both ends of the tube should be connected to a reservoir with a sampling port. Two pressure sensors must be placed at inlet and outlet of the pump in order to measure pressure head difference. Flow rate should be monitored through a flowmeter which is connected to the loop after the outlet of the pump. Between the flowmeter and outlet of the pump, a clamp should be placed in order to control pressure head difference. The temperature of the blood should be kept under control consistently. Figure 5.1 represents the test loop.

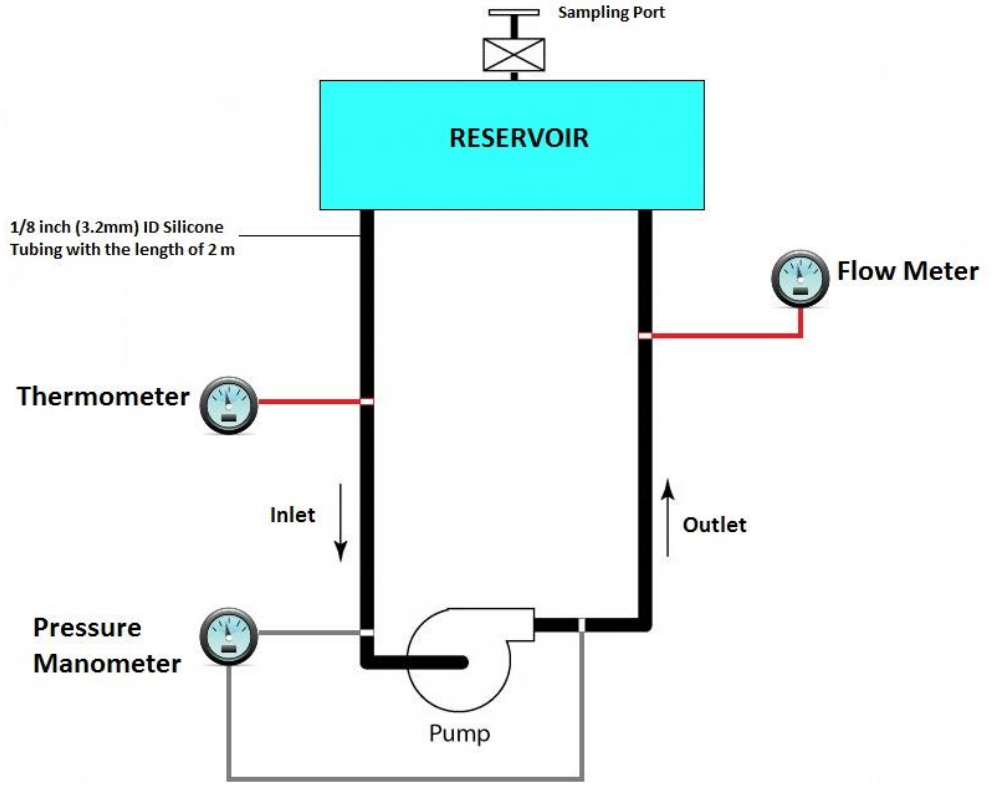

Figure 5.1 – Test loop for in vitro hemolysis tests

After preparing the blood and adjusting the hematocrit value to be in the range of 30 ± 2% by hemodilution, the experiment starts with rinsing the test loop by recirculating phosphate buffered saline for 10 to 20 minutes. Following that blood should be supplied to the loop after draining phosphate buffered saline completely. Besides, air should completely be removed from the loop.

Flow rate should be adapted to 5 ± 0.25 L/min by changing rotational speed of the motor. Pressure head difference should be arranged to be in the range of 100 ± 3 mm Hg. Blood temperature should be fixed at 37 ± 1 ˚C by means of a water bath.

Prior to the test, blood should be circulated through the loop for five minutes to provide complete mixing. Thereafter "time zero measurement can be taken. For "time zero measurement" and at every hour of 6-hours-test, 1 ml blood sample should be taken from the sampling port of the reservoir.

These samples should be subjected to some measurements in order to evaluate the hemolytic performance of the pump. According to ASTM International Standard F1841 –97, this evaluation can be made based on the calculation of Normalized Index of Hemolysis (*N.I.H.*) and Modified Index of Hemolysis (*M.I.H.*). These indices are calculated by following formulas:

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

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

In these equations;

- *V* corresponds to circuit volume [L],
- *Q* corresponds to flow rate [L/min],
- *T* corresponds to sampling time interval [min],
- *Ht* corresponds to hematocrit percentage [%],
- *Hb* corresponds to the total hemoglobin concentration before the test [mg/L],
- $\Delta freeHb$ corresponds to increase in the plasma free hemoglobin concentration over the sampling time interval [g/L],
- $\Delta freeHb_{mg}$ corresponds to increase in the plasma free hemoglobin concentration over the sampling time interval [mg/L].

In the international standard, *M.I.H.* is suggested to be the most applicable index in terms of assessing the hemolysis level caused by the device. On the other hand, there were many studies about blood pumps in literature which were able to reach to the level of in vitro blood testing. In most of these works, *N.I.H.* values were usually preferred in order to present hemolytic performance of the pumps. Therefore in order to make a comparison between NHTC and these pumps, *N.I.H.* calculations have more importance. It can be inferred from the literature that *N.I.H.* values differ from 0.0001 to 0.0096

g/100L [74-77]. However, in order to compete with clinically available pumps, NHTC should have *N.I.H.* values under 0.003 g/100L [74].

5.3. In Vitro Blood Testing

In this study, blood was supplied from volunteer blood donors in the preliminary tests. In the development stage of the pump, a vast number of experiments had to be performed. Therefore it was not feasible to draw 500 ml blood from each volunteer at the initial phase of the pump development. Therefore, the test loop needed to be scaled down in order to be able to take less amount of blood from the donors.

Six tests were conducted in a recirculating flow loop. The loop consisted of the assist device developed for the experiment, 2 m length of 1/8 inch silicone tubing, pressure transducers and a reservoir. The circuit volume was 70 ml where the priming volume of the pump was 35 ml.

Venous blood samples (60 ml) were obtained from healthy volunteers, aged between 23 to 37 years, anticoagulated with sodium heparin (15 IU/ml). Complete blood count was performed by using an electronic hematology analyzer (ABX Micros OT, ABX Diagnostics, Montepellier, France) for including only healthy blood samples into the LVAD tests. Red blood cells (RBC) were isolated from whole blood by centrifugation (1400xg, 5 min). The packed cells were re-suspended at a hematocrit 0.25 l/l in glucose-enriched (5 mM) isotonic phosphate-buffered saline (PBS; pH 7.4). RBC suspension hematocrits were determined using the microhematocrit method (10,000 × g, 4 min). RBC cellular deformability at 37 °C was assessed at various fluid shear stresses via laser diffraction ektacytometry (LORCA, RR Mechatronics, Hoorn, The Netherlands).

In the first hemolysis test (Test 1), Prototype A; in the second and third tests (Test 2 and Test 3) Prototype B; in the fourth test (Test 4) Prototype C; and in the fifth, sixth and seventh tests (Test 5, Test 6 and Test 7) Prototype D were employed. Final test, Test

8 was performed with Prototype E. Test conditions were set to 100 mmHg pressure difference, 0.7 L/min flow rate and room temperature, while the motor was rotating at 2,000 rpm. In order to see the effect of the change in rotation speed, Test 7 was conducted at 3,000 rpm. Flow rate was measured 1L/min and the pressure different was 175 mmHg in Test 7. Temperature was monitored instantly by using infrared thermometer. The circuits were filled with 70 ml blood (25% Hct) and then air bubbles were evacuated from the reservoir. Before and during the test, 1 mL blood samples were collected from the reservoir at specific intervals. Instant hematrocrit rates were calculated for each test. For 5 of 8 tests (Tests 3, 5, 6, 7 and 8), plasma-free hemoglobin amounts were measured by means of a spectrophotometer. Blood samples were centrifuged at 900 g for five minutes at room temperature (20 ± 2°C), and plasma was harvested. Two hundred µl of plasma was mixed with 800 µl of Drabkin's solution (1.13 mM KH_2PO_4, 0.6 mM $K_3[Fe(CN)_6$, 0.8 mM KCN). Absorbance was measured at 540 nm and hemoglobin concentration was calculated using a calibration curve. Finally, *N.I.H.* values were calculated based on ASTM F1841-97 standards. In figures 5.2 and 5.3, experimental setups of Test 1 and Test 5 can be seen.

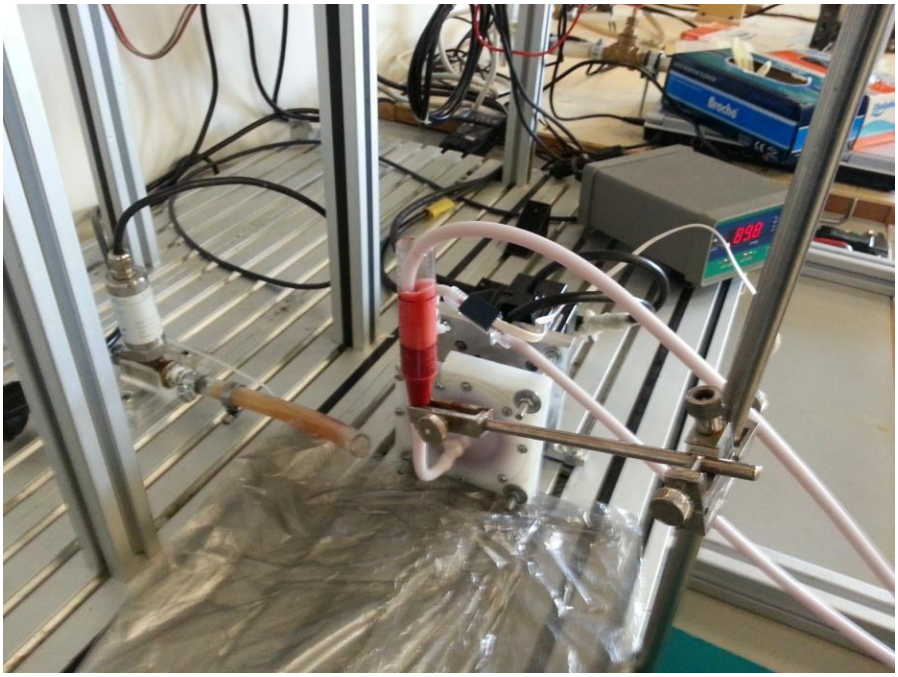

Figure 5.2 – The experimental setup of first blood test performed with first prototype manufactured of UHMWPE

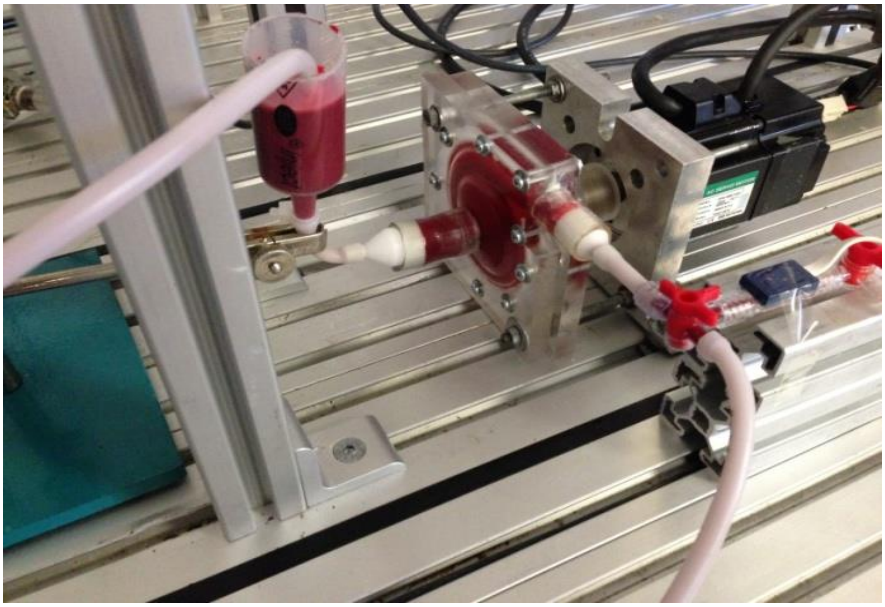

Figure 5.3 – The experimental setup of fifth blood test performed with the final design manufactured of PMMA

5.4. Results

Test 1 was terminated after 75 minutes due to the malfunction of ceramic bearing. In this test, hematocrit rate descended from 25% to 5% at the end of 75 minutes which shows that hemolysis progressed rapidly.

Test 2 lasted for 120 minutes. Due to the blood plasma and acrylic glass interaction, significant amount of blood clots were observed during the test and the experiment was interrupted several times because of the blockage in the tubes. Final hematocrit rate was 8% at the end of the experiment. It was also seen that the upper shaft was worn and the lower shaft was broken due to the friction.

In order to see the effect of polishing, nothing was changed in Test 3 except for surface treatment of the components. Other than that some precautions were taken to prevent blood clotting. The duration of the experiment was 360 minutes and *N.I.H.* was calculated for the first 100 minutes at 10 minutes intervals. The reason for this is that plasma-free hemoglobin level increased to a level which exceeded measurement range of spectrometer after 100 minutes. *N.I.H.* levels ranged between 0.04 and 0.09 g/100L. The hematocrit rate was 9% at the end of 360 minutes. After the test, it was seen that lower shaft of the impeller was broken and upper shaft was slightly worn. Figure 5.4 shows the macroscope images of the shafts after Test 3.

In Test 4, the hematocrit rate decreased from 25% to 8% drastically and after 100 minutes the test was terminated. Significant amount of wear was observed at the upper and lower shaft of the impeller.

The duration of Test 5 was 360 minutes and *N.I.H.* values were calculated for the first 240 minutes by taking PFH measurements at 30 minutes intervals. Final hematocrit rate was 23% at the end of the test and *N.I.H.* values ranged between 0.001 and 0.006 g/100L. Another promising point of this test was that any malfunction or distortion was not observed within the device during and after the experiment.

Test 6 was an extended repetition of Test 5 in terms of experiment duration. The pump was operated for 12 hours and measurements were taken at 60 minutes intervals. The hematocrit level descended from 24% to 23% only after 720 minutes. *N.I.H.* values seemed to be slightly improved such that they ranged between 0.001 and 0.004 g/100L.

The aim of Test 7 was to investigate the effect of increase in the rotational speed of the pump on hemolysis. The test was performed for 6 hours and samples were taken every 60 minutes. Unsurprisingly there was significant hemolysis during the test which led to decrease in the hematocrit rate from 25% to 18% after 360 minutes. Corresponding NIH varied between 0.004 and 0.017 g/100L.

Test 8 was conducted to verify the results with the Ti-6Al-4V prototype of the same design. Hematocrit rate was again 25% initially and descended to 23% after 6 hours. Corresponding NIH varied between 0.003 and 0.006 g/100L.

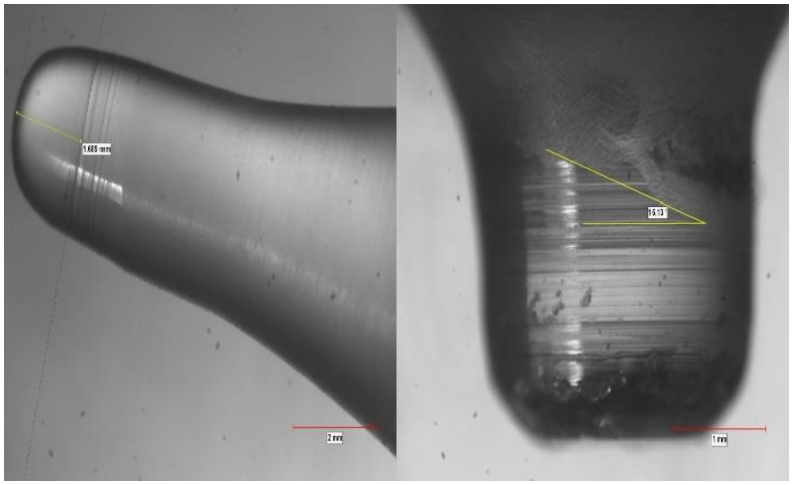

Figure 5.4 – Macroscope images of upper (Left) and lower (Right) shafts after Test 3; wear on the upper shaft and breakage on the lower shaft

Table 5.1 represents the brief summary of the tests:

Table 5.1 – Summary of the tests

Test No	Prototype	Duration(min)	Findings	Bearing Design
1	A	75	bearing failure	Single full ceramic bearing on the bottom face of the impeller.
2	B	120	wear on upper shaft, lower shaft breakage	Cylindrical shaft with 3 mm. diameter at the top and bottom of the impeller.
3	B	360	wear on upper shaft, lower shaft breakage	Cylindrical shaft with 3 mm. diameter at the top and bottom of the impeller.

4	C	100	excessive wear on both of the shafts	Cylindrical shaft with 3 mm. diameter at the top & semispherical shaft at the bottom of the impeller.
5	D	360	no damage	Double full ceramic bearings at the top and bottom side of the impeller.
6	D	720	no damage	Double full ceramic bearings at the top and bottom side of the impeller.
7	D	360	no damage	Double full ceramic bearings at the top and bottom side of the impeller.
8	E	360	no damage	Double steel bearings at the top and bottom side of the impeller.

The charts corresponding to hematocrit and *N.I.H.* levels are presented in Figures 5.5, 5.6 and 5.7.

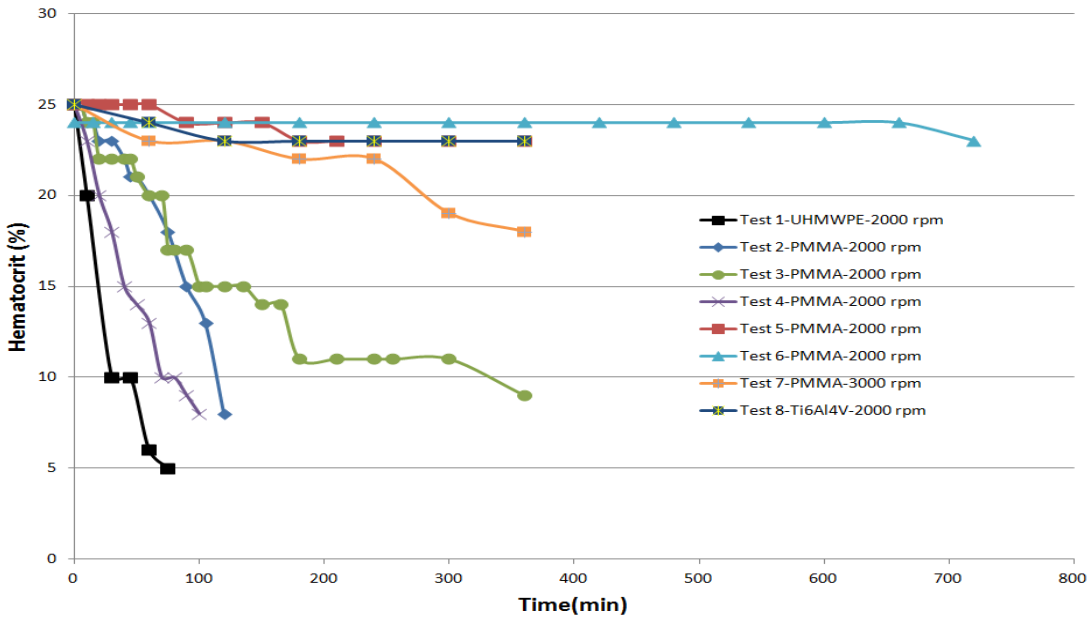

Figure 5.5 – Comparison chart for hematocrit rate measurements

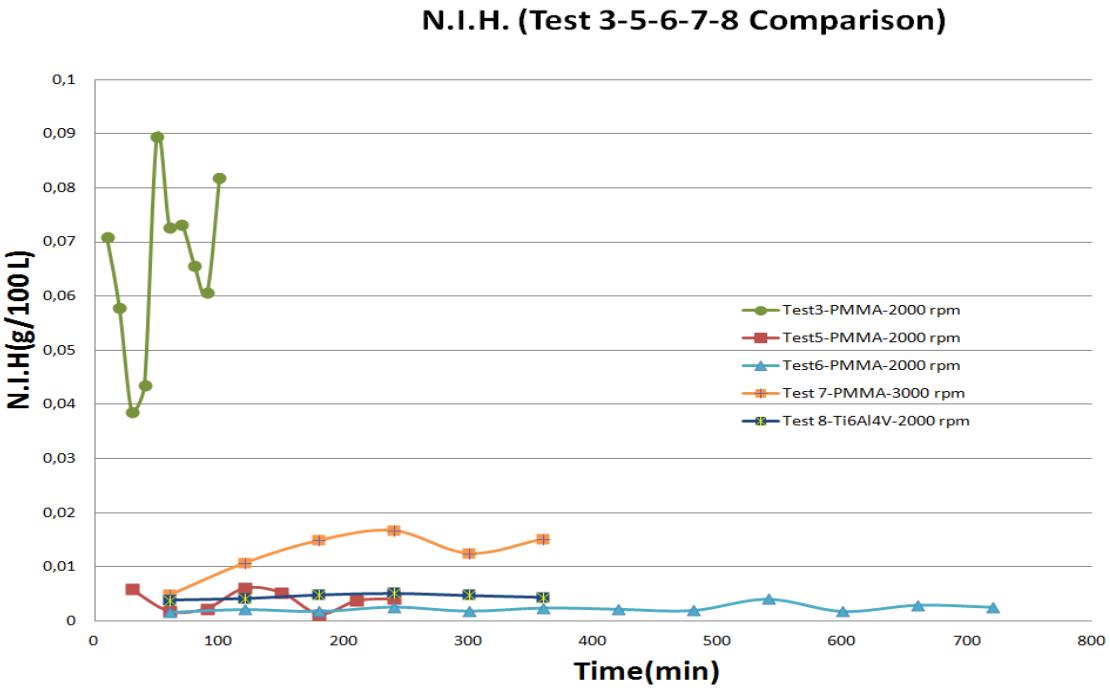

Figure 5.6 – Comparison chart for *N.I.H.* measurements of Test 3, 5, 6, 7 and 8

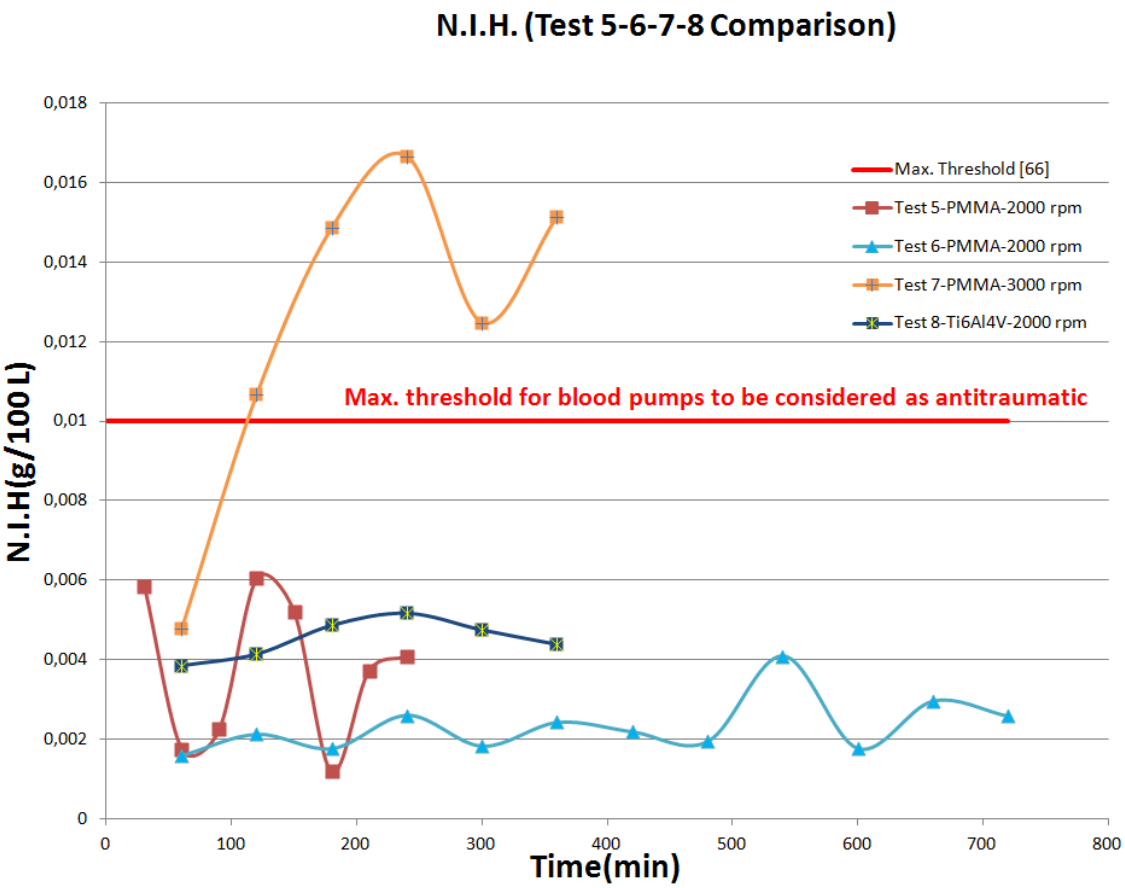

Figure 5.7 – Comparison chart for *N.I.H.* measurements of Test 5, 6, 7 and 8

5.5. Discussion of the Results

Rapid hemolysis in the first 4 tests was based on mechanical failures such as malfunction of ceramic bearing, wearing and breakings on the impeller shafts during the operation. These failures caused instabilities in the rotation of the pump and friction occurs between the surfaces. This fact triggered the hemolysis. Secondly, since polishing procedure was not adopted in Test 1 and Test 2, the rough surface of the pump also contributed to hemolysis. It can also be inferred from Figure 5.5 that after polishing the surface, hemolysis rate significantly declined in Test 3 before which nothing was modified except that polishing was applied to the parts. The design changes in the lower shaft increased the rate of hemolysis in Test 4 significantly. This caused a great deal of

instability in the rotation which also resulted in a big amount of wear on the upper shaft as compared to the Test 3. Figures 5.8 and 5.9 show the macroscope images of the shafts taken after Test 3 and 4. With the final design (Prototypes D and E), instability and friction problems were resolved, as a result of that, low hemolysis levels were achieved in Tests 5, 6, 7 and 8.

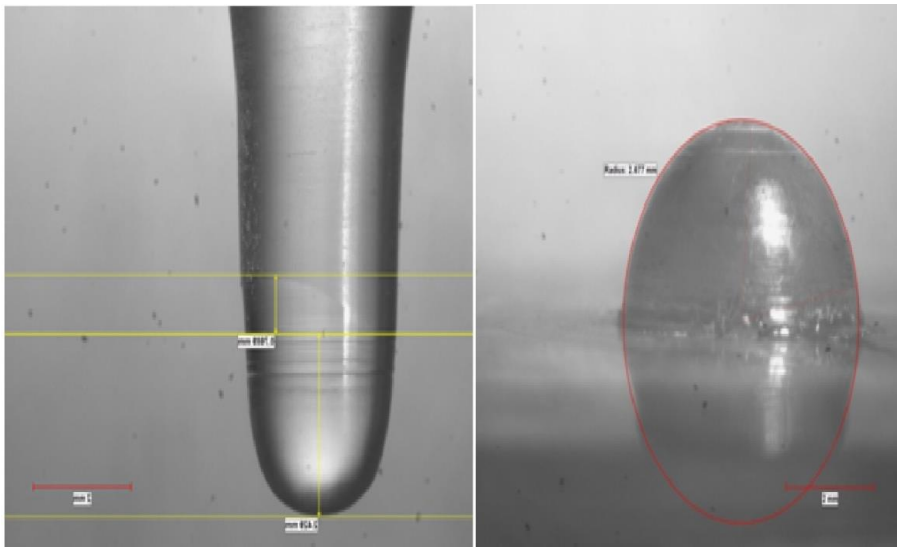

Figure 5.8 – Macroscope images of upper (Left) and lower (Right) shaft before Test 4

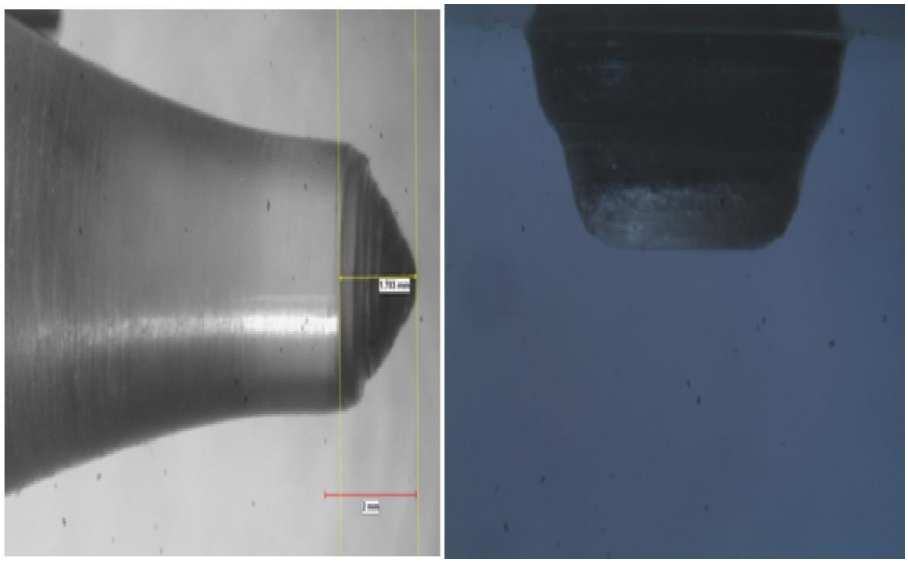

Figure 5.9 – Macroscope images of upper (Left) and lower (Right) shaft after Test 4; excessive wear on the both shafts

Chapter 6 - CONCLUSION AND FUTURE WORK

6.1. Conclusion

There are many people all around the world and in Turkey who are suffering from cardiovascular diseases. Most of these people are in the need of heart transplantation, however there are only a small number of donors. In these circumstances, mechanical circulatory support systems, especially LVADs become a hope for those patients to hold on to life. Nonetheless these devices are not easily affordable for every patient due to their high costs. In this manner, development of NHTC is of vital importance.

In this thesis study, some design modifications like O-ring utilization and strengthening magnetic coupling were made to overcome inadequacies of previous designs at first. Later on, in vitro hemolysis tests started to be performed. According to the results of each test, bearing designs were developed for the next test. Finally, a novel design came up which is durable and has good hemolytic performance. Using this design, the final prototype was manufactured using Ti-6Al-4V which is both bio- and hemocompatible material and prepared for *in vitro* blood tests according to ASTM F1841–97 international standards.

Using new design development NHTC showed promising performance in terms of biocompatibility and durability to be a clinically available left ventricular assist device. It is now in a stage to be simply used in intensive care units for short term. In order NHTC to be an implantable assist device for long term, further research must be conducted based on this design.

6.2. Future Work

First of all, *in vitro* blood tests should be extended and repeated considering international standards. If needed, some modifications could be done considering the test results. After getting satisfactory results from *in vitro* blood tests, in vivo animal experiments should be planned as the next stage. Besides all these, research on controller unit development for NHTC should be conducted in parallel. If all goes well in animal experiments, as a next step, engineers and medical doctors should work together on planning of clinical trials with human volunteers. Device design should be updated in a way that it would be in a condition to be implanted inside the human body.

Finally, one of the main targets of NHTC should be the cost efficiency without compromising on quality in order to be a hope for patients who need such devices.

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VITA

Suat Cömert was born in Istanbul, in 1987. He graduated from Izmir Atatürk High School in 2005. He received his B.Sc. degree in Mechatronics Engineering from Kocaeli University in 2011. Since then, he continued his education with M.Sc. program in Mechanical Engineering in Koç University Manufacturing and Automation Research Center. He has been working on the development of first left ventricular assist device in Turkey. He is expected to pursue his PhD degree in Germany.