Marshall Plan Scholarship Report

Development of an artificial pump and biomaterials to simulate the physiological parameters of the heart

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CONTENT

Acknowledgments

Before the actual topic of this bachelor thesis is addressed, I must say how much I appreciate being granted the Marshall Plan Scholarship. Furthermore, I am thankful for getting the opportunity to study abroad at the University of Portland for one semester. I would not have been able to make this journey without the University of Applied Sciences Upper Austria, Wels.

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INTRODUCTION

The research topic was selected in relation to an exchange program with the University of Portland, located in Oregon, United States of America. The total duration of the research project was set to be one semester from August 24, 2016 to December 16, 2016.

Dr. Olivia Coiado started the cardiac research group in the summer 2016 with a student team of three. The study was continued during the fall semester 2016 and will be continued in the spring semester 2017.

Cardiac ultrasound, also known as echocardiography, describes the ultrasound imaging of the moving human heart *in vivo*. The analysis of imaging the human heart is heavily technology driven and the diagnosis may include various diseases such as inflammatory heart diseases, ischemic heart disease, rheumatic heart disease and others.

Medical institutions might face struggles due to high costs of quality control. To improve the development of low-cost quality control mechanisms of medical equipment such as ultrasound imaging devices, a flow phantom and recipes to mimic blood and tissue were developed. The phantom was manufactured using cheap but high-quality materials. Additionally, a cost calculation was performed to represent the affordability for hospitals or other medical institutions.

The objective of this research was to develop a flow phantom using a peristaltic pump and several biomaterials to simulate the physiological parameters of the human heart *in vivo*. This development enables validation of biomedical equipment and accessibility for medical institutions to ensure quality control. Hence, research in the biomedical engineering sector is vitally important and must be supported.

1 ANATOMY OF THE HUMAN HEART

The human heart is known to be the strongest tissue in a living body. Its shape is described as a cone and it is a muscular pump, which enables blood and consequently nutrition and oxygen supply throughout all body parts (1). A human's heart is usually sized about 14 x 9 centimeters and weighs between 283 grams in males and 227 grams females (Fig.1) (2).

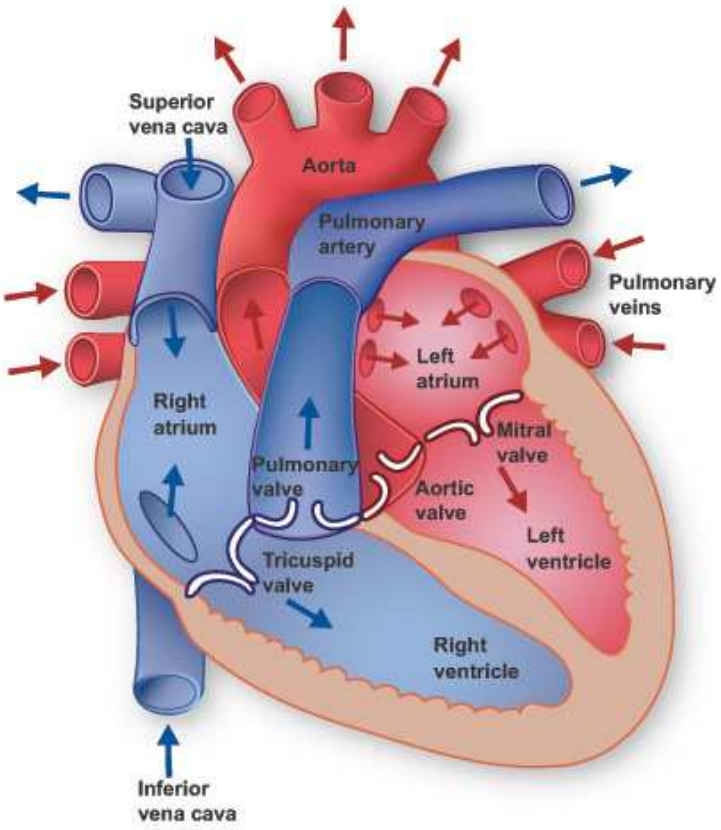

Figure 1: Anatomy of the human heart

Frontal sections of the human heart, with illustrated tricuspid valve, mitral valve, pulmonary valve, and aortic valve (3)

The human heart is bordered between the lungs, the vertebral column, and the sternum. The lower part of the heart is located at the level of the second rib and attaches to several large blood vessels. The heart's location enables detection of the current heartbeat by listening to the chest wall or feeling it. This is normally done between the fifth and sixth ribs. This is located about 7.5 centimeters to the left of the center, from the subject’s perspective (1).

1.1 HUMAN BLOOD

Blood is a connective tissue and promotes homeostasis in the body through the transport of substances through body cells and external tissues and structures. Its cells are suspended in a liquid, extracellular matrix and it consists of 45 % formed elements and 55 % plasma. The formed elements comprise of 95.1 % red blood cells, 4.8 % platelets, and 0.1 % white blood cells. Furthermore, white blood cells are comprised of 54-62 % neutrophils, 25-33 % lymphocytes, 3-9 % monocytes, 1-3 % eosinophils, and under 1 % basophils. The blood plasma consists of 92 % water, electrolytes, and 7 % proteins such as albumins, globulins and fibrinogen. Moreover, blood plasma transports dissolved gases such was oxygen, carbon dioxide, and nitrogen, as well as waste products of metabolism. Blood plasma also transports hormones, enzymes, nutrients, amino acids, vitamins, and minerals to and from cells (1).

The blood volume varies with body size, changes in fluid and electrolyte concentration, and the amount of adipose tissue. An average-size adult has about 5 liters of blood in the range of pH 6.8 to 7.4 and the blood volume is usually about 8 % of body weight.

Furthermore, blood has the ability to maintain body temperature and to regulate body fluid electrolytes, where an excess of salt may be removed from the body in urine. Furthermore, toxins are removed from the body via transport to the kidneys, There, the blood is filtered and the toxins are also, defected in the urine.

Hematopoiesis is the formation of all blood cells, including their formation, their development, as well as their differentiation. It takes place in red bone marrow where blood cells derive from pluripotent hematopoietic stem cells, also known as hemocytoblasts (1).

RED BLOOD CELLS

Red Blood Cells (RBCs), also called erythrocytes, show a lack of nuclei and mitochondria. They cannot divide but have the ability to produce ATP through glycolysis. RBCs are biconcave discs with a mean diameter of about 7.5 micrometer and are thin near their centers and thicker around their rims. This shape increases the surface and enables a closer cell membrane to the oxygen-carrying hemoglobin molecules, hence it is an adaption for the transport of gases. About one third of the red blood cells' volume is hemoglobin, which is an iron-containing oxygen-transport metalloprotein.

Human hemoglobin A consists of two α and two β subunits. The subunits are homologous and show similarities in their three-dimensional shapes. The capacity with which hemoglobin binds oxygen relies upon the occurrence of heme, which is a non-protein constitutent of hemoglobin. The heme group is responsible for the intense red color of blood. Furthermore, it is a bound prosthetic group and its chemical structure shows an organic component and a central iron atom (Fig. 2) (4).

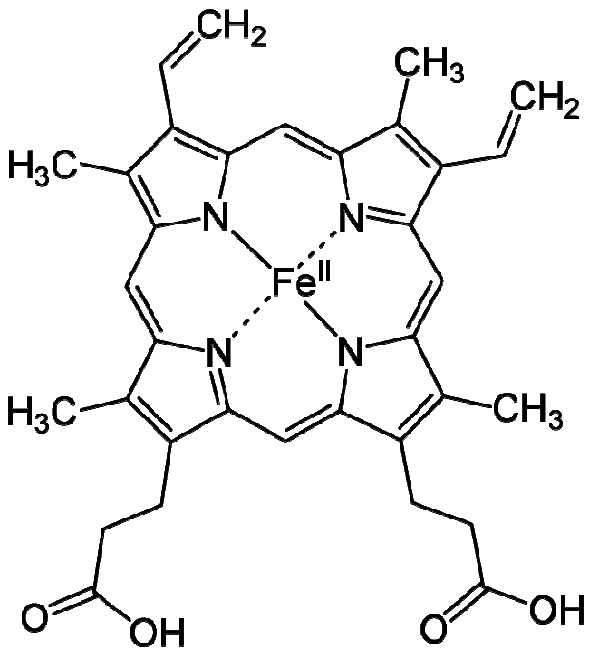

Figure 2: Chemical structure of heme

Heme illustrated with the central iron atom and the two α and two β subunits (4)

Normally, the central iron atom is in ferrous oxidation state (Fe^{2+}) and is able to form two extra bonds, hence one on each side of the heme component. These occured binding sites are known as the fifth and sixth coordination sites of heme. The fifth binding site is usually taken by a histidine residue, and the sixth binding site is able to fix oxygen (4). RBC count is the amount of RBCs measured in a cubic millimeter or microliter of blood and ranges from 4,700,000 to 6,100,000 RBC/ μL in males, 4,200,000 to 5,400,000 RBC/ μL in adult females, and 4,500,000 to 5,100,000 RBC/ μL in children (1). RBC counts are necessary for the diagnosis of diseases and evaluation of progression. Furthermore, a change of RBC count affects the oxygen-carrying capacity of blood (1).

RBC formation is called erythropoiesis which is a type of Hematopoiesis and occurs in the red bone marrow. Low blood oxygen causes release of Erythropoetin (EPO) from liver and kidney, which stimulates the production of RBCs. Through this negative

feedback mechanism, many new RBCs can be formed and emitted into the bloodstream within a few days (1).

White Blood Cells

White blood cells (WBCs) are also known as leukocytes and show the ability to leave blood vessels, which is called diapedesis. This is necessary because they destroy pathogenic microorganisms and parasites, and remove dying cells. Neutrophils phagocytose small particles, lymphocytes provide immunity, monocytes phagoytize larger particles, esinophils kill parasites and moderate allergic reactions, and basophils release heparin and histamin. Heparin prevents and treats blood cloths, whereas histamine triggers inflammatory responses through the increase of permeability of capillaries to permit white blood cells to engage with foreign substances. WBC production occurs in the red bone marrow and is controlled by hormones such as interleukins and colony-stimulating factors (1).

Blood Plasma

Blood plasma is a clear liquid in which cells and platelets are suspended. It consists of approximately 92 % water and contains a complex mixture of organic and inorganic biochemicals, including amino acids, nucleic acids, carbohydrates, and various lipids. It carries nutrients, gases, hormones, and vitamins to and from cells and helps to regulate fluid and electrolyte balance, and stabilizes blood pH (1).

The ABO Blood Group System

The nowadays well-known ABO blood group system was first discovered by the Austrian scientist Karl Landsteiner and distinguishes blood in phenotype A, B, AB and O. Furthermore, blood group O is the most common blood type, looking at Caucasians, Blacks and Asians (Table 1) (5).

Table 1: Frequency of ABO phenotypes differentiated in human descents (5)

Grouping	Group O [%]	Group A [%]	Group AB [%]	Group B [%]
Caucasians	44	43	4	9
Blacks	49	27	4	20
Asians	43	27	5	25

In terms of transfusion medicine, the ABO Blood Group System is necessary due to the possibility of an adverse immune response. A clerical error might cause death due to the incompatibility of the subject's blood type and the injected blood type during a blood transfusion. It has been shown that the different blood group antigens showed importance during human's evolution. It is assumed that a particular blood type had several advantages, such as resistance against infectious disease.

However, the different blood types have been linked to various illnesses. Group A individuals show gastric cancer more commonly, whereas group O individuals show stomach ulcers more often. Furthermore, phenotype O shows lower levels of the Willebrand Factor, which was found to be a protein involved in blood coagulation (5).

Human blood types depend on which antigen and antibody is found in the blood. The human immune system naturally produces antibodies against all antigens, which do not occur on the subject's RBCs. Therefore, subjects with phenotype A show anti-B antibodies, subjects with phenotype B show anti-A antibodies, and subjects with phenotype O show anti-A as well as anti-B antibodies in their blood serum. Phenotype AB is the least common type and those individuals show neither anti-A nor anti-B antibodies. However the absence of both antibodies does not affect the individual's health (Table 2) (5).

Table 2: Antigens, Antibodies and Genotypes of the ABO Blood Group (5)

Blood Type	Antigen	Antibody	Genotype(s)
A	A	Anti-B	AA or AO
B	B	Anti-A	BB or BO
AB	A and B	Neither anti-A nor anti-B	AB
O	Neiter A nor B	Both anti-A and anti-B	OO

Blood group A is divided into two phenotypes due to the different reaction to a particular antibody. This separates the blood group into the phenotypes A1 and A2. About 80 % of all individuals, who show phenotype A, appeared to have the A1 phenotype. Furthermore, the A1 group reacts with antibody A1, whereas the A2 group does not react with antibody A1. RBCs of the A1 phenotype showed to express about five times more A antigen than A2 RBCs do. However, both phenotypes are interchangeable for transfusion purposes. Although additional subgroups of phenotype A were found, that only

express the A antigen in small amounts, RBCs that weakly express B antigens are rare (5).

Since antigens are carbohydrates, the sequence of oligosaccharides defines whether it is the antigen A1, A2, or B. Attached to oligosaccharides chains, which are lie outside of RBCs, these antigen chains are then attached to proteins and lipids which are located in the molecule's membrane (5).

1.2 Human Blood Vessels

Blood vessels are defined as organs and are part of the cardiovascular system. They form a separate circuit through which blood is transported throughout the whole body, including the heart. There are various types of blood vessels such as veins, venules, capillaries, arterioles, and arteries. All of those blood vessels have different functions (Table 3).

Table 3: Blood vessels with specific function, table order is equal to blood circuit in the human body (1)

Blood vessel	Function
Arteries	Carry blood away from the heart's ventricles
Arterioles	Carry blood to capillaries
Capillaries	Enable exchange of nutrients and other substances between blood and body cells
Venules	Receive blood from capillaries
Veins	Carry blood back to the atria of the heart

1.3 Heart Chambers and Valves

The human heart is divided into two hollow chambers on the left, and two on the right side. It must be underlined, that information about direction is always indicated from the subject’s perspective. The two upper chambers, which are called atria, receive blood coming from the lungs and limbs. Therefore, these chambers show thin vessel walls due to low blood pressure in this area. Comparatively, the two lower chambers, known as ventricles, require thicker vessel walls due to higher pressure exposure. This pressure occurs because of the ventricles' function to pump blood into arteries. Looking at the two ventricles it can be seen, that the left ventricle has a thicker muscular wall than its

opposite, which is due to the left ventricle's function to pump blood to all parts of the body and, hence must exert a greater pressure (1).

The interventricular septum separates the two ventricles, whereas the interatrial septum divides the two atria. Furthermore, each atrium communicates with its ventricle through the atrioventricular orifice. This is an opening, managed by the atrioventricular valve, which is embedded within the fibrous skeleton.

The human heart uses four valves, which open and close in coordination with the pumping action, to ensure blood flow in the right direction. These valves are controlled by leaflets, called cusps that open or seal the valve. These valves are called tricuspid valve, mitral valve, pulmonary valve, and aortic valve (Table 4).

Table 4: Heart valves which ensure blood flow in only one direction (1)

Valves	Location
Tricuspid valve	Located between the right atrium and right ventricle
Mitral valve	Located between the left atrium and left ventricle
Pulmonary valve	Located between right ventricle and pulmonary artery
Aortic valve	Located between left ventricle and aorta

The tricuspid valve is composed of three leaflets and is closed when the atrium fills with blood. When the right atrial pressure increases during heart contraction, the valve is forced to open passively. Comparatively, when the ventricular pressure increases, the valve snap shuts and prevents blood from moving back to the right atrium, hence prevents blood from moving in the wrong direction.

The mitral valve consists of two cusps and is also known as bicuspid valve. It also prevents blood flow in the wrong direction during ventricular contraction, hence from moving from the left ventricle back into the left atrium. When the atrial pressure exceeds the ventricular pressure, this function is enabled through the leaflets' passively folding against the left ventricular wall. The mitral valve closes again passively, after the pressure in the atria decreases to a lower level than the pressure in the ventricles.

The base of the pulmonary trunk divides to form the left and the right pulmonary arteries, which lead into the lungs. At that base the pulmonary valve is located, which

consists of three cusps. During right ventricle contraction the pulmonary valve opens, whereas during ventricular relaxation, it prevents blood flow back into the right ventricle due to its closure.

At the base of the aorta, the aortic valve is located. It consists of three leaflets and allows blood flow out of the left ventricle during ventricular contraction. During ventricular relaxation it prevents blood flow from the aorta back into the left ventricle.

Furthermore, the pulmonary and aortic valves show half-moon shaped leaflets, which is why they are also called semilunar valves (1).

1.4 Covering of the Human Heart

The heart is surrounded by a fibroserous sac, also called the pericardium. This fibrous layer is the outermost, and is strongly tied to the central tendon of the body's diaphragm. It covers a double-layered serous membrane, where the innermost layer is called visceral pericardium or epicardium and the outermost is called parietal pericardium. The biochemical structure of these two membranes is similar, since it's the same type of tissue. Their different names are only due to the visceral pericardium's turning back upon itself, to form the parietal pericardium. The potential space between the two tissues is called the pericardial cavity and contains serous fluid, which reduces frictional forces between the layers during heart contraction and relaxation (Fig. 3) (1).

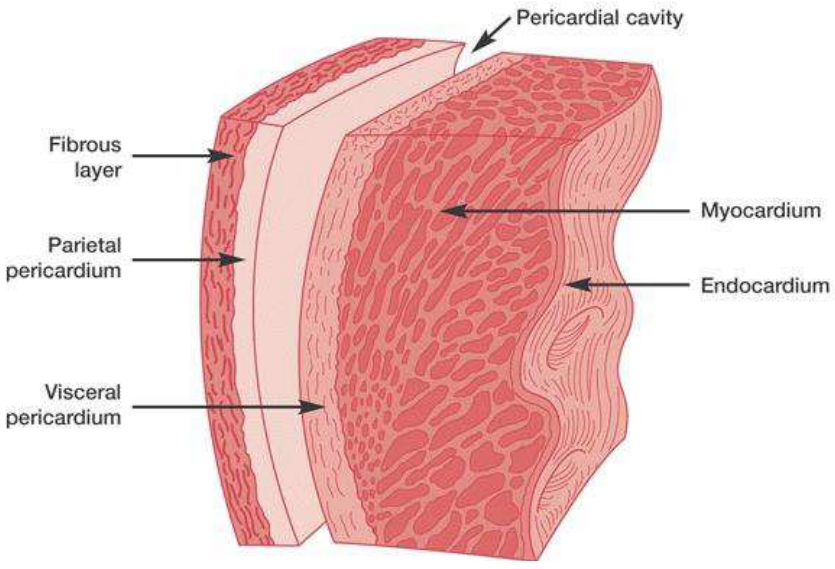

Figure 3: Covering of the human heart

Illustration of the parietal pericardium, the visceral pericardium and the pericardial cavity (6)

1.5 WALL OF THE HUMAN HEART

The human heart's wall consists of an outer epicardium, a middle myocardium, and an inner endocardium (Fig. 4).

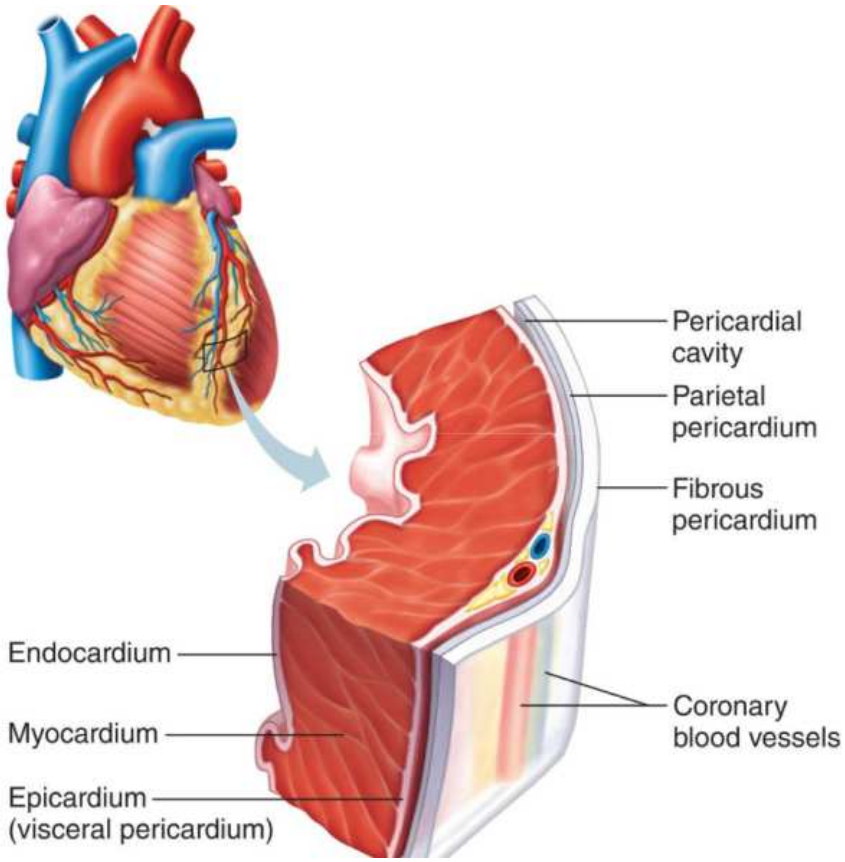

Figure 4: Wall of the human heart

Heart wall with illustrated epicardium, myocardium and endocardyum (1)

The epicardium consists of epithelium, underneath which connective tissue with capillaries and nerve fibers are found. This serous membrane protects the heart by forming an outer covering and secretes serous fluid which reduces friction.

The heart wall's middle layer is called myocardium and is comparatively thick. It mainly shows cardiac muscle tissue structures, which enable enough force to pump blood out of the heart's ventricles. The fibers of the muscle tissue are structured into several levels through connective tissue, including huge amounts of nerve fibers, as well as blood capillaries and lymph capillaries.

The innermost layer is known as endocardium, and consists of connective tissue, including many elastic and collagen fibers, covered with epithelium. Furthermore, it is pervaded with blood vessels for sufficient blood supply. The endocardium also covers

Purkinje fibers, which are special fibers that are able to send impulses for heart contraction. In conclusion, the endocardium forms a perfect inner protection of the different heart chambers and valves (1).

1.6 Skeleton of the heart

The skeleton of the heart is composed of dense connective tissue, including fibrous rings. It surrounds the pulmonary trunk and the aorta at their proximate ends and is known for its functions to fix the heart valve leaflets, to inhibit dilation of all heart chambers during contraction and to act as an insulator. Furthermore, it prevents electrical impulses from being forwarded from the atrial fibers to the ventricles, so that impulses from the AV node only pass through the atrioventricular bundle which is a bundle of electrically-connected cardiomycetes (1).

1.7 Cardiac Muscle

Cardiac muscle tissue is distinguishable from the two other forms of muscle, occurring in the human body. Cardiac muscle cells show the same function as skeletal muscles, but connect in branching networks and are responsible for pumping blood throughout the body. The intercalated disks, which are equipped with gap junctions, join cardiac muscle cells, allowing action potentials to spread throughout a network of cells that contract as a unit. The human heart consists of two functional syncytiums, which are masses of merging cells that act as a unit (1).

1.8 Stroke Volume, Ejection Fraction

The amount of blood that remains within the ventricle at the end of contraction and ejection is called the end-systolic volume, whereas the volume of blood that was in the ventricle prior to contraction and ejection is called end-diastolic volume. The stroke volume is determined by subtracting the end-systolic volume from the end-diastolic volume; hence, it is the amount of blood which enters the arteries during every ventricular contraction. A healthy heart shows the same volume of blood that is ejected into the aorta during each systole (7). The amount of blood which is unloaded by a ventricle each minute is known as cardiac output and can be determined when the stroke volume is multiplied with the heart rate.

The ejection fraction refers to the ability of the ventricle to pump blood with each heart beat. It is defined as the fraction of blood ejected by the ventricle relative to its end-diastolic volume, and is mostly between 55 % and 65 % (7).

1.9 HUMAN HEART RATE

Heart rate can be measured with a heart rate monitor, which is a medical device that measures heart rate in real time or records the heart rate for later studies. Furthermore, some devices may have the ability to determine maximum and average heart rate for a specific period, such as an exercise period. They may be able to produce a sound, when an athlete reaches or exceeds a predefined heart rate. Such devices mostly consist of a receiver worn like a watch on the wrist, which can detect signals from a transmitter worn around the chest, like a belt. With every heart beat, electrical signals are naturally sent through the heart muscle to cause contraction, which are measured through the subject's skin by the device. The transmitter sends electromagnetic signals with this information to the receiver on the wrist, where heart rate is displayed (8).

When an approximate heart rate is in demand, it can also be measured by putting the finger over an artery inside of the elbow, on the side of the neck and on top of the foot. Once the pulse can be felt, the number of beats in 60 seconds is counted. Factors such as temperature, humidity, body position, obesity and drug intake can affect the heart rate.

According to the National Institute of Health, the average resting heart rate for children at the age of 10 years or younger, elderly people and adults is 60 to 100 bpm. Furthermore, the average resting heart rate for well-trained athletes is comparatively lower with about 40 to 60 bpm (8).

A target training heart rate is a good way to avoid over-exercising, which can show adverse health effects. This can be found through determining the maximum heart rate while exercising. For instance, the wrist pulse is taken for 10 seconds and multiplied by six. The target training heart rate normally ranges between 50 and 85 percent of the maximum heart rate while exercising and is normally about 100 to 170 for 20 year-olds, 90 to 153 for 40 year-olds and 80 to 136 for 60 year-olds (8).

The heart rate is often equaled with blood pressure, although they are two separate indicators of health. While the heart rate is the number of times a heart beats each minute, blood pressure is the exerted force of a subject's blood moving through its vessels.

Furthermore, blood pressure is mostly related to pressure in the body's arteries. A rising heart rate does not cause increase of blood pressure at the same rate. Although the heart beats more often per minute, healthy blood vessels dilate; hence, allow more blood running through (8).

1.10 Cardiac Cycle of the Human Heart

The contraction of the human heart is called a systole, whereas the relaxation is called a diastole. The action of the cardiac cycle is organized so that atria contract while ventricles relax followed by the atria's relaxation while ventricles contract. Afterwards, atria and ventricles both relax for a brief interval.

One cardiac cycle refers to the period of time, beginning at a heartbeat's generation to the next, thus including systole, diastole, and the intervening pause. A duration of 0.88 seconds was shown to be the average of one cardiac cycle, quantified by the interval between two successive R wave peaks in a 24-hour electrocardiogram using 16 healthy subjects, differing in age and sex (9). The R wave is a specific amplitude in an Electrocardiogram and is further explained in section "Systole and Diastole".

The term heart rate refers to the frequency of these cycles and is typically expressed as beats per minute. Each heart beat involves five major stages, known as atrial systole, isovolumic contraction, ventricular ejection, isovolumic relaxation and diastole (7).

1.11 Cardiac Conduction System

Cardiac contraction is autorhythmic; hence, it is able to initiate contraction itself without external nervous stimulation. Contraction is initiated by an action potential that is normally sent from the Sinoatrial (SA) node in the right atrium. Sympathetic and parasympathetic fibers modify the heart rate in response to changing conditions, such as physical exercise, body temperature, and concentrations of K^+ and Ca^{2+} ions. The SA node, also called sinus node, is located in the upper posterior wall in the right atrium. It is the normal natural pacemaker of a human's heart and spontaneously generates electric impulses, initiating systole and diastole.

The action potential of the SA node causes a wave of electrical impulses, which travel to the Atrioventricular (AV) node. This node conducts impulses to the AV bundle and delays impulses so that atria can finish contraction before the ventricles contract.
The left as well as the right bundle branches split off from the AV bundle and conduct

impulses to Purkinje fibers on both sides of the heart. Once at the Purkinje fibers, impulses are conducted to the ventricular myocardium and the heart's contraction is triggered. Although the electric impulses are generated spontaneously their rate is set by nerves related with the SA node (1).

1.12 Systole and Diastole

Systole describes the contraction of the left atrial wall, where blood enters the left ventricle after passing through the left atrioventricular orifice. It begins with the occurrence of the QRS complex in the electrocardiogram. A Q wave is any downward deflection, an R wave follows as an upward amplitude, and the S wave is any downward amplitude after the R wave. The QRS complex is commonly the most visually obvious part of an electrocardiogram and corresponds to the depolarization of the ventricular muscle mass (7).

During isovolumic contraction no change in ventricular volume occurs and the left atrial wall relaxes whereas the left ventricular wall contracts. It is described as the period of time, where the ventricular pressure increases but is still less than the aortic pressure. When pressure within the ventricles exceeds the pressure within the aorta, the aortic valve suddenly opens and the ventricle rapidly ejects blood into the aorta, known as ventricular ejection.

The pressure in the ventricle still increases during ventricular ejection, simultaneous with the increase of the aortic pressure. However, the ventricle's volume declines due to the ejection of blood out of the ventricle into the aorta. This stage is followed by isovolumic relaxation in which the ventricular pressure decreases, no blood enters the ventricles, they stop contracting and begin to relax.

About halfway through systole, a T wave in the electrocardiogram appears. This wave represents the repolarization of the ventricles and initiation of relaxation. The relaxation occurs until the left ventricular pressure falls below the aortic pressure, which causes the aortic valve to suddenly slam shut. Ejection stops and no further changes in the left ventricular volume occur. This state is considered the end of the ventricular systole.

Through repolarization of the ventricular muscles the diastole is initiated. After the closure of the aortic valve, the left ventricular pressure rapidly begins to fall.

Simultaneously, the left atrium is relaxed and receives blood from four pulmonary veins of which two come from the right, and two from the left lung.

When the blood pressure within the left ventricle drops below the pressure within the left atrium, blood will suddenly rush from the atrium in the ventricle. The mitral valve opens, shortly afterwards the left ventricle is filled with blood and the ventricular volume decreases.

Action potential of the SA node causes depolarization of the atrial chambers, which can be seen as the P wave in the electrocardiogram. This impulse causes an increase in atrial pressure, which is illustrated as the a wave. Additional blood volume is forced into the ventricle shortly after the end of filling. However, because most of the filling happens passively, this volume accounts for only 10 % of the ventricular filling at resting and up to 40 % of the filling during exercise. This increase is due to an increased heart rate and a decreased time to fill the ventricle (Fig. 5).

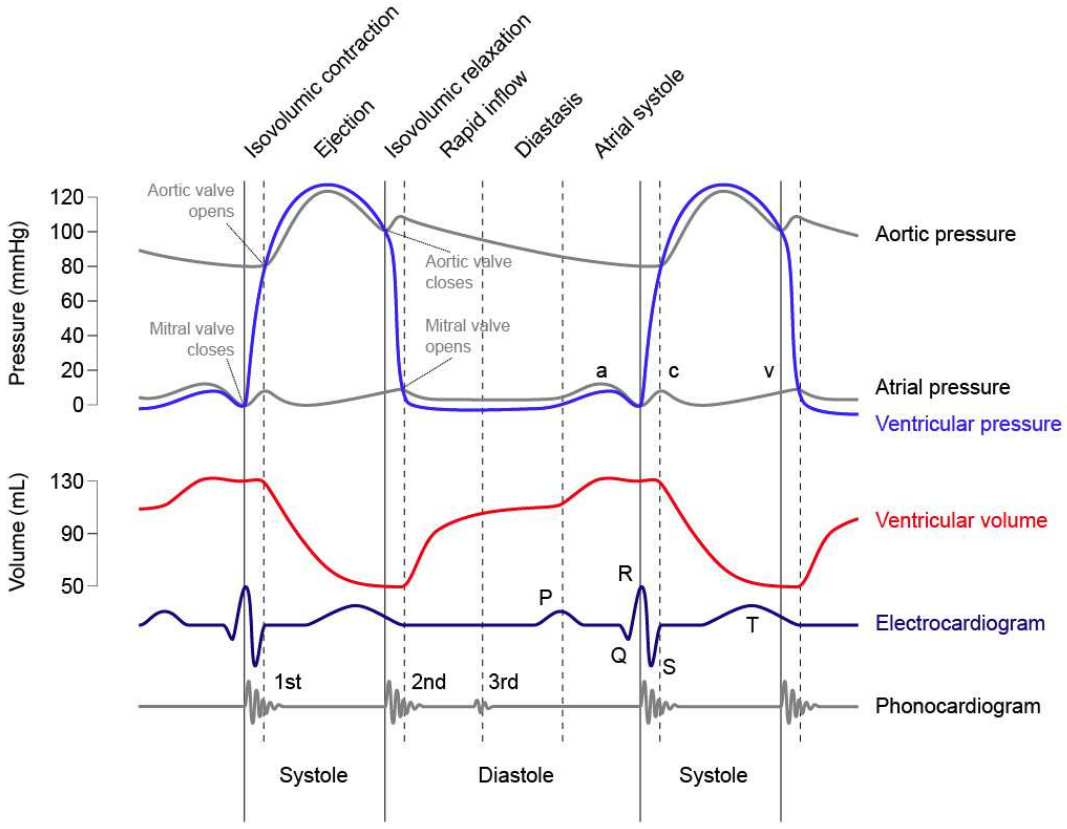

Figure 5: Cardiac events occuring in the cardia cycle

Two complete cycles are illustrated, showing diastole, atrial systole, isovolumic contraction, ventricular ejection and isovolumic relaxation time; furthermore, the ventricular blood volume throughout the cardiac cycle, QRS, P, and T waves of the electrocardiogram, heart sounds of the phonocardiogram, as well as atrial and ventricular pressure are illustrated (10)

Atrial systole, isovolumic contraction, ventricular ejection, isovolumic relaxation and diastole occur just as well on the right side of the heart. Blood from the superior vena cava and the inferior vena cava is transported into the right atrium. The superior vena cava returns low-oxygen blood from head, neck and both upper limbs, whereas the inferior vena cava returns low-oxygen blood from the lower parts of the body. Additionally, a smaller vein called coronary sinus also transports blood which is low in oxygen from the myocardium into the right atrium (7).

1.13 Sounds in Phonocardiogram

A phonocardiogram is a plot of high-fidelity recording of sounds and murmurs occurring from heart contraction through the usage of a machine called phonocardiograph. All sounds caused by the heart during a cardiac cycle are recorded and illustrated in a phonocardiogram.

Shortly after depolarization through the SA node occurs, the left ventricular pressure rapidly increases, although no blood injection is occurring. This happens through the mitral valve's and tricuspid valve's closure, which is also known as ventricular systole. The produced sound through this closure is the first heart sound and can be determined in the phonocardiogram. The second sound in the phonocardiogram is caused by the closure of the aortic valve and the pulmonary valve. As mentioned above, the aortic valve is located on the left, whereas the pulmonary valve is located on the right side of the heart. The explained procedure occurring through closure of the two valves is also known as the ventricular diastole.

The last and low-frequent heart sound is a brief vibration and is associated with heart failure. Occurring in early diastole and after diastolic filling, it is commonly difficult to heart, using a stethoscope. This is not only because it has a frequency which too low for the human ear to detect, but because lung or abdominal noise mostly drowns this heart sound.

It has been shown that adults up to age 35 or 40 as well as children may show a third heart sound but are perfectly healthy. At current stage of knowledge, the reason for this is yet unknown. However, a third heart sound after the age of 40 is considered as unnatural and is referred with volume overload of one or both ventricles, or heart dysfunction (11).

1.14 Blood Circuit of Human Body and Alveolar Gas Exchange

The systemic circulation enables perfect blood supply through every body tissues. Oxygen and nutrients are carried to body cells and simultaneously carbon dioxide is taken away as a waste product. The transport of blood which is low in oxygen, from the heart to respiratory organs, such as the lungs, and afterwards back to the heart is called the pulmonary circuit. Comparatively, the transport of blood which is low in oxygen, from the human heart to all cells throughout the body, and back to the heart is known as systemic circuit (1).

During ventricular ejection, the blood is transported from the right atrium, to its ventricle, and to its connected pulmonary arteries and to the lungs where gas exchange takes place. Gas exchange is the oxygen-delivery to the bloodstream, starting at the lungs, and the transport of carbon dioxide from the bloodstream back to the subject's lungs for further gas exchange. Both procedures work simultaneously.

After inhaling air through the mouth, it is moved to the pharynx, the larynx, and enters the trachea afterwards. This divides into a right and left bronchus within the lungs and further branches into smaller and smaller bronchioles. These are small branches and the smallest bronchioles are defined as alveoli, which are microscopic air sacs. Alveoli deflate during exhalation and inflate during inhalation. The wall of an alveolus consists of a layer of simple squamous epithelium and is associated with a dense network of capillaries on its surface.

The alveolus' epithelium and the capillary's endothelium are separated by an interstitial space, which together with the epithelium forms the respiratory membrane. It is normally about 1 micrometer thin and enables rapid gas exchange rates. More surface area through alveoli, shorter distance through a thin membrane and a steep partial pressure gradient favor increased diffusion (1).

The dissolved gases oxygen and carbon dioxide follow concentration gradients during gas exchange. In terms of partial pressure gradients, a gas will diffuse from a high-pressure area to a partial low-pressure area until the pressure in the two regions reached equilibrium. Therefore, oxygen is passively transported into the capillaries, whereas carbon dioxide is transported into the alveoli. This passive transport is also known as diffusion.

Over 98 % of the oxygen is carried through the body, bound to the protein hemoglobin, which is found in red blood cells. It is bound to iron in hemoglobin, which is responsible for the red color which can be seen when looking at RBCs. The other 2 % of oxygen is dissolved in the blood plasma.

The blood which shows high oxygen levels after gas exchange is transported to the left atrium and exits the aorta and its branches through flowing through the left ventricle. It is then transported to the capillaries throughout body tissues, where the oxygen is used for cell respiration; hence, ATP production. After alveolar gas exchange, blood which is low in oxygen and rich in carbon dioxide is transported back to the right atrium of the human heart (Fig. 6) (1).

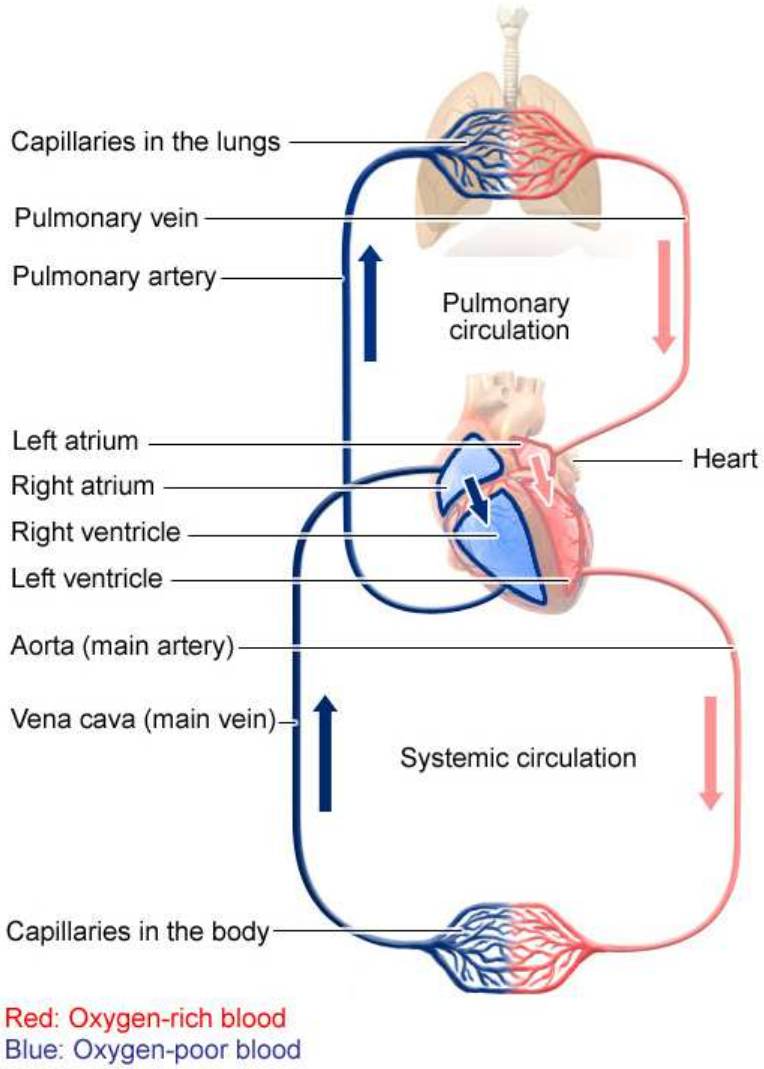

Figure 6: Blood circulation of human body

Blood circulation seperated in pulmonary and systemic circulation; blue illustrates oxygen-poor blood, whereas red illustrates oxygen-rich blood (2)

2 ULTRASOUND

Ultrasound (US) imaging (sonography) is a technique for diagnostic imaging, using US waves to visualize human tissues and organs. The used sound waves show higher frequencies than those which can be audibly noticed by humans. Human ears can detect sound between 20 and 20,000 Hz, whereas US waves typically range between frequencies of 1 million to 15 million Hz (12). Commonly performed US imaging procedures include abdominal US to visualize organs and various tissues, echocardiograms, which enable imaging the heart, breast ultrasound, Doppler fetal heart monitors, in which the unborn child's heart beat is analyzed, and Doppler ultrasound, which visualizes blood flow through vessels in two directions (13). The most commonly used US imaging type is B-mode imaging, which displays a two-dimensional cross-section of human body tissue by its acoustic impedance (Fig. 7).

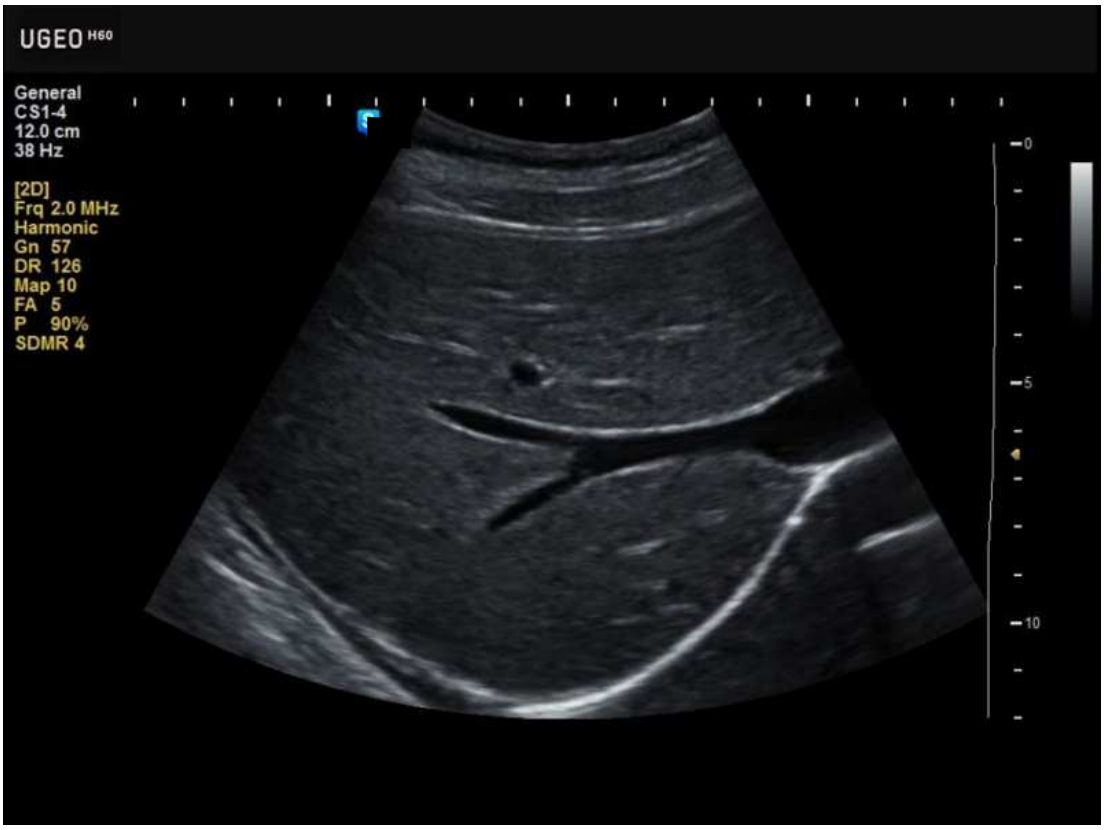

Figure 7: B-mode US image of liver with portal vein

US imaging with a used frequency of 2.0 MHz, received by the US scanner H60 (Samsung) (14)

Other ultrasound modes are A-mode, M-mode, and Doppler ultrasound (Table 5).

Table 5: US modes summarized with basic principles **(**12**)**

US Mode	Explanation
A-mode (Amplitude)	Echoes from tissue interfaces are seen as spikes on the monitor. The height of the spikes equals the amplitude of the echo. A-mode US is rarely used.
B-mode (Brightness)	The spike is converted to a dot and the intensity of the echo is represented in different brightness of the spot, which represents the amplitude. B-mode US is most commonly used.
M-mode (Motion)	The US is sent along a sample line, waves are reflected along this line and converted to a brightness scale. This scale is displayed along a time axis.
Doppler Ultrasound	Doppler US can be differentiated into color Doppler, power color Doppler and pulsed Doppler. Echoes from moving scatterers differ from echoes from stationary tissue. These differences are measured and displayed in color.

US imaging is a portable, non-invasive, low-prized imaging technique which provides real-time images and unlike X-ray imaging, no ionizing radiation is used. In over twenty years of use, excellent safety records have been shown, although US energy shows the possibility to cause biological effects in the body due to heating of tissue when applied too long and in too high frequencies. Bioeffects triggered by too high ultrasound intensity must be considered whenever US is applied to a specific tissue location within the patient's body.

For medical imaging, frequencies ranging from 2 to 20 MHz are commonly used. The intensity, which is measured as the rate of energy per unit area (mW/ cm^2), is detected by amplitude of oscillation, hence intensity increases as amplitude is increased. The unit used to describe the amplitude is decibels (dB) and the amplitude itself is described as the strength of a sound wave (12).

Different US transducers can be used for diagnostic imaging, varying in use, frequency and shape, such as linear, curved or phased arrays (Fig. 8).

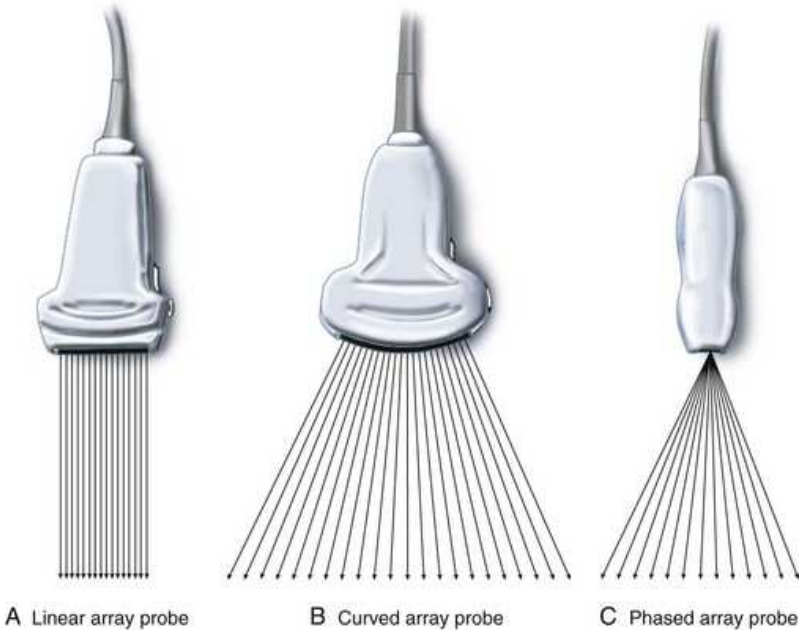

Figure 8: Linear, curved and phased ultrasound transducers with emitted beam (12)

High frequency transducers are used to shallow imaging applications that demand higher resolution, whereas low frequency transducers are commonly used to image deeper structures in the body.

An US transducer converts electrical pulses to mechanical vibration and sends these waves in longitudinal motion into the body. The US transducer is placed inside a body opening or, more commonly, directly on the subject's skin or and - before application - a thin layer of gel is put onto the body surface so that the US waves can be sent from the transducer into the body through the layer of gel. High-frequency waves are sent into the tissue and are reflected at the interfaces between the tissues. When received at the transducer's surface, the mechanical vibrations are again converted into electrical pulses and can be analyzed by the US imaging device (13). The strength of the reflected sound signal, as well as the return time of these waves provides the necessary information to display an image (Fig. 9).

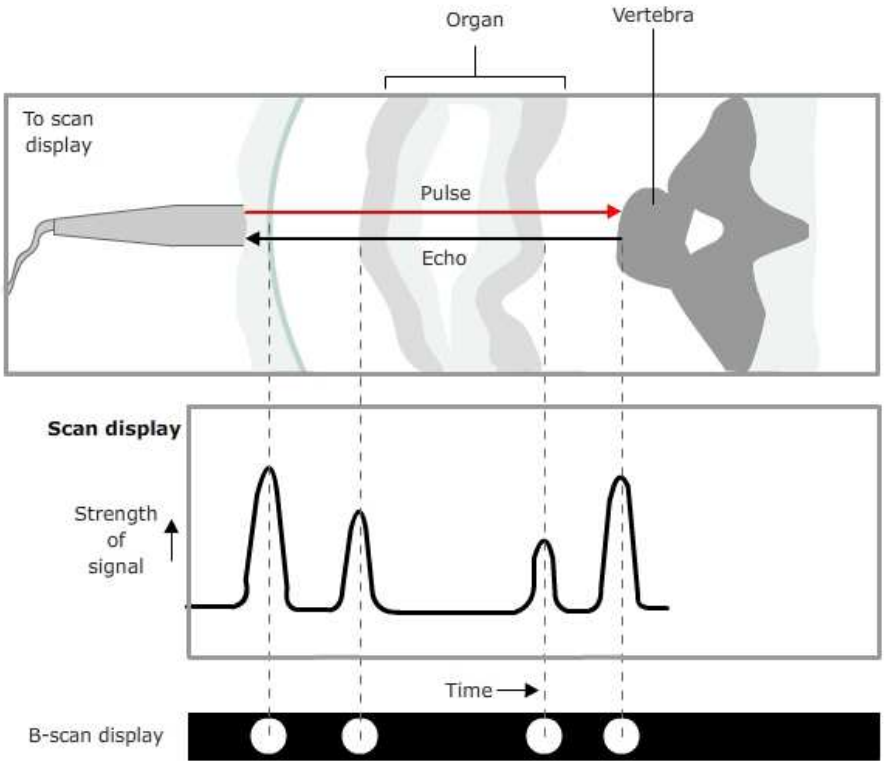

Figure 9: Principle of B-mode US imaging

US waves are transmitted into the body and are reflected at the vertebra, strength of signal depends on type of tissue (15)

When the US waves cross a boundary between two tissues or other media, some of their energy is sent back at the surface through reflection, and some of their energy is let through. The amount which is reflected depends upon the vibrations in the "acoustic impendence" between the two tissues or media. These echo signals are amplified electronically and displayed on a monitor using different shades of grey (from black to white). Tissues, which reflect stronger, show brighter shades of grey and appear white in an image, whereas those with no echoes will appear black, such as a full bladder. Furthermore, the amount of these echoes can also be calculated through the multiplication of the density of the medium and its speed of sound.

The speed of sound is defined as the distance travelled per unit time by a sound wave as it propagates through an elastic medium. Furthermore, the attenuation is defined as the diminishment of intensity due to absorption, scattering, and mode conversion. Increased depth or increased frequency always causes increased attenuation. Acoustic scattering arises from objects that are sized equally to the wavelength or smaller. This effect enables producing gray-scale images through visualizing surfaces, which are parallel to the US waves.

The American College of Radiology (ACR) provides the ACR accreditation, which is recognized as the gold standard in medical imaging and helps assuring the highest level of image quality and safety for patients (16). The ACR has accredited more than 38,000 facilities in ten imaging modalities, since 1987. These imaging modalities are breast Magnetic Resonance Imaging (MRI), general MRI, breast US, Computer Tomography, mammography, nuclear medicine, Positron Emission Tomography, radiation oncology practice, stereotactic breast biopsy, and US (13).

2.1 Quality Control of Ultrasound Equipment

In several medical technology application areas, several procedures for quality control are in daily or monthly use. These enable evaluation of the current quality of the medical devices used for diagnoses or treatments. Assurance of the devices' quality is essential due to a progressive degradation of image quality during the use of extensive ultrasound equipment and patients' safety (17).

A qualified medical employee or appropriate trained personnel is required to perform annually US quality. If this person was trained, he or she has to be approved by the leading physicist in charge. Furthermore, it is recommended by the American College of Radiology to perform routinely quality controls by service engineers, or better by perfectly trained sonographers. During routinely quality controls, reports must be written to document problems or the corrective action taken. This must be done to identify those actions, when problems occur during annual surveys (16).

2.1.1 Routine Quality Control, Annual Surveys and Acceptance Testing

Routine quality control testing refers to a smaller amount of quality control procedures than annual surveys and acceptance testing do. The ACR recommends the performance twice a year by a medical facility's service engineer, or better its sonographer (16).

Annual surveys are more extensive tests, which are performed each year by an appropriately trained personnel or a medical physicist who is qualified in that area. This survey includes mostly the same procedures which are made during the routine quality control twice a year, but additionally includes an evaluation of the medical facility's routinely done quality control program.

Acceptance testing refers to the testing of old, repaired or newly installed US equipment and has to be completed before the device is used clinically. The following acceptance

testing is explained by using a phantom which imitates the liver parenchyma. Therefore, US control settings such as the target gain control (TGC), gain, power, the body slice, as well as the gray level map and settings related with the dynamic range need to be adapted. All these settings are adjusted with the above-mentioned phantom.

At the current stage, phantoms are optional for ultrasound quality control. However, a simulated object or a phantom, if applicable is the needed equipment with which US quality control procedures must be performed.

After completing all US procedures, the final settings must be documented and kept for later use. It needs to be ensured that this document can be found and traced back easily, because this final set up has to be used whenever any US quality control is done. During quality control procedures, this data sheet tells the sonographer if the testing values are above or below the set baseline, and if that is the case, the device has to be repaired (16).

Furthermore, the ultrasound device's baseline should be found and documented shortly after the equipment's installation. Depth and focal zone are set up as necessary and needed information can be found in the quality control guideline chapter in the medical device' operating instructions (17). In conclusion, acceptance testing includes several procedures done to enable appropriate baselines for correct future US imaging results (16).

2.1.2 Phantoms for Quality Control

For medical institutions, purchasing a phantom is currently not necessary. This is due to the ACR's requirement that either test objects, or phantoms can be used. Phantoms may be available by commercial suppliers or manufactured and developed by experienced employees (18).

2.1.3 Quality Control Procedures

The ultrasound device is inspected physically and mechanically. The transducer's cables, plugs and surface transmission are investigated for damages or other issues. The transducer must move smoothly, without vibrations or noisy sounds and must be tested on the phantom or on the test object. It has to be pointed out, that the transducer must be cleaned after each application. Furthermore, the transducer connections must be intact and not be broken. The plug and the power cable are checked of any damage, and the

control buttons must not show any type of dust or dirt. All lights need to be intact and the device's image screen must be free from damage and without dust and dirt. Moreover, the brightness and contrast control must be adjusted on the appropriate level and must function perfectly.

Dust and air filters need to be clean and must not show damage. This is due to the danger of overheating of electrical equipment and risk of other damage caused by filters in a bad
physical condition. Furthermore, rotation buttons have to be handled easily and must not make any noise while usage.

After checking the above-mentioned aspects, an image screen monitor set up as well as the image uniformity must be analyzed. Distance measurements as well as target detection and imaging are performed and the frequency is checked by using the phantom or the test object.

Currently, water-based gels as well as solid materials are used to enable quality control of ultrasound devices. Water-based gels have an advantage in the speed of sound of approximately 1540 m/ s, a proportional attenuation to the frequency and backscatter (19). The drawback is the required storage in containers, a required scanning window as well as the risk of desiccation. Urethanes are commonly used as non-water-based materials. They do not show any risk of desiccation or need for a scanning window. Furthermore, tissue-like backscatter can be produced. Adversely, the speed of sound ranges between 1430 and 1450 m/ s and the surface can be damaged easily, if not cleaned regularly to remove residual gel. Moreover, the attenuation is not proportional to the applied frequency (19).

3 FLOW PHANTOMS AND MEDICAL DEVICES

Flow phantoms in general are specifically designed objects, which involve dedicated biomaterials to simulate special realistic circuits of human beings. At the moment, using phantoms for ultrasound quality control for medical devices is optional (19). However, a phantom or simulated object is the basic equipment that must be used to perform the quality control tests.

Patients suffering from a weakened heart are given several options to improve their quality of life. A ventricular assist device, a total artificial heart or heart transplantation may improve the heart function or completely replace the weakened heart.

3.1 VENTRICULAR ASSIST DEVICES

A ventricular assist device (VAD) supports the heart's ventricular function through its mechanical pump. Therefore, blood flow of the human heart is supported. This device is used when patients are diagnosed with a weaker heart function as usual or for patients with end-stage congestive heart failure who are listed for heart transplantation. These patients often have to wait long periods of time. The average waiting time is about 300 days or more before a suitable donor heart becomes available (20). Therefore, VADs are used as a bridge-to-transplant and are available for short, intermediate and long term support.

The basic parts of a VAD are a control unit, a power source, a pump and small tubes, which carry the blood to the pump and back to the patient's blood vessels. Pumps can operate with pumping action or they can keep up a continuous flow of blood, which is further explained in section 3.1.1 "Pulsatile-Flow Pumps And Continuous-Flow Pumps" (20).

The two basic types of VADs are a left ventricular assist device (LVAD) and a right ventricular assist device (RVAD). Furthermore, both types can be used at the same time, which is then called biventricular assist device (BIVAD). LVADs are used in those patients, to enhance the natural heart's function during the waiting period by providing the required muscle function to force blood from the left ventricle into the aorta. As implied by the name, RVADs pump blood from the right ventricle into the pulmonary artery, and are usually used for short-term support after heart surgery. BIVADs are used if both ventricles show weakened function (20). However, an artificial heart,

explained in section 3.6 "Total Artificial Heart" could be another way to treat this diagnosis.

3.2 Pulsatile-Flow Pumps And Continuous-Flow Pumps

A pulsatile-flow pump creates a flow with periodic variations, whereas a continuous-flow pump does not create any variations in velocity or pressure. A necessary part of our cardiovascular system is the arterial pulse. Human cells have the ability to recognize and adapt to any change in blood pressure or blood flow (21).

Continuous-flow left ventricular assist devices (CFVAD) were mostly used in 2014, looking at devices for mechanical circulatory support (22). Research has shown that continuous flow VADs may decrease complications, the length of hospital stays for patients and improve the patient's survival rate despite the diagnosis of a weakened heart (22). Although CFVADs show benefits compared to pulsatile-flow VADs (PFVADs), which are considered as the first generation, they have also been linked with several complications (21).

PFVADs are bigger than CFVADs. Furthermore, CFVADs seemed to be more reliable and durable, which lead to improvements in patient's survival. However, these devices show lower rates of recovery of subject's left ventricles, which is linked to a decreased blood supply of small arterial vessels, higher pressure gradients on the aortic valve, and reduced pulsatility. Therefore, it is recommended to use pulsability control algorithms in CFVADs to improve long-term usage in patients, or support PFVADs (21).

Several studies have proven that pulsatile flow seemed to have a bigger influence on endothelial regulation than continuous flow. Nishinaka *et al*. revealed a study in 2001, showing a 50 % thinning of the aorta, as well as a lower contractility of smooth muscle tissue by using a CF left heart bypass (23). Furthermore, pulsatile-flow pumps trigger a more effective microcirculation of the renal cortex flow, the liver tissue flow and the stomach mucous flow when these organs were investigated (24). Although it was discussed whether the pulse was significant in human capillaries or not, several studies proved that pulsatility was actually measured at the capillary level. Furthermore, a difference in microcirculatory flow patterns between continuous and pulsatile flow supports was shown (21).

In a study published in 2013 by Cheng, Soucy, Giridharan *et al.* 36 patients underwent an echocardiography comparing subjects with implanted PFVADs (HeartMate XVE) and CFVAD (HeartMate II). Several examinations and echocardiographic images were performed before and after implantation. These procedures were done 30, 90, 180 and 360 days after the device was implanted. It has been shown that CFVAD and PFVAD reduced external work, contractility and end-diastolic pressure similarly, but vascular resistance and aortic pressure ended up being higher with CFVAD (Table 6) (25).

Table 6: LVAD, left ventricular assist device; CF, continuous flow; PF, pulsatile flow; LVPed, left ventricle end-diastolic pressure; LV EW, left ventricle external work; AoPsys, aortic systolic pressure; R, systemic vascular resistance (25)

Parameter	Baseline		Partial LVAD support		Full LVAD support	
CF/ PF	CF	PF	CF	PF	CF	PF
LVPed (mmHg)	18±2	16±2	13±2	11±2	11±1	11±1
LV EW (mmHg·mL)	2,569±44	2,539±26	1,100±26	552±12	420±15	517±23
dP/ dt (mmHg/ s)	787±93	726±63	851±119	453±75	653±61	479±76
AoPsys (mmHg)	48±2	47±4	68±5	51±4	78±2	53±4
R (mmHg·s/ mL)	1,36±39	1,69±30	2,76±3,08	1,27±1,24	10,022±6,16	2,97±2,34

Looking at the echocardiography data, no meaningful difference in the degree of mitral regurgitation, left ventricular (LV) unloading, or LV size could be determined between the compared groups. PFVAD as well as CFVAD pressure reduced external work and exerted stress on the heart and aortic wall, as well as discharge the LV. However, CFVAD influenced the vascular resistance by increasing it (Fig. 10) (25).

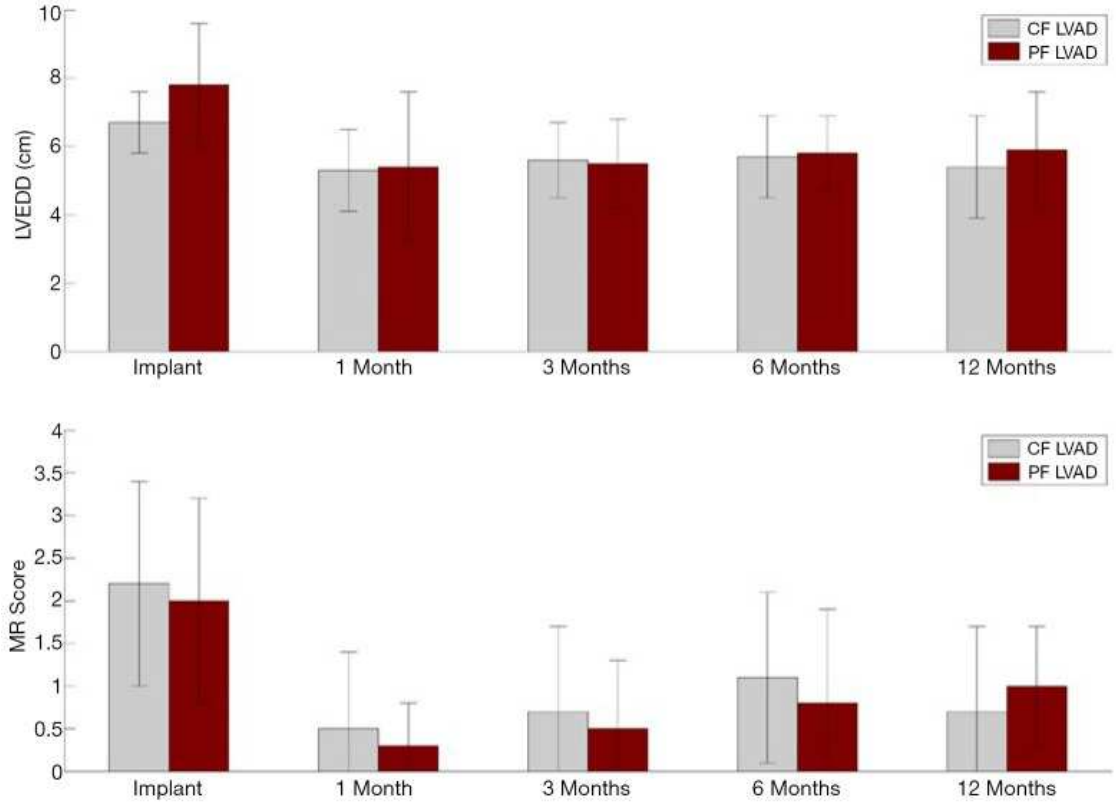

Figure 10: Echocardiographic data of all patients

36 patients were included in this study, 17 had CFVADs, 19 had PFVADs; MR, mitral regurgitation; LVEDD, left ventricular end-diastolic dimension (25)

Furthermore, a study published in 2011 by Krabatsch *et al*. investigated the likeliness of myocardial recovery with PFVADs and CFVADs. In this study, 243 subjects were implanted with CFVADs, whereas 144 subjects were implanted with PFVADs. 34 of these 387 subjects showed health improvements and those who were implanted PFVADs showed a three times increased chance of heart muscle recovery compared to subjects who had CFVADs (26).

3.3 Ventricular Assist Device Implantation

To connect a VAD to a patient's heart, surgery is required, which is performed in a medical institution under general anesthesia. Anticlotting medicine is given intravenously through the subject's arm and a breathing tube delivering oxygen helps the patient breathe. A surgeon opens the chest and connects the heart's vessels to a Heart and Lung Bypass Machine. The pump is connected to the subject's heart after it is placed in the upper abdomen. Afterwards, the VAD has to be connected to its power source and its control unit, which are located outside of the subject's body.

Following this procedure, the Heart and Lung Bypass can be turned off and the VAD supports the subject's heart pumping function and blood flow. A study published by Klotz *et al*. in 2006, showed a similar survival rate between CFVAD and PFVAD patients. However, the rejection rate was lower with PFVAD, which was 33 % vs. 89 % (27).

3.4 TRANSCUTANEOUS VAD VS. IMPLANTABLE VAD

The transcutaneous VAD's power source is located outside of the patient's body and is used for temporary support during or after surgery. Tubes enable the connection of the pump with the heart through small incisions in the abdomen.

In comparison, an implantable VAD is used for patients waiting for heart transplants and as a long-term solution. In that case, the pump is usually smaller than a transcutaneous VAD's pump and is transplanted into the subject's body (22).

3.5 HEART AND LUNG BYPASS

A heart and lung bypass is also known as cardiopulmonary bypass (CPB) and is a technique, which temporarily replaces the heart and lung function while the human heart is arrested to allow a surgery.

Cannulas are put into the subject's right atrium and transfer blood from the subject's heart to a device, which oxygenates the blood and removes carbon dioxide through a membrane oxygenator. The transfer of blood to the device is ensured by using a non-pulsatile flow pump with a flow of 2.4 L/ min/ m^2. Furthermore, the temperature of blood is controlled by a heat exchanger and is mostly 28 to 34 °C. A lower temperature than normal provides a slower metabolism. Air bubbles are removed by a 40 mm filter and blood is returned back into the aorta distal to a cross clamp. Distal means farthest away from the body and an aortic cross clamp is a surgical instrument, which clamps the aorta and separates the systemic circulation from the outflow of the heart. During surgery, suction is used to remove blood from the operative field and is returned to the patient via a cardiotomy reservoir. This is a temporary storage for solutions before filtration of particulate materials such as blood clots or blood cell aggregates takes place (28).

Extracorporeal Membrane Oxygenation

For long term treatment, Extracorporeal Membrane Oxygenation (ECMO) can be used. Extracorporeal means located outside the body and through ECMO, support of the cardiac as well as the respiratory system is enabled. This device is used, when a subject's heart and lungs are too weak to provide the required amount of oxygen for the body to maintain life. To apply ECMO, a specially trained team of about thirty people is needed (29). This intervention is mostly used in babies and children, but can also be used in adults suffering from respiratory or cardiac failure.

The principle is similar to the Heart and Lung Bypass and the term extracorporeal refers to a medical procedure, which is performed outside of the human body. Through an ECMO device, circulation of blood including oxygenation and removing carbon dioxide outside of the subject's heart is enabled (Fig. 11).

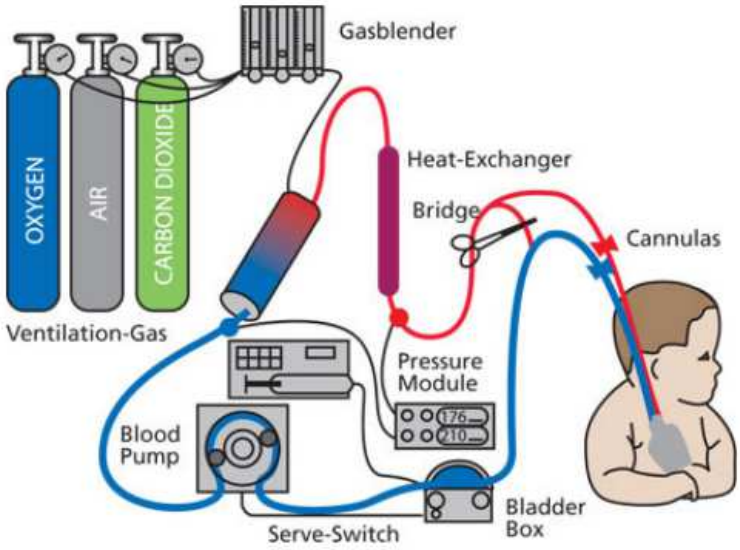

Figure 11: Extracorporeal Membrane Oxygenation (ECMO) device

ECMO device with illustrated circulation of blood; from subject to gas exchange, warming of blood and leading the blood back to subject (29)

3.6 Total Artificial Heart

A total artificial heart (TAH) is a device, which replaces the two ventricles of the human heart and is mostly used for patients who are diagnosed with end-stage heart failure. End-stage refers to the patient's severe situation, meaning that all treatments except a heart transplant have failed. Unlike a donor heart, the TAH is immediately available for surgery and is, therefore, applied in patients who are on the waiting list for heart

transplantation and immediately need surgery, or as a long-term solution for those who are not qualified for a heart transplant (Fig. 12) (22).

Figure 12: Portable motor driver attached to a SynCardia TAH (30)

TAHs provide immediate blood flow of up to 9.5 liters per minute through each ventricle, which can speed up the recovery of vital organs due to recent lack of blood, oxygen and nutrient supply (30). A TAH implantation can eliminate failing ventricles controlled by medication. Furthermore, needed surgeries caused by problems form LVADs, RVADs or malfunctioning heart valves can be avoided.

In 2001, the New England Journal of Medicine published important data from a clinical study lasting 10 years. In this study, which led to FDA approval, 79% of the subjects who received a donor heart were stabilized with a TAH before heart transplantation. This helped the subjects survive until the matching donor heart was found and they were called to be bridged-to-transplant (30). Until then, this has been the highest rate of bridge-to-transplant cases for any approved cardiovascular device worldwide. Furthermore, approximately 65 % of the patients were out of bed by the fifth day after implant and 60 % were able to walk more than 100 feet after two weeks of surgery (30).

During surgery, both ventricles as well as the four native heart valves are taken out of the subject's body. Quick Connects are entries, which enable fast attachments, and are sewn into the atria, aorta and pulmonary artery. Subsequently, the TAH is implanted and attached to those four entries. The quick connects include a mechanical valve, which replaces the natural heart's valve (Fig. 13) (30).

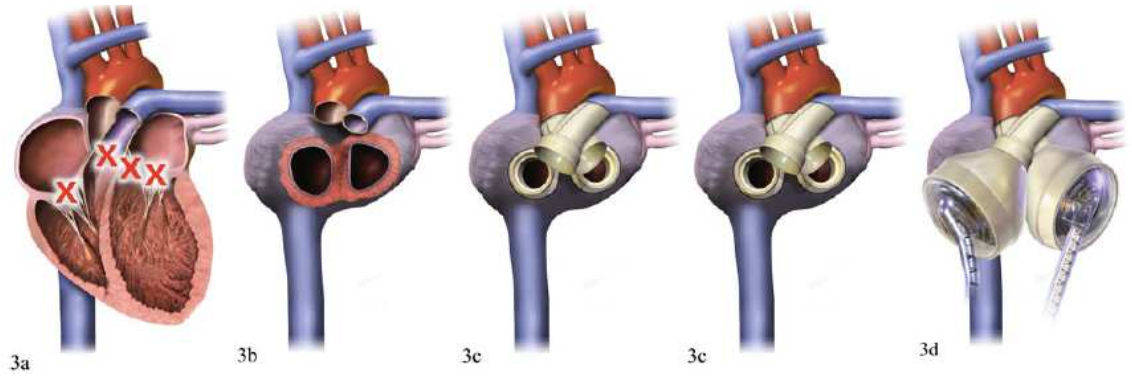

Figure 13: Chronological order of human heart removal and implantation of the TAH (SynCardia) (30)

Currently, CardioWest and AbioCor are the two available types of TAHs. In October 2010, approximately 850 patients were implanted a SynCardia TAH, which is also known as the CardioWest TAH (30). The main difference between CardioWest and AbioCor is, that the CardioWest THA is connected to an outside power source, whereas the AbioCor is completely contained inside the chest. The battery, which powers the AbioCor TAH is contained in the chest and is charged with an external, magnetic charger through the skin. Furthermore, the controller which controls and monitors the pumping speed of the heart is also implanted in the patient's body. In comparison, the battery and the controller of the Cardio West TAH is located externally and is connected to the artificial heart with tubes through incisions in the abdomen (22).

3.7 Heart Transplantation Overview

Cardiac transplantation is a treatment for patients who suffer from heart failure, where no helping medical treatment can be found. An improved medical treatment, which enables suppressing of the subject's immune system and preventing infection during surgery has led to improved survival among patients.

Unfortunately, the number of subjects in need for a heart transplantation increased much more than the number of heart donors over the past years. Worldwide, more than 5,000 cardiac transplants are performed every year, although up to 50,000 patients are estimated to be in need for heart transplantation (31). Therefore, the American Society of Transplantation set guidelines for medical institutions, informing about which group of people should be taken into account for heart transplantations (32). In 2012, the Registry of the International Society of Heart and Lung Transplantation reported 104,000 heart transplantations in 2012, based on data of 394 transplant centers worldwide (31).

4 HEART PUMP PROJECT

The aim of this research work was to develop an affordable system, which mimicked physiological conditions of the human cardiovascular system in order to simulate the parameters of the human heart *in vivo*. A portable system for quality control of Doppler ultrasound imaging was designed and manufactured through development of a flow phantom with vessel mimicking material, as well as blood mimicking and tissue mimicking fluid.

Furthermore, a proper circulation of the blood mimicking fluid as well as pump settings to simulate the human heart as good as possible, needed to be ensured. Therefore, a consistent flow rate rate of 45 mL/ min to 150 mL/ min was planned to be achieved. Finally, the flow was planned to be measured with an ultrasound transducer to prove the simulation of a human resting heart rate as well as a heart rate of an exercising heart.

The development of the above-mentioned system enables mimicking the human blood flow in its vascular system and guarantees quality control regarding usage of future medical equipment. Although the system was designed for this specific biomedical application, it is possible to use the pump for different applications or use the flow phantom for another type of fluid.

The system can successfully be enhanced and in this way research in the biomedical sector is supported. The pump device can, therefore, improve patient care, provide a higher quality of life in the waiting period for patients who suffer from cardiac insufficiency waiting for a new heart, and achieve appropriate diagnostic ultrasound image quality.

A student team of four developed the described flow phantom. The team was selected by Dr. Olivia Coiado, who started the cardiac research at the University of Portland in summer 2016. Due to lack of time and blood mimicking material, the planned fluid circulation, the production of the tissue mimicking fluid and the ultrasound application was not performed. However, this is seen as a future goal for continuous research.

4.1 BACKGROUND

Flow phantoms in general are specifically designed objects involving dedicated biomaterials to simulate special realistic circuits of human beings. At the moment, using phantoms for ultrasound quality control for medical devices is optional (19). However, a phantom or simulated object is the basic equipment that must be used to perform the quality control tests. The American College of Radiology recommends routine quality controls performed by perfectly trained service engineers or sonographers. Deeper evaluations should be applied annualy for any equipment which has clinical usage, more specifically, if it's used for treatments or for diagnoses. These quality control guidelines refer to the basic procedures for US quality control in diagnostic US equipment (16) (17).

4.2 FLOW PHANTOM

The developed phantom included a peristaltic pump and two acrylic containers, one for mixing a blood mimicking fluid, and the other for testing the ultrasound equipment (Fig. 14).

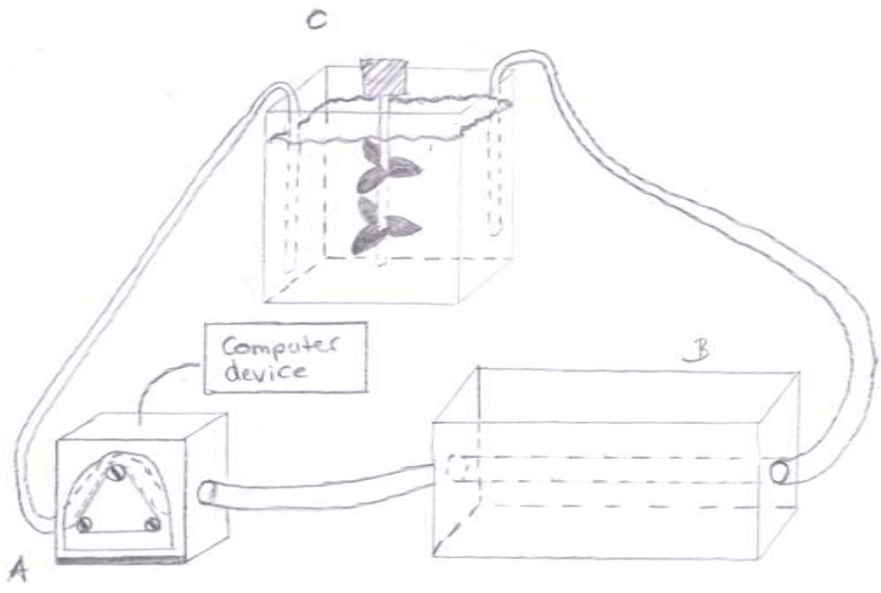

Figure 14: Hand drawing of flow phantom

A peristaltic pump, rotates in clockwise direction and pushes liquid through, controlled by a computer device; B: acrylic container with a passing silicon tube, tissue mimicking fluid will be poured in; C: acrylic container, with a DC motor connected to an aluminum shaft, and a 3D printed plastic propeller to mix the fluid

4.3 PERISTALTIC PUMP

The pump for the portable flow phantom was designed with the 3D design software Solidworks (SolidWorks Corporation) and manufactured afterwards (Fig. 15).

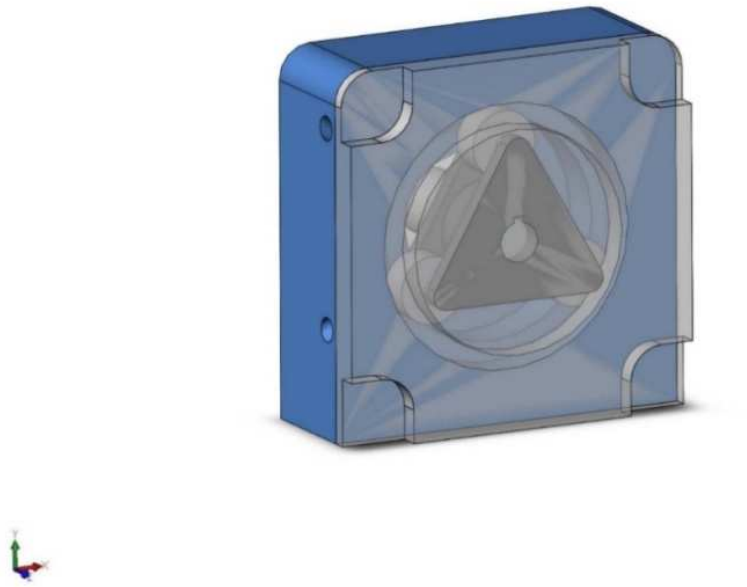

Figure 15: First draft of the peristaltic pump

The draft was made with the 3D design software Solidworks (SolidWorks Corporation)

During manufacturing of the pump, easy access to the inside of the pump was considered. Therefore, the finished pump can be opened using two wing nuts placed in the aluminum part of the housing, which can move up and down. Furthermore, the impeller and the housing were made of aluminum, whereas the base, the cover and the front mask were made of acrylic. Furthermore, the shaft was made out of steel because it is subjected to high forces provided by the contact between the small bearings and the aluminum component. The shaft center of the mass is placed in the same vertical plane as the 5/8” bearing center, providing the minimum deflection to the axis.

The pump was powered by a stepper motor (Zyltech Engineering LLC, 23HD76002Y-21B), controlled by an Arduino and had a keyboard pad for the input of data and a liquid-crystal display (LCD) screen to display the pump's output. A stepper motor is a special type of DC motor and produces mechanical energy through conversion from electrical energy.

This electrical energy creates the pulses, with which the motor is driven (33). The motor driver circuit (Toshiba) was developed by two students in summer 2016 (Fig. 16).

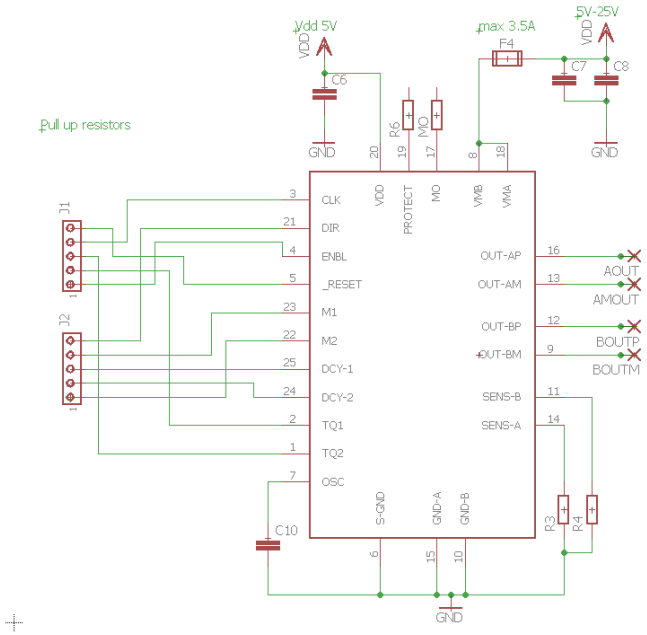

Figure 16: A schematic of the Toshiba motor driver circuit

The stepper motor shows high compatibility with numerical control systems and provides accurate direction, position, and speed. Furthermore, a DC motor is an electrical machine, which converts direct current electrical power into mechanical power. The principle of a DC motor is described as, whenever a current carrying conductor is placed in a magnetic field, it experiences a mechanical force (34). An Arduino is a microcontroller basket kit, which is used in communications and in controlling or operating different devices (35). The Arduino was developed with a specific code to convert the flow rate, given by the keyboard pad to rotations per minute (RPM), so that the motor runs at a certain speed corresponding to required flow rate.

During the rotation of the motor shaft and the impeller of the pump, the small bearing wheels rotate toward their respective bolts and towards the steel shaft, the small bearings also push the hose against the aluminum piece, closing the hose in contact points. This combination of movements creates a vacuum and the fluid moves in the direction of the vacuum because of the difference between pressures (Fig. 17).

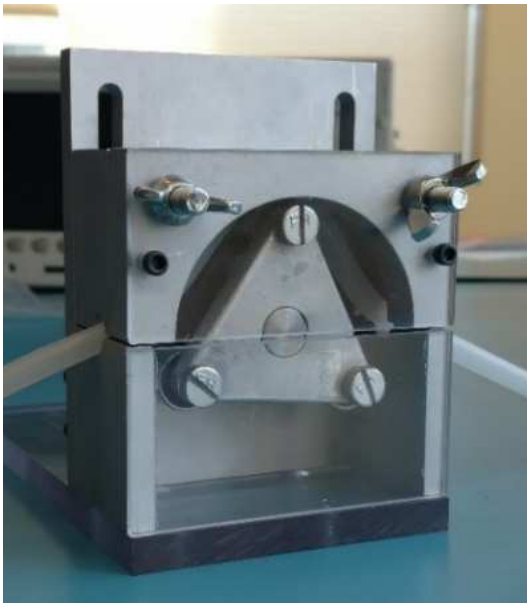

Figure 17: Illustration of the peristaltic pump

The pump was powered by a stepper motor and controlled by an Arduino, using a 4 mm silicone hose

ACRYLIC CONTAINERS

The first container had dimensions of 20 x 20 x 20 cm and was constructed using a DC motor connected to an aluminum shaft and a 3D printed plastic propeller to mix the fluid. Mixing is important due to the red blood cell mimicking particle's ability to settle on the bottom of the acrylic container (Fig. 18).

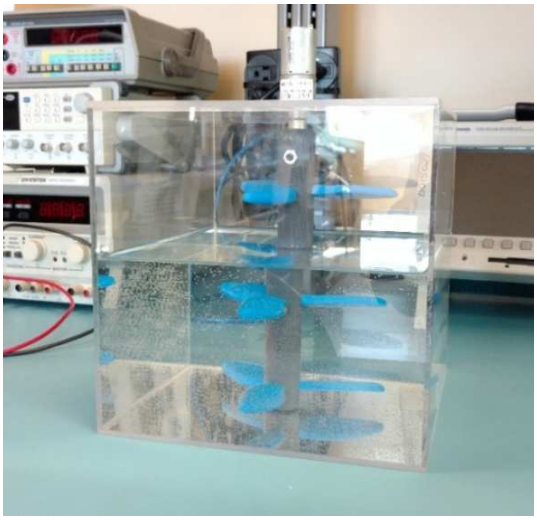

Figure 18: Illustration of the acrylic container

A DC motor connected to an aluminum shaft and a 3D printed plastic propeller to avoid settling down of red blood cell mimicking particles was used

The second acrylic container had dimensions of 13 x 8 x 10 cm and had a continuous 4 mm silicon tube that passed through. The tissue mimicking fluid was planned to be poured in this container so that the vessel is covered at a specific depth, measured from the top. This depth can be varied, depending on the to-be mimicked tissue. To simulate the human heart muscle, a depth of about 1 cm would be appropriate (Fig. 19).

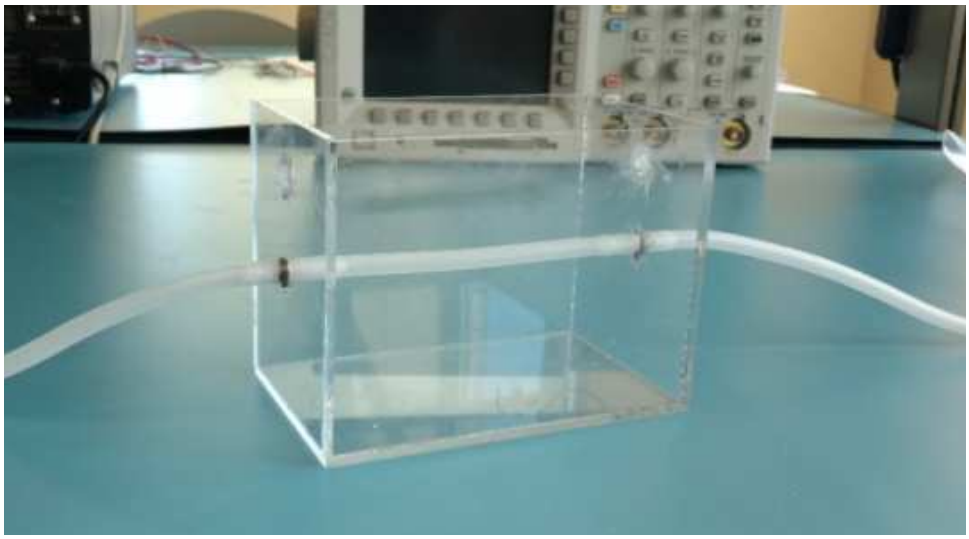

Figure 19: Illustration of the second acrylic container

It was filled with tissue mimicking fluid; a 4 mm diameter silicon hose mimicked a human vessel and was planned to be covered with 1 cm of tissue mimicking fluid, measured from the top

4.4 BIOMATERIALS

For mimicking human blood vessels, silicon tubes were used. Furthermore, a commercially available blood mimicking fluid was found. However, due to the high expenditure of costs, it was decided to only mimick red blood cells. Therefore, polyamide particles were found to be a possibility as a mimicking material. Lastly, a recipe for tissue mimicking fluid consisting of water, glycerin, graphite powder and agar was found.

4.4.1 VESSEL MIMICKING MATERIAL

During the development of the flow phantom, research has shown, that vessels can best be mimicked using a 4 mm diameter silicon tube. Although this diameter is higher than the vessel diameter in the human body, this diameter is needed to ensure proper circulation of fluids. Furthermore, through adjustment of the peristaltic pump, it is assumed that the radius of the silicon vessel will not affect the ultrasound results.

However, the blood vessel radius in the human body is a primary factor of blood pressure. A smaller radius results in a greater resistance to the blood which flows within the

vessel. The aorta shows an average luminal diameter of about 25 mm, whereas muscular arteries show a diameter from 1 cm to 0.3 mm. Capillaries are known to have a diameter of 8 µm to 10 µm, whereas veins show diameters ranging from 2.3 mm up to 4.0 mm at specific locations in the human body (1) (36).

An ideal biomaterial is considered to not cause any allergenic, immunological, inflammatory, thrombotic, or toxic reactions. Today, there is no material, which completely meets these criteria. However, silicone has shown several advantages in biomedical applications and research. Since the developed flow phantom has no contact with test subjects, the purchased silicon tubes could be used without any concerns (37).

Silicon has found applications in orthopedic hand and foot joint implants and catheters, shunts, drains as well as aesthetic implants and others. Hence, it shows biological compatibility which is why silicon tubing commonly used in medical procedures and research. It is flexible, provides sealed fluid transfer and shows lower cost expenditure, compared to PVC and latex (38).

Furthermore, it is a subcategory of synthetic polymers whose backbone consists of a repetition of oxygen to silicon bonds, where the silicon atoms are additionally bonded to methyl groups (Fig. 20) (39).

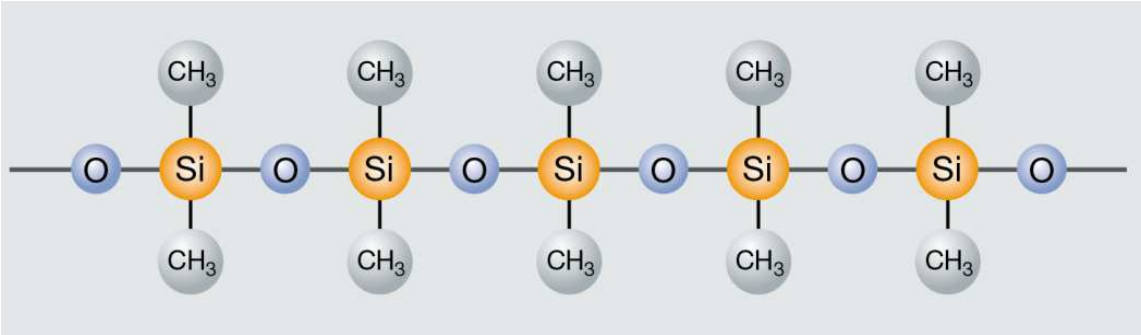

Figure 20: Chemical structure of silicon

The backbone consists of a repetition of oxygen to silicon bonds, silicon atoms are then bonded to methyl groups (39)

4.4.2 Blood Mimicking Fluid

The minimum amount of blood mimicking fluid needed, was estimated to be 3.5 liters and was intended to have a scatter of about 7 micrometers in diameter due to the mean diameter of 6 to 8 micrometer of human red blood cells.

CIRS (Computerized Imaging Reference Systems, Inc.) was contacted and information was gathered. The product "Blood Mimicking Fluid, Model 046" showed a velocity of 1570 ± 30 m/ s, which was similar to the velocity of 1583 m/ s of human blood at 37 °C. Moreover, the attenuation of the fluid with less than 0.1 dB cm^{-1} MHz was close to the attenuation of human blood with 0.15 dB cm^{-1} MHz. The mean viscosity of blood is 3 mPa's, whereas the viscosity of the blood mimicking fluid was given to be 4 ± 0.5 mPa's. Adversely, information about the backscatterer of the blood mimicking fluid was not provided. Furthermore, the fluid showed characteristics of a Newtonian fluid, whereas blood is a non-Newtonian fluid (40).

Although the blood mimicking fluid showed deviations to human blood, it had to be considered, that those deviations were relatively small compared to studies, which used self-made blood mimicking fluids. However, this blood mimicking fluid could not be purchased due to too high costs.

Further research provided recipes for blood mimicking fluids. However, the research group decided to focus on a red blood cell mimicking material, because it also enables proper ultrasound measurement in the first draft of the phantom. Therefore, the companies Rilsan® by Arkema, Innovative Chemistry, and Orgasol® Powders were contacted.

Rilsan® informed that the company only provided fine powders with a mean diameter down to 35 micrometer, which was too big to fulfill the intended project goal (41).

The product Orgasol® 2001 EXD NAT 1 by Orgasol® was a spheroidal powder of polyamide 12, with an average diameter of 10 micrometers and a particle size distribution of maximal 2% particles under 5 micrometers, and maximal 2% particles over 20 micrometers diameter. To fulfill the project goal, this product could not be used due to the high average diameter of the particles. Considering a mean diameter of 6 to 8 micrometers of human red blood cells, the mean particle diameter of 10 micrometers was too large (42).

Furthermore, the Orgasol® Product Information Center provided information about one specific product, which showed the possibility to meet the requirements. For mimicking the human red blood cells, a sample of the product Orgasol® 2001 UD NAT 1 was planned to be requested. This was also a spheroidal powder of polyamide 12, with an average diameter of 5 micrometers and a particle size distribution of maximal 2% particles under 2.5 micrometers, and maximal 5% particles over 10 micrometers diameter

(42). Although a sample was requested, nothing was shipped to the University of Portland. Consequently, no blood mimicking fluid could be produced and the study could not be carried out as planned. However, this product is seen to be as an approach for mimicking human red blood cells for future studies.

4.4.3 Tissue Mimicking Fluid

The minimum amount needed was estimated to be 0.5 liter of tissue mimicking fluid.

During research, several recipes for tissue mimicking fluid were found. One of them was a recipe for a mimicking fluid which consisted of evaporated whole milk, a hydroxyl compound such as n-propanol, deionized water, and a gel-forming material (43). Due to the lack of information in the patent's description, the complete recipe could not be found.

Dr. Coiado published the article "Pulsatile Flow Phantoms for Quality Control of Doppler Ultrasound Imaging" in 2009. The recipe used for tissue mimicking fluid in this study was chosen to be the used as tissue mimicking fluid in the flow phantom. This type of tissue mimic consisted of 500 mL pure water, 80 g glycerin, 5 g graphite powder and 12.5 g of agar (44).

Due to the lack of red blood cell mimicking material, the tissue mimicking fluid was not produced. Hence, the ultrasound equipment could not be used for the developed flow phantom. However, the ultrasound application and the production of blood and tissue mimicking fluid are a future project for other research students.

4.5 Cost calculation of flow phantom

The costs were attempted to be kept as low as possible to enable the intended development of low-cost quality control mechanisms of medical equipment such as ultrasound imaging devices. The total costs of the flow phantom summed up to US$ 166.86. Glycerin, which would have been needed to produce tissue mimicking fluid, aluminum as well as the acrylic and plastic parts for the peristaltic pump were not included in the cost calculation due to the availability at the University of Portland. Furthermore, the amount of US$ for agar and graphite powder is related to an online source, including the estimated shipping costs to the University of Portland (status: October 2016) (Table 7).

Table 7: Cost calculation of peristaltic pump and tissue mimicking material; glycerin, aluminum, acryl and plastic parts excluded due to availability at the University of Portland; amount of US$ for agar and graphite powder is related to online source (status: October 2016), all other amount are actual costs

Material	Costs (US$)
NOW Foods Agar Powder, Pure, 2 Ounce Bottle (4)	10.19 (45)
Graphite Dry Lube [C] 99.9% ACS Grade Powder 4 Oz	16.67 (46)
2 pc. 5 feet silicone Tubing (5/ 32" I.D. x 9/ 32" O.D.)	29.36
8 pc. 4 mm plastic connectors	4.48
Arduino A000067 DEV BRD, ATMEGA2560, Arduino Mega 2560 R3	38.86
Membrane 3x4 matrix keypad + extras	3.29
ZyltechNema 23 stepper motor 3.0 A 1.3 Nm 184 oz. in 56 mm body w/ 1 m cable for 3D printer/ CNC	19.99
Toshiba motor driver- TB6560AHQ,8	5.87
Uxcell DC 5V standard 16 x 2 character blue backlight LCD display module black green	5.93
12 Volts DC motor	14.00
Total costs of peristaltic pump with biomaterials	166.86

4.6 SCHEDULE

Following, the project schedule is illustrated. Tasks from July until December 2016 were finished at the University of Portland, whereas tasks in January were completed at the University of Applied Sciences Upper Austria in Wels (Table 8).

Table 8: Planned tasks referred to period; at current stage all mentioned tasks of September and October 2016 have already been completed in the specific month

Period	Tasks
July 2016	Cardiac study by Dr. Coiado was started, Peristaltic pump and circuit to mimic human heart was planned
August 2016	Motor driver circuit was developed, Peristaltic pump was built
September 2016	Structure of research paper was drawn up, Research of literature was started, Background information about biomaterials was gathered, Companies were contacted to gather information
October 2016	Biomaterials were chosen, Research of literature was continued
November 2016	Research of literature was completed, Flow Phantom was developed and circuit was finished
December 2016	Research Paper was proofread by supervisor
January 2017	Research Paper was adapted, Final release of research paper for the University of Applied Sciences Upper Austria and the Marshall Plan Foundation

5 SUMMARY

During the research period at the University of Portland, a newly developed peristaltic pump to simulate the physiological parameters of the human heart was connected to a pump system to fulfill the requirements of the planned flow phantom. At the beginning of the project, the pump was manufactured by using low-cost but high-quality equipment, a 3D SolidWorks model was created to appropriately plan the manufacturing process.

The flow phantom consisted of two acrylic containers, one to mix the blood mimicking fluid and one to enable tissue and vessel simulation. Before developing this flow phantom, information about the human heart and possible biomaterials had to be gathered. Afterwards, possible biomaterials were selected by the research team in order to fulfill the research and material requirements.

Furthermore, detailed information about ultrasound was gathered to gain knowledge for future research goals. These goals include application of the found recipes for tissue and blood mimicking fluid in the developed flow phantom. Afterwards, an ultrasound transducer that is covered in tissue mimicking material can be applied to the vessel. Since the pump flow rate and the pressure of the blood mimicking fluid is known, the ultrasound equipment can then be validated. This enables low-cost ultrasound quality control for medical institutions. Hence, research in the biomedical engineering sector is very important in the development of quality control devices for the medical field.

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