Diploma Thesis

Is the decrease of thrombocytes count after aortic valve replacement with a bioprostheses dependent on its valve type?

submitted by

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attaining the academic degree

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Graz, Datum…….. (Unterschrift)

1 Affidavit

I, hereby, declare that the following diploma thesis has been written only by the undersigned and without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

Graz, Date…….. (signature)

2 Acknowledgement

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3 Abstract

OBJECTIVS: After aortic valve replacement with the bioprosthesis Freedom Solo (FS) by Sorin a postoperative thrombocytopenia with a sluggished recovery of platelet count was noticed. The Department of Cardiac Surgery in Graz wants to consider the question whether the thrombocytopenia is dependent on the different bioprosthetic heart valve designs. The FS (unstented bioprosthetic heart valve) was compared to Epic by St. Jude Medical, Trifecta by St. Jude Medical, Mosaic by Medtronic, Magna Ease by Edwards, Perceval by Sorin and Mitroflow by Sorin (these are all stented bioprostheses).

METHODS: Statistical analyses with SPSS of a created study population consisting of 293 patients who received an aortic valve replacement with bioprostheses and at least one CABG at the Department of Cardiac Surgery in Graz between December 2007 to November 2011. Patients with further surgical implantation of prosthesis, additional heart valve implantation, dissected aorta, aneurysm operation, development of HIT or pseudothrombocytopenia were excluded. The study population has a mean age of 76,38 +/- 5,25 years, 42% are female, 58% male. The median of EuroSCORE is 9,45 (minimum 2,23 and maximum 76,84).

RESULTS: A significant difference on the base of Bonferroni correlation was found between FS and the other designs regarding to platelet count postoperatively. On the first three days after surgical treatment the difference was significant between FS and Epic p= 0,0 as well as Mosaic p= 0,0. A strong tendency is seen between FS and Mitroflow (p= 0,011) as well as Trifecta (p= 0,481). On the 8-10th day the Epic and Mosaic still have a significant difference (both p= 0,0) and the Mitroflow (p= 0,270) as well as Trifecta (p= 0,101) a strong tendency in platelet count and in comparison with FS. The Magna Ease and Perceval were excluded due to an implantation rate lower than 10%.

CONCLUSION: An aortic valve replacement with the bioprosthesis FS leads to a mild to moderate thrombocytopenia and a sluggished recovery of platelet count postoperatively. Surprisingly same is for Mitroflow and Trifecta although the thrombocytopenia is not that distinct. Although no statistical significance, a strong tendency is given. Nevertheless no bioprostheses showed higher incidence of hemorrhagic complications.

Unless the biocompatibility of FS is not refused, the implantation in well-chosen patients is still an option. Strict monitoring would be necessary during first two weeks of hospitalization. The platelet suppressive effect should be beard in mind and be involved in further therapeutic decisions.

4 Zusammenfassung

EINLEITUNG: Nach der Implantation der biologischen Aortenklappe Freedom Solo (FS) von Sorin entwickelten Patienten postoperativ eine Thrombozytopenie mit verlangsamter Plättchen Regeneration. Die Abteilung für Herzchirurgie der Universitätsklinik in Graz möchte nun der Frage nachgehen, ob die Thrombozytopenie im Zusammenhang mit dem Klappenmodell steht. Die FS (ungestentet) wird verglichen mit der Epic von St. Jude Medical, der Trifecta von St. Jude Medical, der Mosaic von Medtronic, der Magna Ease von Edwards, der Perceval von Sorin und der Mitroflow von Sorin (alles gestentete Herzklappen).

METHODIK: Statistische Auswertung der Daten mit SPSS. Die erhobene Kohorte besteht aus 293 Patienten, die im Zeitraum vom Dezember 2007 bis November 2011 an der Abteilung für Herzchirurgie, Graz einen biologischen Aortenklappenersatz in Kombination mit mindesten einem CABG erhalten haben. Alle Patienten, die noch eine zusätzliche Prothese, einen weiteren Klappenersatz erhielten, bei denen eine Dissektion oder ein Aneurysma saniert wurde, die eine HIT oder Pseudothrombozytopenie entwickelten, werden aus der Studie ausgeschlossen. Das Alter der Kohorte ist im Mittelwert 76,38 +/- 5,25 Jahre. 42% sind Frauen und 58% Männer. Der EuroSCORE zeigt einen Median von 9,45 (Minimum 2,23, Maximum 76,84).

ERGEBNIS: Es ist ein signifikanter Unterschied zwischen der FS und den anderen Klappenmodellen bezüglich der postoperativen Thrombozytenzahl gefunden worden. An den ersten drei Tagen postoperativ zeigten die Epic (p= 0,0) und Mosaic (p= 0,0) einen signifikanten Unterschied. Die Mitroflow (p= 0,011) und Trifecta (p= 0,481) gaben eine starke Tendenz an. Am achten bis zehnten Tag postoperativ zeigten die Epic (p= 0,0) und Mosaic (p= 0,0) immer noch eine signifikante Differenz, die Mitroflow (p= 0,270) und Trifecta (p= 0,101) eine starke Tendenz. Die Auswertungen erfolgten nach Bonferroni. Die Magna Ease und Perceval wurden wegen einer Implantationsrate <10% aus weiteren statistischen Auswertungen ausgeschlossen.

SCHLUSSFOLGERUNG: Der Aortenklappenersatz mit der biologischen Aortenklappe FS führt zu einer postoperativen leichten bis mittelschweren Thrombozytopenie sowie verzögerter Erholung der Thrombozytenzahl. Überraschenderweise zeigten auch die Mitroflow und Trifecta postoperativ eine Thrombozytopenie, wenn auch deutlich milder. Diese ist zwar statistisch nicht signifikant, aber eine starke Tendenz. Dennoch führte kein Klappenmodell zu höheren Raten an Blutungskomplikationen.

Solange also bei der FS die Biokompatibilität nicht widerlegt wird, ist dieses Modell eine gute Wahl für sorgfältig ausgesuchte Patienten. Es sollte im Krankenhaus eine strenge Überwachung der Thrombozytenzahl zwei Wochen nach der Operation erfolgen. Weiters sollte der thrombozytensuppressive Effekt dieser Bioklappe im Auge behalten und beim Ansetzen zukünftiger Therapien mit bedacht werden.

5 Table of Contents

6 Abbreviations and its Explanation

ADP	Adenosine Diphosphate
ACC	American College of Cardiology
A-Fib	Atrial Fibrillation
AHA	Aamerican Heart Association
AHV	Artificial Heart Valve
AKE	Aortenklappenersatz
ATP	Adenosine Triphosphate
ATP	Adenosin Triphosphat
AV	atrioventricular
AVR	Aortic Valve Replacement
BHV	Bioprosthetic Heart Valve
BHV	Bioprosthetic Heart Valves
CABG	Coronary Artery Bypass Grafting
CCT	Cross-Clamping Time
CMR	Cardiac Magnetic Resonance
CO	Cardiac Output
CRP	C-reactive Protein
CX	Circumflex Branch
DD	End-Diastolic Dimension
DIC	Disseminated Intravascular Coagulation
ECC	Extracorporal Circulation
ECF	Extracellular Fluid
ECG	Elektrocardiography
EDTA	Ethylenediaminetetraacetic Acid
EDV	End-Diastolic Volume
EF	Ejection Fraction
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FFH	Fetal Fatal Hemorrhage
FS	Freedom Solo (by Sorin)
GP	Glycoprotein
HCT	Hematocrit
HIT	Heparin-induced Thrombocytopenia
HITT	Heparin-induced Thrombocytopenia with Thrombosis
HLM	Heart-Lung-Machine
HR	Heart Rate
HTN	Hypertension
HVR	Heart Valve Replacement
ICU	Intensive Care Unit
ICU	Intensive Care Unit
INR	International Normalized Ratio
IntraOP	Intraoperative Value
ITP	Idiopathic/ Immune Thrombocytopenia Purpura
IVC	Inferior Vena Cava
IVS	Interventricular Septum
LAD	Left Artery Descending
LCA	Left Coronary Artery
LIMA	Left Internal Mammary Artery
LMWH	Low-Molecular-Weight Heparin
LV	left ventricular
MAP	Middle Arterial (blood) Pressure
MDP	Maximum Diastolic Potential
MHV	Mechanical Heart Valve
min.	Minutes
MRI	Magnetic Resonance Imaging
MSP	Main Surgical Procedure
NAITP	Neonatal Allo-immunthrombocytopenia
NYHA	New York Heart Association
PDGF	Platelet Derived Growth Factor
PF4	Platelet Factor
PostOP 1	Postoperative Value from day one to three
Postop 2	Postoperative Value on day eight to ten

PP	Prepotetial
PreOP	Preoperative Value
PTP	Post-transfusions Purpura
RCA	Right Coronary Artery
Rima	Right Internal Mammary Artery
RVG	Radionuclide Ventriculography
SA	Sinuatrial
SD	End-Systolic Dimension
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SJM	St. Jude Medical
SLE	Systemic Lupoid Erythematoides
SV	Stroke Volume
SVC	Superior Vena Cava
TEE	Transesophageal Echocardiogram
TMA	Thrombotic Mikroangiopathy
TPO	Thrombopoietin
vWF	Willebrand Factor

7 Introduction

7.1 Anatomy of the human heart [1-5]

The human heart is positioned at an angle in the medial mediastinum of the thorax. It is covered with pericardium that is connected to the pleura, diaphragm and to the structures of anterior and posterior mediastinum. The heart has the shape of a cone; the base of this cone points cranial, dorsal and to the right side. The apex, however, points to caudal, ventral and the left side. This position is important for the understanding of many physiological facts of the cardiovascular system. The heart is often described as a muscular hollow organ which is be divided into two sides, the left and the right heart. Each side has two chambers: the atrium and ventricle. It consists of three layers called epicardium, myocardium and endocardium. The epicardium is the external layer of the heart, it is a serous pellicle and already a part of the pericardium. The myocardium is the thickest layer and made of complex arranged muscle fibers which transfer the action potential and perform heart action. The endocardium is the internal layer and consists of simple squamous epithelium. It encases all structures and leads into the first passage of the great vessels. The complex arranged muscle fibers of myocardium can be divided into a superficial and a deep layer. They are linked by a whirling structure of the long cardiac muscle fibers. The muscle of the left side of the heart is more distinctive than that of the right, thus being capable of building up the necessary blood pressure for circulation. From deeper cardiac muscle layer trabecular and papillary muscles extend into the ventricles of the heart. They are covered with epicardium.

The blood flow through the heart is unidirectional and leads through its cavities: right atrium, right ventricle, left atrium and left ventricle. At the beginning of the cardiovascular cycle the heart receives blood from superior vena cava (SVC), inferior vena cava (IVC) and coronary sinus. This confluence of the veins transports the poorly oxygenated blood to the right atrium of the heart. About 80 % of the blood volume is stored in the venous system and a blood pressure of about 2-4 mmHg predominates. The blood flows through the right atrium with its auricular appendage, a wall composed of pectinate muscles and the tricuspid heart valve that discharges the blood to the right ventricle. In the right AV (atrioventricular) or tricuspid orifice there are irregular muscular elevations called trabeculae carnae. The three cusps of tricuspid valve are attached to three tendinous cords

on three papillary muscles to the endocardium. The anterior papillary muscle is the major and largest muscle, the posterior papillary muscle is a bit smaller and the septal papillary muscle is attached to the interventricular septum. The cusps, however, are fastened to a fibrous ring which is has an important function for support of the heart and surrounds the tricuspid orifice. The valve is closed throughout ventricular contraction and prevents a backflow of the blood. By contrast the pulmonal valve positioned at the end of the right ventricle is open during systole and discharges the blood to the pulmonary trunk and further on through its pulmonal arteries to the lung for oxygenation of the erythrocytes. After this process it flows from the lung through four pulmonal veins into the left atrium which is smaller than the right atrium but has an auricular appendage as well as pectinate muscles. Now the blood flows through the mitral valve which is situated between the left atrium and ventricle and thus reaches the left ventricle. The mitral valve consists of the anterior and posterior cusps which are both fixed to the fibrous ring. More than one large papillary muscle with its tendinous cords supports the mitral valve leaflets during their opening and closing phase. These papillary muscles lie in the left ventricle which forms the apex of the heart. In addition the wall is covered with a mesh of trabeculae carnae and is three times as thick as that of the right ventricle. The aortic valve is in the aortic orifice of the left ventricle. It has the same structure and performs in the same way as the pulmonary valve.

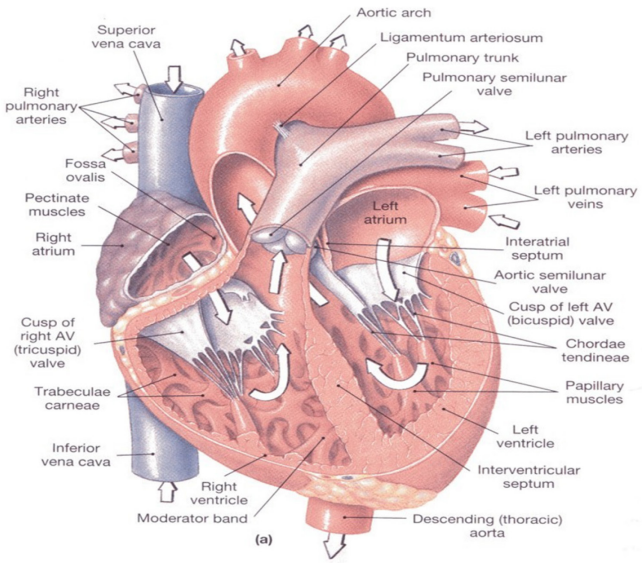

Figure 1) The general anatomy of human heart
(figure adapted from http://www.edoctoronline.com/medical-atlas.asp?c=4&m=1&p=22&cid=1108&s=)

The high pressure system starts at the left ventricle and the myocardium is able to build up a blood pressure of about 120 mmHg in a healthy person. After passing through the aortic valve the blood flows into aorta abdominalis. From that point it is distributed to smaller arteries and in the end to capillaries for oxygenation.. After passing through the capillaries the blood flows through smaller veins into bigger ones until it reaches the SVC and IVC. It transports CO_2 back to the lung as described above to start a new cycle of oxygenation.

The heart has a fibrous skeleton which lies in the base of the human heart and is a complex framework consisting of dense collagen, connective and fat tissue. It consists of four fibrous rings and is important for the support of the heart valves. Additionally it provides an attachment for the myocardium. Furthermore it cuts the atrium off the ventricle and is responsible for electric isolation between them.

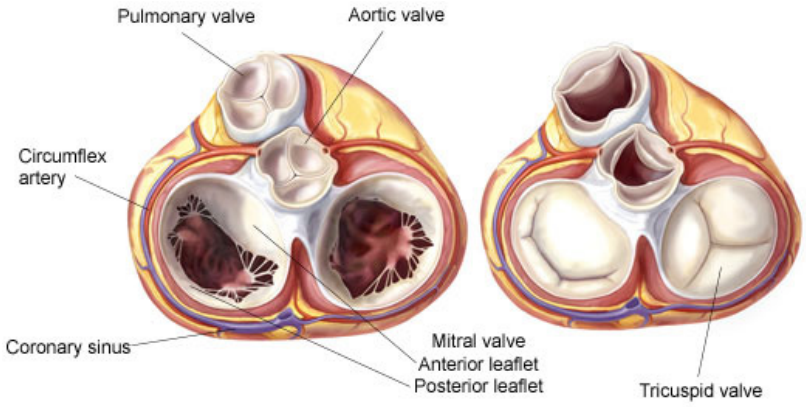

Figure 2) Valvular level of human heart
The four heart valves with its cusps are shown during systole and diastole. Around the valves lies the fibrous skeleton. (This figure is adapted from http://www.mitralvalverepair.org/content/view/51/)

The human heart has four valves which lie at the base in coronary sulcus and are attached to the skeleton of the heart. Generally speaking one distinguishes between the AV and semilunar valves. They are responsible for the unidirectional blood flow through the heart. The AV valves lie between atrium and ventricle and have cusps that prevent the backflow of the blood during systole. The closure of these valves causes the first heart sound (S_1). The right one has three leaflets and is therefore called tricuspid valve: anterior, posterior and septal cusp. Three papillary muscles support the leaflets- one muscle for each. The papillary muscles are fixed to tendinous cords which are important for the correct closing procedure during systole. The left AV valve is named bicuspid or mitral valve due to its two big leaflets which are called anterior and posterior cusp.

The semilunar valves lie between a ventricle and arterial vessel. They have three half-moon shaped leaflets which are named posterior, right and left cusp due to their position when viewed from above. They are smaller than the AV valves and have no tendinous cords for support. They must be able to endure less than half of the force that is exerted onto the AV valves. During systole the semilunar leaflets are open for the blood to flow towards arteries. During diastole the cusps snap together thus closing completely and catch the reversed blood flow to prevent any amount of blood from returning to the ventricle. The closure of the semilunar valves leads to the second heart sound (S_2).

The aortic valve lies in the orifice of the ascending aorta. The three cusps have a crescent-shaped area each, a margin which is called lunula. In the middle of each lunula is a nodula arantii that seals the wedge- shaped space between the three leaflets during diastole. Close to the right and left aortic cusps lie the entrances to the right and left coronary arteries.

The heart pumps constantly and in variable moods. For this it needs a never-ending supply of O_2, glucose and other substances. It receives the necessary 11% of O_2 in rest and its 4% of the average blood flow from the arterial system of the heart, called coronary system. The coronary arteries lie in epicardium protected by fat tissue.

This system is divided into two main vessels: the left coronary artery and the right coronary artery. The ostium of the left coronary arteries originates in the left aortic sinus that lies directly at the aortic valve. The same applies for the right coronary arteries ostium which starts in the right coronary sinus. The left coronary artery (LCA) passes between the left auricle which leads to coronary sulcus and is also called left main until it separates into two big branches: the circumflex branch (CX) and the left anterior descending (LAD). The CX leads through the coronary sulcus and in 40% of cases it gives off a branch to sinu-atrial node (SA node or node of Keith-Flack). The LAD points to the left side of the heart and ends at the apex**.** The right coronary artery (RCA) leads into the right coronary sulcus to the posterior aspect of the heart. In 60% of humans the RCA gives off a SA nodal branch close to its origin. Later on it emits the right marginal branch which supplies the right border of the heart with blood. And finally the RCA sends off the atrioventricular nodal branch (AV node or Aschoff-Tawara node).

The venous system of the heart accompanies its arterial siblings and is divided into the magna, media and parva cardiac vein. All veins lead to coronary sulcus which ends in the coronary sinus in the right atrium.

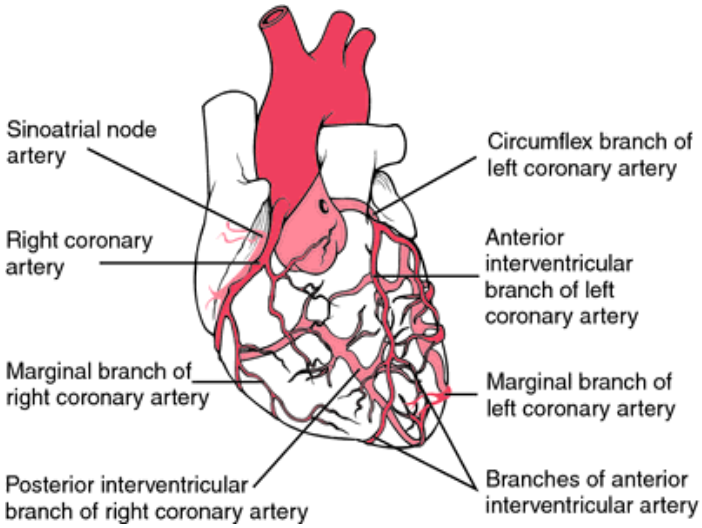

Figure 3) Coroary artery system.
The main coronary artery vessels are shown. The heart has many small branches thar are not shown due to a clear presenting (This figure is adapted from http://medical-dictionary.thefreedictionary.com/coronary+artery+disease)

The innervation of heart is purely vegetative. On the one hand parasympathetic fibers of the vagus nerve emit to the cardiac plexus and from there pull to SA and AV nodes. The transmitter is acetylcholine which bonds with muscarinerge receptors. It decelerates the heart rate by slowing the depolarization of the pacemaker cells, atrioventricular conduction as well as by decreasing the atrial contractility (negative chronotropism). It reduces the force of contractility (negative inotropism) and also constricts the coronary arteries to save energy for time with more demand.

On the other hand sympathetic fibers lead to the cardiac plexus. The fibers end at the SA and AV nodes, the myocardium and in the coronary vessels. Noradrenalin and adrenalin bonds with the beta-1- adrenergic receptors of the autorhythmic cardiac cells that increase the heart rate (positive chronotropism), force of contractility (positive inotropism), impulse conduction (positive dromotropism) and it raises the blood flow through the coronary vessels.

The sympathetic and parasympathetic fibers of the cardiac plexus (at the base of the heart and along the coronary vessels; innervations of heart), the thoracic aortic plexus (is enwinding thoracic aorta as well as esophagus and lung) and the pulmonal plexus (at the vessels of the lung, cooperates with the innervations of the heart) build up one big plexus. This explains the difficulty to distinguish between different etiologies and similar symptoms in diseases of this region.

The cardiac muscle cells are able to contract. But they have different molecularbiological preconditions and regulations as skeletal muscle fibers. They are generally speaking smaller and have more cell cores per fiber. There are many gap junctions in cross-striations and therefore the fibers are affiliated with each other as an electric syncytium like one huge smooth muscle cell. As a consequence, action potential is able to float quickly through all cardiac muscle fibers so that a nearly simultaneous depolarization and contraction of the heart is possible. Cardiac fibers have more mitochondrias than skeleton muscle fibers. The t-tubulis are bigger and the sarcoplasmatic reticulum is smaller- a sign that extracellular Ca^{2+} is more important for the hearts action potential process.

About one percent of the cardiac muscle cells are specialized to generate action potential without induction of the nervous system. They are called pacemaker system or impulse generating tissue, they are autorhythmic cells. The primary pacemaker cells are situated in the sinus node. They generate an action potential 60-70 times per minute in rest. If these cells die, for example due to an ischemic occurrence, the secondary pacemaker cells will generate the action potential. These are the cells of AV node which generate about 40-50 hits per minute. Pacemaker cells have a special chain of action potential. They do not have a continuous resting potential. After each repolarization they slowly depolarize again. The most negative potential is around -70 mV and is called maximum diastolic potential (MDP). It increases until the prepotential (PP) is reached (around -40 mV) and an action potential can be triggered again. This is possible due to special which are continuous for sodium and potassium. The more positive the cells potential becomes the more I_f-channels close. Instead of the I_f-channels, calcium channels open now until the prepotential followed by depolarization start. This leads to the opening of more calcium channels which close as soon as the maximum of action potential is reached. Potassium channels open slowly and lead to repolarization.

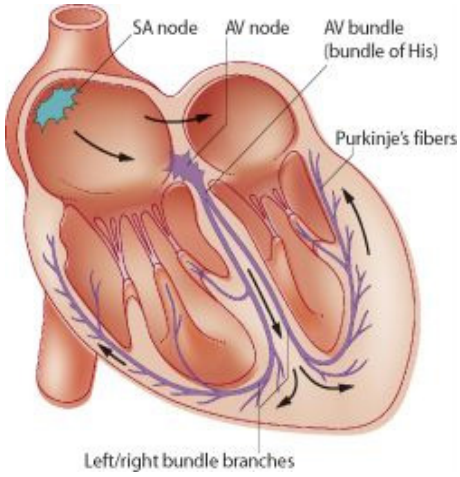

Figure 4) Conducting system of human heart
In this picure the anatoy of conducting system is show (This figure is adapted from http://medical-dictionary.thefreedictionary.com/Electrical+conduction+system+of+the+heart)

The SA node is about one cm^2 in length and lies on the posterior surface of the right atrium near the ICV underneath the epicardium. It is the first structure of the conducting system of the heart. It activates the myocardium of the atriums with every action potential. The action potential is passed on to the ventricles, but it is stopped by the fibrous skeleton. As explained before it is an electric isolating structure. A passing through is only possible at the AV node. The AV node is about 5 mm long and lies in the Koch´s Triangle close to the coronary sinus. It is responsible for leading the action potential to the atrioventricular bundle and decelerating it and lies between the AV node and the papillary muscles. The His bundle is around 5-8 mm long and lies in the proximal musculary part of the ventricular septum. It is divided into a right and a left bundle (also called Tawara´s bundle). The right bundle runs in an arch into trabecula and continues to the papillary muscles. The left bundle is divided again into two bundles, they expand over the IVS to the papillary muscles. The His bundle is about 2 cm long and lies subendocardial in the ventricle. It is responsible for a simultaneous depolarization of the ventricles. The subendocardial branches are also called Purkinje fibers, the last part of the conducting system of heart.

To assess the cardiac function there are a few physiological heart parameters. The cardiac output (CO) is defined as heart rate (HR) times stroke volume (SV). It describes the blood volume which is discharged from a ventricle per time and is around 5 liters per minute in an average, resting person

The end diastolic volume (EDV) is the volume that remains in the ventricle after systole. The preload influences the EDV. The preload itself is influenced by venous backflow like the skeleton muscle pump, breathing pump and the constriction of the veins

The afterload is the resistance of the blood flow during systole. It is the force that is necessary to push the blood out of the ventricle into the arterial system. The middle arterial (blood) pressure (MAP) is often used in clinical work.

The ejection fraction (EF) is the end-diastolic volume in percent pushed out of the ventricle during one contraction. This is important for assessing the function of the ventricle.

7.2 Heart Valve Disease in Adults

The human heart is a fascinating organ, developed in the context of evolution. A highly complex structure that enables our life. And in the same way high complexity is made out of many interacting parts leading to kind of simple perfection, in the same way it has many starting points for errors.

In terms of tissue this error is called pathology and regarding to aortic valves of adults there are two possible kinds of pathology: aortic valve stenosis and aortic valve incompetence with their typical clinical signs. Nowadays a therapy is established including valve replacement with a prosthetic as last resort. Since the last 60 years many models made of different materials and shape have been designed. To make sure that affected people live a life on a qualitative high level these prosthetics must be controlled in terms of complication, morbidity and mortality.

7.2.1 Definition

The ***aortic stenosis*** is defined as narrowness of the aortic valve[6] which in some cases lies above the valve (supravalvular) or below (subvalvular)[7]. This leads to an immobilization of cusps and due to this fact forward blood flow is disturbed. With an echocardiography or sonography a gradient can be assessed in mild, moderate and severe degree. The aortic stenosis is the most common non-congenital heart valve disease in the Western world. Epidemiological studies show a prevalence of over three percent in people over 65 years whereas nearly 80 % are male. The aortic valve area must decrease to less than 1.5 cm^2 of aortic valve orifice area to cause symptoms. The average aortic valve orifice area is more than 3.0 cm^2[6].

Aortic stenosis	Mild	Moderate	Severe
Jet velocity (m/sec)	<3,0	3,0-4,0	>4,0
Mean gradient (mmHg)	<25	25-40	>40
Aortic valve orifice area (cm^2)	>1,5	1,5-1,0	<1,0
Orifice area index (cm^2/m^2)	/	/	<0,6

Table 1) Classification of severity of aortic valve stenosis in adults
(adapted from Braunwald´s Heart Disease- A textbook of Cardiovascular Medicine, 9th ed. 2012, Elsevier Sounders, Philadelphia, p. 1472)

The definition of ***aortic insufficiency*** is the incompetence of the aortic valve to perform a complete closure without forward flow of blood into the ascending aorta during diastole. Three degrees of aortic incompetence can be measured with a color duplex sonography: mild, moderate and severe incompetence can be scaled. The disease can occur in an acute or a chronic form. In both cases the elevated left ventricular end-diastolic volume leads to regurgitation. Overall the prognosis for a patient suffering from incompetence is better than for one who suffers from stenosis[6].

Aortic Regurgitation	Mild	Moderate	Severe
Color Doppler jet width	Central jet, width < 25% of LVOT	>Mild but no sign of severe AR	Central jet, width >65% LVOT
Regurgitant volume (ml/beat)	< 30	30-59	≥ 60
Regurgitant fraction (%)	< 30	30-49	≥ 50
Regurgitant orifice area (cm^2)	< 0,10	0,10-0,29	≥ 0,30

Table 2) Classification of the severity of valve insufficiency in adults
(adapted from Braunwald´s Heart Disease- A textbook of Cardiovascular Medicine, 9th ed. 2012, Elsevier Sounders, Philadelphia, p. 1472)

7.2.2 Pathogenesis and clinical signs

If a person develops an ***aortic stenosis*** it will lead to typical symptoms. This pathogenesis is caused by the lower aortic valve area with outflow obstruction. Hemodynamic consequences will develop if it falls below 1.5 cm^2. Studies show that many patients with an aortic stenosis have no symptoms for years. The obstruction leads to a high pressure in the left ventricle and furthermore to a concentric hypertrophy of the cardiac muscle cells. Therefore the cardiac ejection fraction is maintained for a long time. For that reason in some cases even an area of less than 1.0 cm^2 does not cause any symptoms due to a compensating muscular hypertrophy of the left ventricle with a higher cardiac output. Mostly a diastolic dysfunction develops first and leads to backflow insufficiency with dyspnea-especially on exertion, restricted exposure and fatigue. The hypertrophic muscle cells of the left ventricle need more O_2 for an appropriate function. Additionally does the

stronger tension of the myocardium disturb the coronary blood flow. These changes can lead to the typical angina pectoris symptoms of aortic stenosis. Due to the diminished ejection fraction a low cerebral perfusion can occur and induce other typical symptoms like vertigo or even syncope. The worst case would be sudden death of the patient. This, however, occurs very rarely today because of the better conservative medical treatment[6, 8].

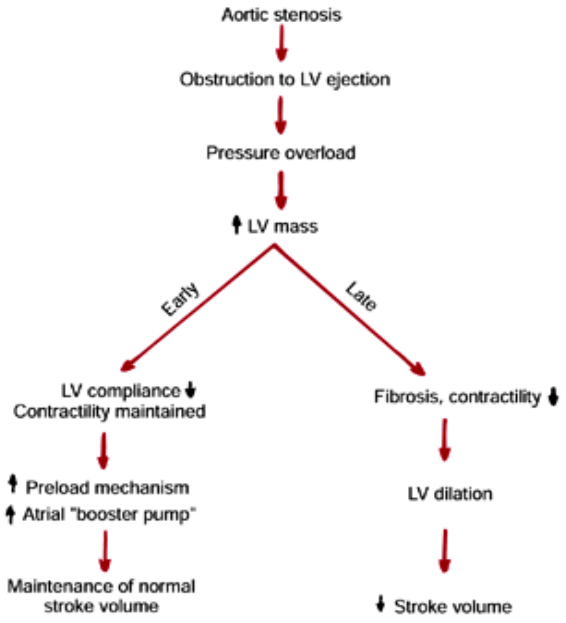

Figure 5) Pathophysiology of aortic stenosis
(This figure is adapted from http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/v04/040033r00.HTM)

The pathogenesis of symptoms in ***aortic insufficiency*** is based on a pendulum volume that leads to an exceeded stroke volume and a higher exposure of the left ventricle. Hence the regurgitation produces an exposure of the left ventricle so that it dilates and develops an eccentric hypertrophy that stretches the muscle fibers. At first the end-diastolic pressure does not decrease and therefore the cardiac output per minute does not change. Therefore an affected person may not suffer from symptoms for a long time, with the exception of palpitations. Later on the ventricle hypertrophies as for so much (critical heart weight is 500g, cor bovinum) that the heart is not able to keep the stroke volume up any more. Finally the end-diastolic pressure as well as the end-diastolic volume increases and leads to the typical symptoms like exertional dyspnea, orthopnea and uncomfortable awareness of heart beat especially when lying down. Fatigue, vertigo, syncope, and weakness are additional symptoms. In critical cases the patient may complain of paroxysmal nocturnal dyspnea and rarely of angina pectoris[6].

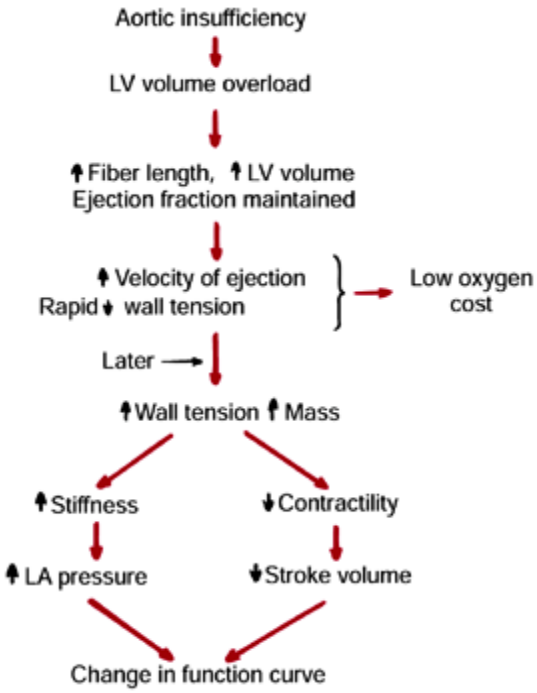

Figure 6) Pathophysiology of aortic insufficiency
(This figure is adapted from http://web.squ.edu.om/med-Lib/MED_CD/E_CDs/anesthesia/site/content/v04/040033r00.HTM)

7.2.3 Etiology

There are three etiologies leading to an ***aortic stenosis***: calcification, rheumatic disease and/ or atherosclerotic changes.

1. In humans older than 20 years calcification is a slow but progressive process in heart valves. Unicommissural valves calcify earlier than bicuspid valves (50-70 years of age) and bicuspid valves calcify earlier than tricuspid valves (70-90 years of age). Moreover men's valves calcify earlier than women´s[6, 8].
2. Rheumatic changes to aortic valves rarely occur nowadays because of the consistent treatment with antibiotics. However, sometimes a patient needs a bioprosthetic and the anamnesis might show no hint of rheumatic fever. During the surgical operation the typical morphology occurs: the cusps are thickened and the commissures clotted. Maybe they are already calcified as well. In this case rheumatic changes are the cause of the patient's symptoms[8].
3. The risk to suffer from atherosclerotic/ degenerative stenosis increases with age, especially in patients older than 65 years. As a result of the degeneration the cusps calcify additionally to common degenerative processes of the tissues[8].

The etiology of ***aortic insufficiency*** is more widespread than in aortic stenosis. Here is a short summary:

1. Rheumatic aortic incompetence is a different cellular response of the valve caused by an infection with beta-heamolysing Streptococcus of the group of A. The leaflets are cicatricial shortened and other changes are minor just like in rheumatic stenosis. After some time the aortic root starts to widen due to the ongoing infection and the incompetence will increase[8].
2. An annulo-aortic ectasia is a process which develops over years and may lead to severe stages of regurgitation. It is caused mostly by cystic degeneration of the arterial media. Round about 30% of patients with Marfan-syndrome suffer from an annulo-aortic ectasia that needs to undergo a surgical treatment. The same seems to be true for patients with Ehlers-Danlos-syndrome although there are no exact data. Nevertheless there is some evidence that annulo-aortic ectasia is an inherited disease even if no Marfan-syndrome or Ehler-Danlos-syndrome is diagnosed[8].
3. The native valve endocarditis is a common cause of valve incompetence in healthy, structural as well as in degenerately changed valves. An infected pannus infects the valve and leads to inflammation. This pathogenesis can occur in all four valve types[8].
4. In congenital aortic valve disease leads the valve to a prolapse of the free edge of a redundant leaflet and therefore to closure incompetence. The valve can be bicuspid or unicuspid[8].
5. In case of a floppy aortic valve the cusps are mildly thickened and myxomatous which leads to a prolapse. Sometimes the leaflets are even dilated[8].
6. An aneurysm of the ascending aorta caused by atherosclerotic or syphilitic changes may produce regurgitation. In general it is associated with dissection[8].
7. Like an aneurysm, an aortitis may lead to the dilatation of the ascending aorta. The cause could be a rheumatoid arthritis, ankylosing spondylitis or Reiters disease[8].
8. One other cause of an aortic incompetence may be a cusp rupture (f. e. after myocardial infarction), spontaneously or after trauma. Severe hypertension (HTN) over the course of many years may give rise to aortic root dilation. Furthermore arthropathies, Psoriasis vulgaris, giant cell aortitis or Takayasus disease should be mentioned[8].

7.2.4 Clinic and Diagnosis

The diagnosis of ***aortic stenosis*** is in first line done clinically and on the base of inspection, palpation and auscultation. The patient is mostly pale, suffers from dyspnea (NYHA III/ IV), or dizziness or periods of unconsciousness. A palpation might show parvus and tardus carotid impulse as well as a whirring above aorta and carotids. A trained ear might hear an ejection of a systolic murmur in the base of the heart that conducts to the carotids. Further diagnostics include an electrocardiogram (ECG). Changings might develop in cases of severe or critical stenosis. Signs would be a left ventricular hypertrophy and/ or a negative t-value**.** Other diagnostic ways are possible with Magnetic resonance imaging (MRI), transthoracal-echocardiography (TTE) and/ or left ventricular catheterization. The MRI enables an assessment of aortic valve area, assessment of the anatomy and functioning of the heart. The TTE issues an opinion on aortic valve orifice area, the size of atrium and ventricle, functioning of ventricle, analysis of pressure conditions, calcification, valve movements, cardiac muscle cell hypertrophy and dilatations. A left ventricular catheterization shows the aortic valve area and the peak-to-peak gradient[6].

The clinic of ***aortic insufficiency*** may occur in an acute or chronic form. Acute cases are accompanied by a fast decompensation of the left heart and an edema of the lung. The chronic form is a clinic diagnosis and its symptoms are described above. Inspection might show a pale skin. Palpating suspects may be a water hammer pulses and an low diastolic blood pressure amplitude. In some cases pulsatory phenomena occur. Auscultatory signs may be a diastolic decrescendo murmur above Erb point as well as an apical displaced and diffuse impulse. Further diagnostics are an ECG that may show signs for left ventricular dilatation. The TTE can bring to light a backflow through the valve during diastole, a bicuspid valve, an endocarditis, aortic aneurysm, excentric ventricular changes, enables an assessment of ventricular and atrial sizes as well as functioning and the pressure conditions in pulmonary circulation. The MRI might show changes of aortic size, a left ventricular dilatation and aortic regurgitation. To catheter the left heart leads to assessment of the degree of insufficiency, the pressure condition of the left heart, ventricular function, coronary disease as well as the size of ascending aorta[6].

7.2.5 Therapy

The therapy of ***aortic stenosis*** depends on the degree. A mild stenosis should be controlled every year. A moderate stenosis without symptoms should be controlled every 6-12 month. In case of a severe or critical stenosis should be performed a replacement or catheter intervention.

The conservative therapy includes self-observation regarding to any changes in health condition and an avoidance of exertion. The medical treatment is not very effective until this day, it is just able to delay progression. The typical risk factors of coronary artery disease should be evaluated and treated as per established guidelines. Finally a replacement of aortic valve will be necessary[7].

Conditions which lead to replacement are (ACC/AHA guidelines for the management of patients with vascular heart disease, 2006):

1. Symptomatic patient with severe or critical stenosis (class I indication)
2. Symptomatic patient (class I indication)
3. Patient without symptoms but severe or critical stenosis. Following parameters exist:
4. An ejection fraction < 50% (class I indication)
    a. Symptoms during stress tests (drop of blood pressure, abnormal symptoms, poor functional capacity) (class IIb indication)
    b. Fast progression of calcification (class IIb)
    c. Severe or critical left ventricular hypertrophy without a history of HTN (class IIb)
    d. Pathological stress test with a decline of blood pressure +/- developing complex heart rhythm disorder (class IIb)[6]
5. Patient with moderate aortic stenosis and necessarily of another cardiac surgery (CABG, surgery on the aorta, or another heart valve must be replaced) (class IIa indication)[6, 7]
6. In case of a symptomatic patient whose condition is too bad to be operated due to co-morbidities, a balloon catheter dilatation method or a transcatheter femoral aortic value replacement is a good choice.

LV dimension in aortic insufficiency disease	
SD > 55 mm or DD 70-75 mm	Class IIa indication
SD 50-55 mm or DD > 75 mm	Class IIb indication
	Stable: clinical evaluation and echo every 6 month.
	Not stable: consider hemodynamic response to exercise: Abnormal: class IIb indication. Normal: treated like the stable form.
SD 45-50 mm or DD 60-70 mm	Stable: Clinical evaluation every 6 month, Echo every 12 month
	Not stable: Reevaluation and echo every 3 month
SD < 45 mm or DD > 60 mm	Stable: clinical evaluation every 6-12 month, echo every 12 month.
	Not stable: Reevaluation and echo every 3 month

Table 3) LV dimension, a parameter for aortic valve replacement
SD= end-systolic dimension, DD= end-diastolic dimension (adapted from Braunwald´s Heart Disease- A textbook of Cardiovascular Medicine, 9th ed. 2012, Elsevier Sounders, Philadelphia, p. 1486)

The therapy guidelines for ***aortic valve incompetence*** are as follows:

1. Asymptomatic patients with mild hemodynamic changes who are still in conservative therapy are told to practice sport but should avoid serious sport.
2. Patient with mild to moderate degree of insufficiency receive no medical treatment, but should be followed clinically by echocardiography
3. Medical treatment fo patients with mild to moderate aortic valve insufficiency are ACE inhibitors, diuretics or/ and digitalis.
4. Symptomatic patient with NYHA II or angina pectoris should undergo replacement (class I indication)
5. Symptoms during exercising test indicates for replacement (class I indication)
6. Rapid decrease of left ventricular (LV) function is also considered as class I indication
7. In case of a symptomatic patient but uncertain LV function a radionuclide ventriculography (RVG) or Cardiac magnetic resonance (CMR) should be done to verify the diagnosis
8. If the results of RVG or CMR are subnormal, it would be a class I indication. If the results are normal, the LV dimensions should become controlled.
9. In case of a symptomatic patient with normal EF and normal RVG or CMR the LV dimension should be controlled [6, 7]

7.2.6 Combined aortic stenosis and incompetence

The etiology and morphology as well as the symptoms of combined aortic stenosis and incompetence are similar to those of aortic stenosis. Although most patients with a severe aortic stenosis have proportionally a regurgitation and vice versa. Just in seldom cases are both processes are in balance. The symptoms of those patients are like the symptoms of aortic stenosis. But patients suffer from a volume as well as pressure overload of the left ventricle[8].

7.2.7 Combined aortic and coronary artery disease

All patients older than 40 years with symptoms like angina pectoris or with a family history of arteriosclerotic disease should undergo a coronary arteriography before operation. Alternatively a cardiac CT to evaluate the Calzium Score can be performed. If a coronary artery disease is found in addition to aortic changes, a combined operation will be necessary to prevent early mortality. If a less significant coronary artery disease is found (< 50% luminal diameter narrowing) in addition to mild aortic changes, no operation will be indicated. Some patients have severe coronary artery disease and just mild changes of the aortic valves. In this case valve replacement must be done in addition to coronary artery bypass grafting (CABG) in order to prevent severe symptoms in future[8].

7.2.8 Decision guidelines for bioprosthetic or mechanic heart valve

The indication for a heart valve replacement is explained in detail above. If time has come for a surgical treatment, the question must be asked whether a biological or a mechanic prosthetic should be chosen. Therefore the advantages and disadvantages of these two main types of artificial heart valves should be considered. It depends on the following:

1. Age of the patient. If the patient is older than 65 years a bioprosthetic heart valve (BHV) will be the choice. After 10-15 years valve deteroriation, calcification and shrinking start to occur. These valves may get incompetent. Valves made out of pericardium often tear at the commissures and become incompetent[9]. A reoperation with a bioprosthesis has a twice higher mortality compared to the initial procedure and must be avoided. Most patients with a bioprosthesis will die before a replacement would be necessary[7], thus the re-operation rate is low.

   For patients younger than 60-65 years a mechanic prosthesis is chosen, they last forever and do not need to be replaced. If thrombembolic complications occur in a

patient, a reoperation might be necessary, if systemic lysis was not successful. In this case a bioprosthesis should be implanted[6].

2. Anticoagulation. Patients with mechanic prosthetic need anticoagulation for the rest of their lives. Patients treated with coumarins have higher risk for bleeding complications due to incomplete formation of the progenitor anticoagulating factors. If a patient suffers additionally from atrial fibrillations (A-Fib) or other preconditions a mechanic prosthesis would be a good choice since the patient needs anticoagulation in any event. The more co-morbid a patient, the more sense it makes to implant a mechanic prosthesis. It has less valve-related complication like endocarditis, valve and systemic thrombosis[7].

   In case of no special preconditions and appropriate age, a bioprosthetic is chosen. After implantation of biological a valve a patient with sinus rhythm needs anticoagulation for around three months after the replacement[6].

3. Hemodynamics. The muscular hypertrophy of the left ventricle as well as the diastolic and/ or systolic dysfunction leads to non physiological hemodynamics in the chambers of the heart. Implanted heart valves must be able to handle a higher pressure as well as velocity peaks in blood flow to interrupt the cycle of systemic decompensation. Non-stented heart valves can deal with cardiac muscle hypertrophy better than stented heart valves due to a smoothening of the heart at each beat.

4. Pregnancy. This special situation needs a lot of professional consideration due to the hypercoagulable state of the pregnant women. On the one hand pregnant women have an increased risk for thrombosis. On the other hand there is a high risk of fatal fetal hemorrhage (FFH) and for congenital disorder due to the teratogenic effects of coumarins in the first trimenon.

   Surgical treatment of symptomatic aortic stenosis in pregnant women should be delayed as long as possible, preferably several days after delivery. In case of severe aortic stenosis the balloon catheter dilatation method should be considered.

   The following medical treatment is possible in pregnant women with a mechanic heart valve:

   a. between the first to 36 week the patient can continue coumarins to maintain in a therapeutic INR
   b. when the risk of fetal defects is very high (6-12 week) the patient can continue with dose adjusted heparin.

c. or dose adjusted heparin during whole pregnancy[7]

7.3 Operation technique for aortic valve replacement

The patient is prepared for the operation with anesthesia and intubation. When the patient is anaesthetized, a median longitudinal sternotomia is performed. Now the pericardium is opened and attached to the cutis above to widen the view. Heparin is applied and the cannules are put to SVC, IVC and the ascending aorta. When they are placed starts the surgeon with extracorporal circulation and orders to cool down the patient´s core temperature to around 34°C for a lower consumption of O_2 of the tissues. An extra suction drain is put in the right upper pulmonary vein and the aorta is cross clamped. The coronary arteries are rinsed with a blood cardioplegic solution made out of potassium, magnesium and other components. It is infused into the orifice of coronary arteries lying in the aortic root. This solution flushing is repeated every 20 minutes. When cardiac arrest occurs, a horizontal aortotomy is done about two fingers above the valve level to reach the aortic heart valve. Subsequently the valve is assessed, positioned and excisioned. If the valve shows calcifications the surgeon will remove the calcified parts carefully. The heart is rinsed and cleaned from all small calcified particles. Then the aortic annulus is sized and the valve brand decided. The valve is put into place with a single suture technique with plaggets forcing the ventricle. During this the coronary artery orifices are carefully attended to hold them open. After sewing the valve is tested: does it move or does it leak. Now the surgeon closes the atriotomy with a double continuous suture and de-aerates the left side of the heart thouroughly. Then normothermia is performed. When the effects of the cardioplegic solution wear off the heart either starts to fibrillate or to beat with sinus rhythm. In case of fibrillation the surgeon carries out a cardioversion. In case of sinus rhythm he goes ahead. Epicardial, atrial and ventricular pacemaker electrodes are sewed onto the heart. After reperfusion time, HLM is reduced and terminated. Now the surgeon starts to remove the extracorporal circulation and inserts a drainage in the mediastinal cavity and if necessary in the pleural cavities. At this instant the closing of the sternum with wire-cerklagen is performed. Afterwards the suturing of subcutis and cutis takes place. If revasculation of the coronary arteries is necessary it takes place before the aortotomy.

After the operation the intubated patient is brought to ICU. There ventilation is performed for the next four hours. The bleeding is controlled (wound, drains) and the hemodynamic stabilized. If the neurologic check is fine, the patient is going to be extubated.

7.3.1 Heart-Lung-Machine

It is also called extracorporal circulation and it is essential for a calm and bloodless view on the operation field. It is also necessary to perform cardiac arrest for an immobile heart to enable precise working. It consists of two steps, the venous cannulation and drainage as well as of the arterial cannulation. Firstly the arterial cannulation is performed by catheterization of ascending aorta with arterial cannula. Secondly the venous cannulation is done by insertion of cannulas into the SVC and IVC[10]. To undertake the heart function are roller pumps and an oxygenator essential. The oxygenator can be based on different principles, but it always has to saturate the venous blood with O_2. It also must remove CO_2 from the blood. A heat exchanger is another part of the heart-lung-machine (HLM) and important to cool down the patient´s body temperature during the operation to 28-32°C and warms it up to the normal body temperature after replacement. The extracorporal circulation is just possible using 400 IE/kg heparin of patient´s weight to avoid coagulation on surface of the plastic hoses. After replacement heparin must be antagonized with protamine sulfate. Complications are caused by the plastic surface hoses and the hydrodynamic shearing of the roller pumps. Those lead to a traumatisation of corpuscular and plasmatic parts of the blood and hence to an activation of complement system and a systemic inflammatory response syndrome (SIRS)[9].

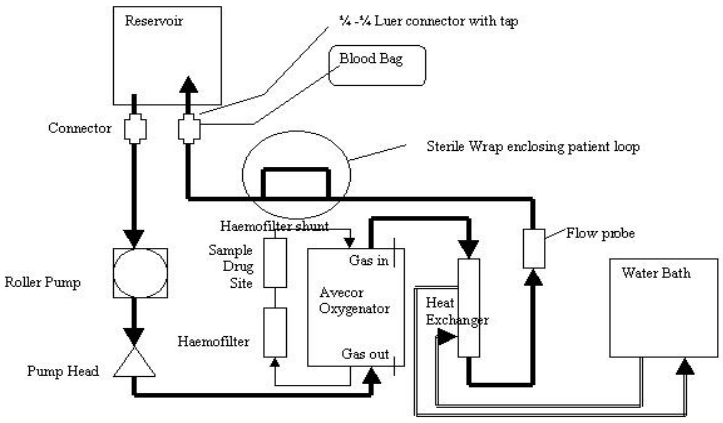

Figure 7) Principle of heart-lung-machine.
This figur is one possible schema of the HLM. (It is adapted from http://meditronics.wordpress.com/)

7.4 Description of the different types of aortic bioprosthetic valves

The first prosthetic heart valve replacement happened in 1952 and since then more than 50 designs have been developed. Nowadays nearly three million prosthetics have been implanted and there is even a branch of economics consisting of engineers and scientists who work together to improve the quality of the fluids, the implantation techniques, the durability of valves and to minimize possible complications[11].

In this chapter the most often implanted aortic bioprosthetics of department of heart surgery in Graz shall be described.

The bioprosthetic valves have following characteristics:

1. Different materials: is it made out of bovine pericardium or made of a porcine native valve
2. Different designs: is it stented what means reinforcement with a rigid annulus or is the bioprosthetic not stented. In this case it has a smooth annulus.

7.4.1 Freedom Solo ® by Sorin Group

This BHV is made out of bovine pericardium without stainless-steel or polymer stent. It is stabilized in buffered glutaraldehyde. This BHV is designed for supra-annular position and fixation with one single suture line. Two pericardial leaflets are shaped in a patented way. It is stabilized and fixated in glutaraldehyde. These leaflets are sewed together in one line with a CarbofilmTM filament which is coated with turbostratic carbon. The FS is stored in aldehyde-free solution. There are five sizes available[12].

7.4.2 Mitroflow ® by Sorin Group

It is made out of one piece of bovine pericardium that is preserved in glutaraldehyde and sewn onto a polymer stent which is covered with polyester. A radiopaque made of silicone is fixed onto an external perimeter of the inflow side of the valve. The valves are sterilized in glutaraldehyde as well as in formaldehyde and packaged in a sealed plastic jar filled with 4% formaldehyde solution. There are six sizes available for replacement (19, 21, 23, 25, 27, 29 mm)[13].

7.4.3 Perceval ® by Sorin Group

This BHV is made of double-sheeted bovine pericardium that is stabilized in buffered glutaraldehyde solution. The tissue is combined with elastic metal-alloy that expands by

itself. The elastic metal-alloy is responsible for hemodynamic behavior comparable to stentless BHV. The pericardium is supported by commissural struts, sinusoidal struts anchor the BHV in vasalva sinus. It is positioned supra- and intra-annular. There are two sizes available (S and M)[14].

7.4.4 Trifecta™ by St. Jude Medical (SJM)

This is a tri-leaflet and stented bioprosthetic made of porcine pericardium for supra-annular replacement in the aortic position. This valve is produced with a polyester- covered stent of titanium. The stent is covered with pericardium, the sewing cuff is the only part that is not covered. A specially designed silicone insert inside the polyester sewing cuff leads into the annulus for a good adjustment of the prosthetic. The leaflets of valve are made out of bovine pericardium. The porcine and bovine tissue is preserved and crosslinked in glutaraldehyde. For the sterilization glutaraldehyd, formaldehyde and ethanol are used. The bioprosthetic is treated with the Linx anticalcification process. There are six sizes available (19, 21, 23, 25, 27, 29 mm)[15].

7.4.5 Epic™ SJM

The bioprosthetic family sells three products: Biocor, Epic and Epic-supra. Biocor and Epic were developed for aortic and mitral replacement and allow an intra-annular placement of the inflow edge of the valve and a supra-annular placement of the sewing cuff. There are five sizes for aortic replacement (21, 23, 25, 27, 29 mm). The Epic-supra design was invented for aortic replacement and is manufactured in six sizes (19, 21, 23, 25, 27, 29 mm). The placement of the valve and sewing cuff is intra-annular, it contains a silicone filler.

In general the Epic is an aortic heart valve bioprosthetic made out of porcine aortic valve cusps and a framework developed by SJM. After tissue fixation it is mounted onto the FlexFit^{TM} polyester covered stent that is made out of acetal copolymer. A piece of bovine pericardium is sutured onto the outflow edge of the valves to protect the closure and opening of the leaflets. All used tissues are preserved and crosslinked in a glutaraldehyde solution. For sterilization glutaraldehyde, formaldehyde and ethanol are used. Therefore the bioprosthetics are sterile and not pyrogenic. All porcine bioprosthetics with stent contain stainless steel underneath the sewing cuff for a better x-ray visualization. The Epic as well as the Epic-supra design are treated with the Linx anticalcification process[16].

7.4.6 Mosaic by Medtronic

This bioprosthesis is made out of aortic valves of pigs which are preserved in 0,2% buffered glutaraldehyde solution to destroy porcine antigens. After this the tissue is fitted and fixed onto a cloth-covering stent. Physiologic fixation with hydrostatic pressure is applied for the cross-linking of the porcine aortic root tissue. An alpha amino oleic acid antimineralization process reduces the calcification of the porcine valves. The stents of the valves are produced from acetal homopolymer. Six different sizes of the mosaic aortic valve design 305 are available (25, 27, 30, 33, 36, 39 mm) and six sizes of the mosaic ultra small root system 305 (24, 26, 28, 30, 32, 34 mm). The inflow aspects are adapted to the natural anatomy of the annuli. The aortic valve stent as well as the sewing ring are scalloped. All stents contain stainless steel stent post markers for a better visualization under x-ray. The stent is wrapped with a polyester fabric, the sewing ring is scalloped to enable its mounting in supra or in infra-annular position. The bioprostheses are attached to a holder to simplify implantation[17].

7.4.7 Magna Ease by Edwards

This bioprosthesis is made out of bovine pericardium which is preserved in glutaraldehyde solution and fixed onto a flexible frame. In addition, it is treated with an Edwards ThermaFix process under the influence of heat in a glutaraldehyde solution, ethanol and polysorbat-80. The sterilization and packaging occur with glutaraldehyde. The stainless steel frame is constructed with flexible and ductile commissures at the valves to reduce the stress there and at the edge of the cusps. This concept reflects the natural physiology and mechanics of heart valves. The stainless steel frame is made of elgiloy, an alloy which is chosen because of its bouncing ability and its resistance to wear. This frame is covered with polyester tissue. For structural support of the opening process another elgiloy ribbon surrounds the basis of the stainless steel frame. One more sewing ring made out of soft silicone rubber wrapped with porous seamless polytetrafluoranethylen tissue is fixed onto this frame. The aortic sewing ring is adapted to the natural shape of the aortic root. This flexible sewing ring eases the fixation to irregular or calcified tissue. The valve is fixed to a holder to simplify implantation of the bioprosthesis. The Magna Ease is available in six sizes (19, 21, 23, 27, 29 mm)[18].

7.5 Thrombocytes[2, 19-21]

The thrombocytes or platelets are the smallest corpuscular components of blood. They are an important part of hemostasis and have an average lifespan of 7-10 days.

The formation is called thrombopoiesis and takes place in the red bone marrow. Megakaryocytes are the progenitor cells of platelets and their proliferation and maturation are promoted by thrombopoetin (TPO). TPO itself is produced in the liver (and partly in the kidneys, too). The formation of the next generation takes at least ten days from induction. Megakaryocytes must go through some stages during thrombopoiesis until they are able to split off platelets: The first stage of their development is the omnipotent stem cell that develops into the pluripotent myolid stem cell. If TPO now come into contact with them, thrombopoiesis is induced and megakaryoblasts will occur. The next stage are the megakaryocytes. They are autochthonous cells arranged around blood vessels of bone marrow and able to split off 4.000-8.000 platelets in their lifespan. They are about 50-70 µm in size and have a huge core which can vary in its shape. The core of mature megakaryocytes is polyploidy due to many endo-mitosises and only these matured cells are able to split off thrombocytes. Around 2/3 of the platelets circulate in the cardiovascular system the other third is stored in the spleen, where the process of degradation takes place.

Thrombocytes themselves are flat, biconvex and coreless discs that have an average diameter of 1-3 µm. The ultrastructure of platelets consists of mitochondria, glycogen-granules, ribosomes and

- Delta-granules or so-called dense bodies that store serotonin, calcium, ADP and ATP. These factors are excreted firstly after activation. The ADP is necessary to activate the GPIIb/IIIa-receptor (see below) that is hence able to bind fibrinogen and build up a connection to adjacent platelets.
- Alpha-granules are excreted when it encounters the content of delta-granules. It stores many proteins like fibrinogen, fibronectine, coagulation factors, platelet derived growth factor (PDGF), chemotactic factors, thrombospondines and von Willebrand factor (vWF).at last the primary lysosomes should be mentioned. They store hydrolytic enzymes and are important for the organization of a thrombus.
- Moreover platelets have two endomembrane systems: the dense tubular system (Ca^{2+} reservoir) and the open canalicularly system (membrane reserve).

The cytoskeleton consists mainly of actinium and has a marginal microtubule-bundle that enwinds in 8-20 spirals around the extracellular fluid (ECF).

Thrombocytes have surface integrins, these are glycoproteins (GP coupled with active or non-active coagulating factors) and are important for cell adhesion processes.

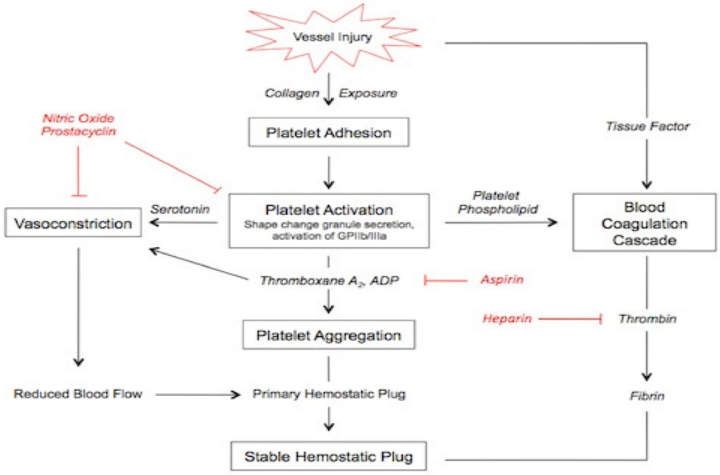

Figure 8) Physiology of Thrombocytes
This figure simplifies the physiology for a better understanding. (It is adapted from http://sharinginhealth.ca/biology/hemostasis.html)

The thrombocytes circulate marginally in the bloodstream of the vessels. If a vessel wall is injured, the thrombocytes will bind with their only permanent active receptor onto the now exposed different collagen types of ECF. The name of this receptor is GPIa/IIa and it is necessary for the initial steps of adhesion. After activation the thrombocytes change their shape and build up pseudopodia. This first fixation is not strong enough for a constant attachment to the exposed ECF collagen. It is called aggregation of platelets and is a part of primary hemostasis. Another important side effect of primary hemostasis is a vasoconstriction of the affected vessel wall.

For a firm fixation the vWF is very important. The vWF is produced in the platelets (as mentioned before) as well as in the endothelial cells. The endothelial cells excrete a small part of it into bloodstream and store most of it as granules called Weibel-Palade bodies. If the endothelial cells are activated due to an injury, the content of the Weibel-Palade bodies will be emitted into bloodstream. The vWF stabilizes the binding between the thrombocytes and couples them to fibrin. This leads to a strong fixation, the secondary hemostasis.

At the same time the activated coagulation cascade is performed. The final step is the formation of fibrin which is caused by the activity of thrombin and fibrinogen that build up a bandage of the wound and lead to continuity of the vessel wall.

7.6 Thrombocytopenia

7.6.1 Definition

The definition of thrombocytopenia is a diminishment of thrombocytes in the peripheral blood to lower than 100.000/µl. On the basis of platelet count a classification into three different grades is possible:

1. mild thrombocytopenia → 100.000 - 60.000/µl
2. moderate thrombocytopenia → 60.000 - 20.000/µl
3. severe thrombocytopenia → < 20.000/µl [22]

For a working microcirculation in vessels around 5.000-10.000/µl functioning and healthy platelets are necessary[20]. Finally thrombocytopenia is the main cause of hemorrhagic diathesis[19].

7.6.2 Etiology

Three main etiologies and one more rare etiology should be taken into account: Formation disturbances in the bone marrow, a higher peripheral usage or a combination of both these etiologies.

On the one hand formation disturbances lead to an impaired thrombopoiesis. It might be caused by a diminishment of megakaryocytes or by marred bone marrow due to chemicals (benzene), drugs (for example chemotherapeutics, immunosuppressive drugs), radiation, infections, hematopoietic cancer or osteomyelosclerosis. In some cases it might be congenital.

A maturing disturbance of megakaryocytes might be an etiology. This is caused by a deficiency of vitamin B_{12} or folic acid. On the other hand platelets may be diminished due to a higher peripheral usage. Normally the thrombopoiesis increases easily when needed (secretion of TPO). If the usage is still higher than the production, however, a thrombocytopenia will develop.

There are four possible etiologies:

1. If no underlying illness is known, a primary immune/ idiopathic thrombocytopenia purpura (ITP) would be the most appropriate cause. An acute or chronic form is possible. The acute form is mostly postinfectious. It is spoken of chronic ITP form once the thrombocytopenia lasts longer than six month.

2. If a thrombocytopenia occurs in a patient with an underlying illness, it is called secondary ITP. This can be associated with a malign lymphoma, an autoimmune disorder (for example systemic lupoid erythematoides), an infection (like HIV), after a bone-marrow transplantation or due to a disseminated intravascular coagulation (DIC). In last case an overactivity of thrombin and hence a high peripheral platelet usage is the pathogenesis.
3. An ITP might develop due to drugs that induce auto-antibodies (for example fludarabine, procainamide or sulfamethoxazole). A Heparin-induced thrombocytopenia is described in detail below.
4. A thrombocytopenia can be caused by allo-antibodies after transfusion, called post-transfusion purpura (PTP), passive allo-immunothrombocytopenia, neonatal allo-immunthrombocytopenia (NAITP).

The last etiology category "others" consists of splenomegaly, mechanic heart valves or extracorporal circulation and thrombotic mikroangiopathy (TMA).

A combination of formation disturbance and an elevated peripheral usage can develop in the final stage of alcoholtoxic livercirrhosis accompanied by a higher sequestion in the spleen and additionally a decreased production in the bone marrow (vitamin B_{12} and/or folic acid deficiency)[6].

7.6.3 Clinic and Diagnosis

The clinic shows a petechial bleeding type[19] or even purpura on skin and/ or on mucosa or in some cases both[20]. It occurs mostly when the platelets diminish to lower than 140.000/µl. But there is no acute bleeding risk if enough, which means more than 30.000/µl working thrombocytes are present in the cardiovascular system[19].

Most important for diagnosis is anamnesis. The following questions should be asked: Did the thrombocytopenia occur acute or chronic? What about family history concerning thrombocytopenia? Were there any infections in the past weeks? What about the intake of drugs in the last two weeks? In the end a conclusion leading to a hypothetic etiology- whether a formation disturbance or high peripheral usage exist- should be possible.

To confirm the hypothesis auto- as well as allo-antibodies should be checked.

The final diagnostic step is the analysis of bone marrow: is the count of megakaryocytes elevated or diminished. This diagnostic process should be choosen in complicated cases only[6].

7.6.4 Therapy

The therapy should be causal or symptomatic. In case of causal treatment every possible drug, especially heparin-contending drugs, should be avoided. The symptomatic therapy includes the substitution of platelets. Indication is a major bleeding or a planned operation with a platelet count of around 50.000 µl. If a minor bleeding is present, a platelet count of around 20.000 µl should be aspired. No antiplatelet drugs!

If a patient suffers from cancer and is treated with chemotherapeutic agents, intermittent formation disturbances might occur. If the thrombocytes count drops to lower than 10.000-20.000 µl it should be substituted.

HIT II is the only contraindication of a therapy of substitution.

But the substitution therapy has some complications like infection with HIV, herpes viruses or hepatitis virus. Furthermore an allo-immunisation due to a contamination with leukocytes, graft-versus-host reaction after hematopoietic stem cell transplantation or an allergic transfusions reaction (wheal response to anaphylaxis) can develop when a patient is treated with the substitution therapy[6].

7.6.5 Pseudothrombocytopenia

If a patient's lab values show a platelet count which is lower than 150.000/µl but the patient has no clinic signs like petechial hemorrhages or gingival bleeding, a pseudothrombocytopenia can be excluded as etiology. It develops due to an antibody inducing the agglutination of thrombocytes (mostly IgG, sometimes IgA or IgM). This occurs when the calcium level decreases in ethylenediaminetetraacetic acid (EDTA), which is the preparation substance in blood tubes. Should a pseudothrombocytopenia be expected because of a sudden diminishment of platelet count and no clinical signs, the patient's blood should be taken with citrate or heparin or a smear of EDTA prepared blood should be done[23].

7.6.6 Heparin-induced Thrombocytopenia Type 1 and 2

As listed below there are many drugs which might induce a thrombocytopenia. But the HIT is different to these causes due to two facts: first a thrombocytopenia is not that severe, only in some cases are platelet counts lower than 20000 µl reached. And second off a HIT does not lead to bleeding complications. On the contrary it causes an increased risk of thrombosis.

1. Type I is a not- immunological and early form developing in around 5% of the patient within five days of treatment with unfractionated heparin. The platelets drop 30% of the initial value but to go on with therapy leads to normalized thrombocyte counts.
2. Type II is induced by antibodies against a complex consisting of a protein on thrombocytes, platelet factor (PF4) and heparin. This complex is able to activate platelet and leads to the white clot syndrome. If a patient receives low-molecular-weight heparin (LMWH) (has a 0, 1% risk to make a HIT II) or unfractionated heparin (3%, has a thirty-times higher risk of HIT) within 5-10 days a HIT II may occur. The platelet count drops lower than 100.000/ µl and more than 50% of initial lab value.

But only few patients who develop antibodies show a diminished platelet count and only around 50% of them develop a thrombosis. This is defined as heparin-induced thrombocytopenia with thrombosis (HITT).

A HIT complication may develop when the patient receives heparin for duration of five to ten days. If a patient develops it after less than five days, he was treated with heparin in the last 100 days and still has antibodies against the antiheparin/PF4 complex.

In some cases a patient develops a HIT after having received heparin for more than ten days. This is called delayed-onset HIT[22, 23].

7.6.7 Infectious-induced Thrombocytopenia

Many viral and bacterial infections lead to thrombocytopenia. It can affect the production or the lifespan of platelets. It is the most common reason for a non iatrogenic caused thrombocytopenia. In laboratory examination signs of a DIC can be seen in addition to the low platelet count. This is mostly seen in patients with a gram negative bacterial infection. In children an immune-induced thrombocytopenia occurs often after a viral infection but it heals on its own after a while[23].

7.6.8 Drug-induced Thrombocytopenia

Many drugs can potentially suppress the platelets count. Of course chemotherapeutics are the most obvious substance due to their effect on bone marrow. Below I attached a list which provides information on drugs with single effects on thrombocytes. But there are many other drugs that might also affect the platelet count, especially contenting plant drugs.

The typical interaction is an induction of antibodies after receiving a drug. These antibodies interact with a special receptor on the membrane of the platelets and lead to its death. This develops mostly after a latency (median 21 days after intake) or just after the second intake. It normally takes 7-10 days until the thrombocytopenia regresses.

Abciximab	Danazol	Phenytoin
Diatrizoat	Chinin	Chlorpropamid
Acetaminophen	Diclophenac	Rifampicin
Aciclovir	Digoxin	Tamoxifen
Aminosalicylsäure	Eptibifatid	Tirofiban
Amiodaron	Hydrochlorothiazid	Trimethoprim/ Sulfamethoxazol
Amphotericin B	Ibuprofen	Vancomycin
Carbamazepin	Levamisol	Octreotid [23]

7.6.9 Congenital Thrombocytopenia

There are four known inherited forms of thrombocytopenia:

1. The Fanconi syndrome follows an autosomal recessive heredity pattern and its typical clinic is an aplastic anemia accompanied by a couple of other congenital abnormalities.
2. The Wiskott-Aldrich syndrome is inherited x-chromosomal. Typical symptoms of this syndrome are severe eczema, a higher susceptibility to infections and severe thrombocytopenia that drops with increasing age. The platelets are smaller than normal.
3. The Alport syndrome has an autosomal-dominant inheritance pattern and leads to a proliferative and sclerosing glomerulonephritis or an interstitial nephritis with fibrosis which develops as the disease progresses. It shows a thrombocytopenia and a dysfunction of platelets with hematuria and other bleeding complications.
4. The Gray-Plättchen syndrome is transmitted as an autosomal recessive trait and is linked to petechial hemorrhages, purpura, ecchymosis or severe bleedings. The

platelets do not have their specific granules which are necessary for functioning. Moreover they have no beta-thromboglobuline and no platelet factor 4. However the functioning of the platelets is not affected[22].

7.7 Aim of this study

The aortic bioprosthetic Freedom Solo (FS) designed by Sorin is suspected to cause a diminishment of platelets after an aortic valve replacement (AVR).

This study shall prove that FS does not degrade platelets to advanced levels compared to the other bioprosthetic brands. Moreover shall it prove that patients with a FS HVR do not have higher bleeding complications than the other patients.

7.8 Hypotheses

1. The design FS by Sorin does not cause a drop of thrombocytes count.
2. The design FS by Sorin does not cause bleeding complications.
3. The design FS by Sorin does not cause a higher drop of platelets and more bleeding complications than the other described bioprosthetic brands.
4. There is no difference between male and female regarding to complication after HVR.

8 Material and Methods

8.1 Study Population

The cohort for this study consists of all patients who received an aortic valve bioprosthesis as well as at least one CABG at the Graz department of heart surgery between December 2007 and November 2011.

Additional operation steps affecting the ascending aorta or additional mitral valve replacement were a reason for exclusion. Patients with diagnosis of aortic dissection, aneurysm and or endocarditis were excluded as well. Patients who developed a perioperative HIT or had perioperative intake or therapy of platelet suppressive drugs (see 1.6.8) were excluded also.

All participants of this single-center study were white and of Central European origin. These 293 patients represent the study cohort.

8.2 Data processing and statistic software

For data extraction following data bases were used:

1. MEDOCS (EDV Ges.m.b.H., debis Systemhaus, SAP)
2. CARDIAC (S2engineering GmbH, Steyer-Gleink, Austria)

For data processing and statistical analyses the following software was used:

1. Microsoft Excel 2010 (Microsoft Corporation, Albuquerque, New Mexico, USA)
2. SPSS 20 (Polar Engineering and Consulting; Illinois, USA)

8.3 Statistical Parameter and intervention

For this study the following data were collected:

1. Date of birth
2. Date of surgery
3. Age of patient at time of surgical intervention
4. Sex of patient
5. Diagnoses at the time of replacement
6. List of medication of the last two weeks before surgery

7. EuroSCORE
8. Surgical procedure
9. Duration of surgery
10. Valve design (name and brand)
11. Size of implanted valve
12. Perioperative platelet count
    a. One preoperative value
    b. One intraoperative value
    c. Two postoperative values
        i. The first postoperative value recorded on day one to three.
        ii. The second value recorded on day eight to ten
13. Perioperative hematocrit values (these values recorded at the same days as the platelet count)
14. Perioperative substitution of blood products (red blood cell units, fresh frozen plasma units, cryoprecipitate units and platelet units)
15. Aortic cross-clamping time (CCT)
16. Intra- and postoperative complications. Mainly bleeding complications (reoperation, tamponade, gastrointestinal bleeding), stroke (until 72 hours after surgical intervention), acute limb ischemia or anticoagulant complication
17. Information about intra- and postoperative mortality

Every parameter is set in relation to the platelet count with the exception of hematocrit. This measure is necessary to assess the blood loss during cardiac surgery and to make a valid statement. If an association or significance is present, further analyses with subgroups consisting of the different valve designs are done.

Moreover, if an aortic valve replacement leads to a diminishment of platelets, results are analyzed. Afterwards a subgroup analysis with the different types of bioprostheses as well as with independent parameters is done and compared. Here we looked at the design Freedom Solo by Sorin in more detail.

8.4 Data management and analysis[24]

8.4.1 Data input

The clinical data were extracted from MEDOCS and CARDIAC regarding to necessary information and received as Excel file. These data were merged and useless information deleted. Missing data were collected from MEDOCS and CARDIAC and summarized to one final file which was imported to SPSS Statistics 19.0 for further analysis. To protect the identity of the patient, the first name, surname and date of birth were replaced with ascending numbers. Altogether 46 variables per sample were available.

8.4.2 Data cleaning

Before starting to analyse the data, they were controlled for errors. False or missing values as well as outliers can mess up further analysis. So the data set was screened for errors and corrected.

8.4.3 Exclusion of HIT and Pseudothrombocytopenia

Unfortunately a retrospective exclusion of HIT is not possible with an enzyme immune assay any more if no clinical signs have been diagnosed and noticed then. The same applies to pseudothrombocytopenia. Nevertheless a screening was performed including all recorded platelet counts of the patients. In case of a sudden thrombocyte drop we controlled the particular patient regarding to his in MEDOCS registered diagnosis and therapies. Should a suppressing factor be present in the medical history of the patient, we will exclude him from cohort.

8.4.4 Data analysis

8.4.4.1 EuroSCORE

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is specific for cardiac surgery to predict mortality of patients by identifying risk factors. This is an easy tool for comparison with good predictive ability. Following parameter with special coefficients are developed:

1. Age (continuous) 0.0666354
2. Female 0.3304052
3. Serum Creatinine >200 µmol/l 0.6521653
4. Extracardiac arteriopathy 0.6558917

5. Pulmonary disease 0.4931341
6. Neurological dysfunction 0.841626
7. Previous cardiac surgery 1.002625
8. Recent myocardial infarct 0.5460218
9. LVEF 30–50% 0.4191643
10. LVEF <30% 1.094443
11. Systolic pulmonary pressure >60 mmHg 0.7676924
12. Active endocarditis 1.101265
13. Unstable angina 0.5677075
14. Emergency operation 0.7127953
15. Critical preoperative state 0.9058132
16. Ventricular septal rupture 1.462009
17. Other than isolated coronary surgery 0.5420364
18. Thoracic aortic surgery 1.159787
19. Constant β_0 4.789594
20. LVEF, left ventricular ejection fraction is defined more complicated and the explanation of this feature would be by far too much at this point. Further information can be seen at http://www.euroscore.org

For this score all listed risk factors must controlled and added. The sum can be handled as a percentage of mortality risk[25].

8.4.4.2 Platelet count

For a faster overview a new variable for the platelet count was performed. The physiological range for platelets is (150–400) $\times 10^9$ per liter. The data of study population were shortened to 150-400, relinquishing each zero that has no influence on interpretation but might lead to confusion. Every recorded platelet count (preoperative value, intraoperative, first to third day postoperative and 8^{th} to 10^{th} days postoperative) was set into following pattern:

1. = 0 - 4,9
2. = 5 - 9,9
3. = 10 - 19,9
4. = 20 - 59,9
5. = 60 - 99,9

6. = 100 - 149,9
7. = 150 - 449,9
8. = 450 - 499,9
9. = 500 -

A thrombocytopenia with platelet count lower than 4.9 (1) is very critical and must be treated on ICU at once due to severe spontaneous bleeding complications! A platelet count in range of 5-9,9 (2) is considered to be the absolute necessary minimum that is able to prevent bleeding complication, in case of a healthy thrombocyte function. A range of 10-19,9 (3) defines a severe thrombocytopenia. Thrombocyte level in range of 20-59,9 (4) defines a moderate thrombocytopenia and in between 60-99,9 (5) defines a mild one. 100-149,9 (6) platelet count is unspecific low and does not need further treatment but is important to bear in mind. A range of 150-449,9 (7) defines the physiological range. 450-499,9 (8) is unspecific high and might depend on the fluid balance or other independent causes. A thrombocyte level more than 500 (9) defines thrombocytosis.

8.4.4.3 Information from CARDIAC

Information about the study population was collected from MEDOCS and CARDIAC. Our cohort consists of patients that received surgical operation between December 2007 and November 2011. CARDIAC is used as database at the Department of Cardiac Surgery in Graz since the Juli 2008. Therefore the CARDIAC specific data are not available for 41 participants. The missing data are listed in each case.

9 Results

9.1 Statistical Analysis [26, 27]

9.1.1 Description of Study Population

The mean age of all 293 participants was 76,38 +/- 5,25 years.

In terms of gender shows that 42% (absolute: 123n) were female and 58% (170n) male.

The EuroSCORE had a median of 9,445. The minimum is scored as 2,23 and the maximal value as 76,84.

All participants underwent an AVR with a bioprosthesis combined with CABG. 81,9% (240n) received a CABG made out of saphenous vein. 17,4% (51n) of all participants received an arterial graft for CABG, exclusively the right or left internal mammary artery (RIMA or LIMA).

Age at Surgical Operation	Number		293
	Mean		76
	SD		5
Sex of Patient	female	Number	123
		Percentage	42,0
	male	Number	170
		Percentage	58,0
Major Procedure	AVR combined with CABG	Number	242
		Percentage	82,6
	AVR combined with CABG and IMA	Number	51
		Percentage	17,4
EuroSCORE	Median		9,45
	Maximum		76,84
	Minimum		2,23

Table 4) Age at surgical operation, Sex, Major procedure and EuroSCORE are shown in detail. SD= Standard Deviation

In 1.4) were the seven bioprostheses brands introduced. The design and size had been chosen intraoperative due to physiologic parameters of patient (body surface area) as well as the experience of the surgeon. The Mosaic by Medtronic had been used most frequent with 44% (129n). Second main implanted had been the Epic by SJM with 24,9% (73n). The third place is served for FS by Sorin with 13,3% (39n) followed by Mitroflow by Sorin with 7,2% (21n). The Trifecta by SJM had been implanted for 6,1% (18n), the Magna Ease by Edwards 3,4% (10n) and the Perceval by Sorin with 1% (3n).

Bioprostheses that were implanted less than 10% will be excluded from further statistics due to its lack of statistical power.

The bioprosthetic heart valves (BHV) are available in different sizes of annulus to enable an individual implantation. Moreover an implantation is possible in the supra-or intra- or infra-annular position. The size influences the hemodynamic of the blood flow and might be associated with higher platelet activation. The size of 19 mm was used for 10,2% (30n), the 21 mm size was used for 41,0% (120n) and 33,4% (98n) needed the 23 mm annulus. 11,3% (33n) received 25mm and for 4,1% (12n) the 27 mm annulus was implanted. The mean was 22,16 +/- 1,921 mm.

Implantation frequency	Magna Ease	Number	10
of different		Percentage	3,4
Designs	Mosaic	Number	129
		Percentage	44,0
	FS	Number	39
		Percentage	13,3
	Mitroflow	Number	21
		Percentage	7,2
	Perceval	Number	3
		Percentage	1,0
	Epic	Number	73
		Percentage	24,9
	Trifecta	Number	18
		Percentage	6,1
Size of Valve [mm]	19 mm	Number	30
		Percentage	10,2
	21 mm	Number	120
		Percentage	41,0
	23 mm	Number	98
		Percentage	33,4
	25 mm	Number	33
		Percentage	11,3
	27 mm	Number	12
		Percentage	4,1

Table 5) The implantation frequency of the different Designs, The Size of Valve.
FS= Freedom Solo

The mean of surgery duration was 4 hours 13 minutes +/- 57 min. This information includes all surgical techniques.

The CCT lasted in mean 107 minutes +/- 26 minutes.

The perfusion time yields information about how long the ECC has run during a surgical operation. The mean perfusion time lasted 152,29 minutes +/- 38,55 minutes.

The median of ICU stay was 72,512 hours. The minimum was zero hours and is associated with intraoperative death. The maximum was 1040,0 hours.

Duration of surgical Operation [min]	Number	293
	Mean	04:13
	SD	00:57
CCT **[min]**	Number	292
	Mean	107
	SD	27
ECC Time [min]	Number	252
	Mean	152
	SD	39
ICU-time [hours]	Number	252
	Median	72,3
	Maximum	1040,0
	Minimum	0,0

Table 6) Duration of surgical Operation, CCT, ECC time and ICU Duration. SD= Standard Deviation

The preoperative thrombocyte count in mean was 214,61 $\times 10^9$ µ/l +/- 58,377 $\times 10^9$ µ/l which defines a physiologic platelet count in human. The median of the intraoperative platelet level was 103 $\times 10^9$ µ/l. Its minimum was 43 $\times 10^9$ µ/l and the maximum 270 $\times 10^9$ µ/l. The median of postoperative platelet count of the first three days was 110 $\times 10^9$ µ/l. The minimum was 31 $\times 10^9$ µ/l and the maximum 353 $\times 10^9$ µ/l. The median of postoperative level of thrombocytes of day eight to ten was 273 $\times 10^9$ µ/l. The minimum was 35 $\times 10^9$ µ/l and the maximum 834 $\times 10^9$ µ/l.

PreOP	Number	285
	Mean	215
	SD	58
IntraOP	Number	292
	Median	103
	Maximum	270
	Minimum	43
PostOP 1	Number	292
	Median	110
	Maximum	353
	Minimum	31
PostOP 2	Number	176
	Median	273
	Maximum	834
	Minimum	35

Table 7) Platelet count preoperatively, intraoperatively, on the first three days after Surgical treatment and on day 8-10 postoperatively [µ/l]. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l], SD= Standard Deviation

The preoperative hematocrit (HCT) in mean was 38,003% +/- 4,3018%. The intraoperative HCT was very low and in mean 27,88% +/- 4,672%. The postoperative HCT on the first three days was in mean 29,25% +/- 3,425%. The postoperative HCT on day eight to ten was 32,95% meanly +/- 3,52%.

Hematocrit preoperatively [%]	Number	285
	Mean	38,0
	SD	4,3
Hematocrit intraoperatively [%]	Number	291
	Mean	28
	SD	5
Hematocrit 1-3 Day postoperatively [%]	Number	292
	Mean	30
	SD	3
Hematocrit 8-10 Day postoperatively [%]	Number	172
	Mean	33
	SD	4

Table 8) Hematocrit preoperatively, intraoperatively, on the first three days after Surgical treatment and on day 8-10 postoperatively [%]. SD= Standard Deviation

In this study population 53,2% (156n) received a blood product. 32,8% (96n) received no substitution. 14% (41n) of data were missing.

The intraoperative use of Red Blood Cell Units was as followed: 33,8% (99n) did not receive any substitution. 7,5% (22n) one unit. 16,7% (49n) two units, 13,0% (38n) three units, 9,6% (28n) four units, 24,% (7n) five units, 2,0% (6n) six ones, 3,0% (one person) receives nine units and 0,7% (2n) ten units. 14% (41n) of data is missing. The median was 2, the minimum was 0 and the maximum was 10 red blood units.

83,6% (245n) did not receive Fresh Frozen Plasma Units intraoperatively. 0,3% (1n) received one unit. One patient received two units (0,3%). 1,4% (4n) were treated with four units and one patient (0,3%) with six units. 14% (41n) of data is missing. The median was 0, the minimum was also zero and the maximum was 6.

For 84,3% (247n) patients a intraoperative therapy with Cryoprecipitate Units was not necessary. 0,3% (1n) received one and 1,0% (3n) received two units. 0,3% (1n) was treated with three units. 14% (41n) of data is missing. The median was 0, minimum was 0 and the maximum was 3.

The intraoperative use of Platelet Units was not necessary in 77,1% (226n) of cases. 5,5% (16n) received one unit and 3,1% (9n) two units. 0,3 (1n) was treated with three units. 14% (41n) of data was missing. The median was 0. The minimum value was also 0 and maximum 3.

Blood Product Use	Frequency	Percentage	Valid Percentage
No	96	32,8	38,1
Yes	156	53,2	61,9
Total	252	86,0	100,0
Missing	41	14,0	/
Total Number	/	293	100,0
Red Blood Cell Units	**Frequency**	**Percentage**	**Valid Percentage**
No	99	33,8	39,3
1	22	7,5	8,7
2	49	16,7	19,4
3	38	13,0	15,1
4	28	9,6	11,1
5	7	2,4	2,8
6	6	2,0	2,4
9	1	0,3	0,4
10	2	0,7	0,8
Total	252	86,0	100,0
Missing	41	14,0	/
Total Number	/	293	100,0
Fresh Frozen Plasma	**Frequency**	**Percentage**	**Valid Percentage**
No	245	83,6	97,2
1	1	0,3	0,4
3	1	0,3	0,4
4	4	1,4	1,6
6	1	0,3	0,4
Total	252	86,0	100,0
Missing	41	14,0	/
Total Number	/	293	100,0
Cryoprecipitate	**Frequency**	**Percentage**	**Valid Percentage**
No	247	84,3	98,0
eine	1	0,3	0,4
2	3	1,0	1,2
3	1	0,3	0,4
Total	252	86,0	100,0
Missing	41	14,0	/
Total Number	/	293	100,0
Platelet Units	**Frequency**	**Percentage**	**Valid Percentage**
No	226	77,1	89,7
1	16	5,5	6,3
2	9	3,1	3,6
3	1	0,3	0,4
Total	252	86,0	100,0
Missing	41	14,0	/
Total Number	/	293	100,0

Table 9) Intraoperative Blood Product Use.

60,1% (176n) of the participants did not need Blood Products postoperatively. In just 25,9% (76n) of cases a treatment was necessary. 14% (41n) of data was missing.

Around 60,4% (177n) did not need Red Blood Products after surgery. 7,2% (21n) received one unit, 10,2 (30n) two units and 4,1% (12n) three units. 2,4% (7n) were treated with four units, 0,3% (1n) with five units, 0,7 (2n) with six ones, 0,3 (1n) with ten units and 0,3% (1n) with16 units. 14% (41n) of data was missing. The median was o, the minimum was also 0 and the maximum was 16 units.

85,0% (249n) of the patients did not need Fresh Frozen Plasma Units postoperatively. 0,3% (1n) needed one unit, 0,3% four and 0,3% 12 units. 14% (41n) of data was missing. The median was 0, the minimum was 0 and the maximum was 12.

Just one patient (0,3%) received one unit of Cryoprecipitates postoperatively. 14% (41n) of data was missing. The median was also 0 as well as the minimum. The maximum was 1 unit.

The postoperative usage of Platelet Units was rare, too. 83,3% (244n) did not need a treatment. 2,0% (6n) needed one unit and 0,7% (2n) needed two units. 14% (41n) of data was missing. The median was 0, the minimum was also 0 and the maximum were two units.

Blood Product Use	Frequency	Percentage	Valid Percentage
No	176	60,1	69,8
Yes	76	25,9	30,2
Total	252	86	100
Missing	41	14	/
Total Number	/	293	100
Red Blood Cell Units	**Frequency**	**Percentage**	**Valid Percentage**
No	177	60,4	70,2
1	21	7,2	8,3
2	30	10,2	11,9
3	12	4,1	4,8
4	7	2,4	2,8
5	1	0,3	0,4
6	2	0,7	0,8
10	1	0,3	0,4
16	1	0,3	0,4
Total	252	86	100
Missing	41	14	/
Total Number	/	293	100

Table 10) Postoperative Blood Product Use.

Fresh Frozen Plasma	Frequency	Percentage	Valid Percentage
No	249	85	98,8
1	1	0,3	0,4
4	1	0,3	0,4
12	1	0,3	0,4
Total	252	86	100
Missing	41	14	/
Total Number	/	293	100
Cryoprecipitate	**Frequency**	**Percentage**	**Valid Percentage**
No	251	85,7	99,6
1	1	0,3	0,4
Total	252	86	100
Missing	41	14	/
Total Number	/	293	100
Platelet Units	**Frequency**	**Percentage**	**Valid Percentage**
No	244	83,3	96,8
1	6	2	2,4
2	2	0,7	0,8
Total	252	86	100
Missing	41	14	/
Total Number	/	293	100

Table 11) Postoperative Blood Product Use.

In 71,0% (208n) no serious complications occurred after the surgical operation. In 17,4% (51n) cases complications were present. 5,5% (16n) needed a reoperation because of a bleeding or tamponade. 0,3% (1n) suffered from a tamponade without a need for reoperation. 0,3% (1n) suffered from a heart block and one case of gastrointestinal complications were present0,3% (1n). 2,4% (7n) died during surgical operation and 1,7% (5n) of the patients died postoperatively. Thus 95,9% (281n) of the participants are still alive. There were no cases of postoperative stroke (>72 hours), no case of acute limb ischemia, no anticoagulant complication as well as no case of infectious endocarditis.

List of Complication	Frequency	Percentage	Valid Percentage
No Complications	208	71,0	71,0
Yes Complications	51	17,4	17,4
Death	5	1,7	1,7
Intraoperative Death	7	2,4	2,4
Reoperation for Bleeding/Tamponade	17	5,8	5,8
Tamponade	1	0,3	0,3
Heart Block	1	0,3	0,3
Gasrtointestinale	1	0,3	0,3
Others	2	0,7	0,7
Total Number	293	100,0	100,0

Table 12) List of Complications.

9.1.2 Correlation with platelet count

The platelet count of our cohort describes a curve over time. The preoperative value drops intraoperatively and recovers slowly over the following ten days. This curve is typical for platelet count after surgical treatment.

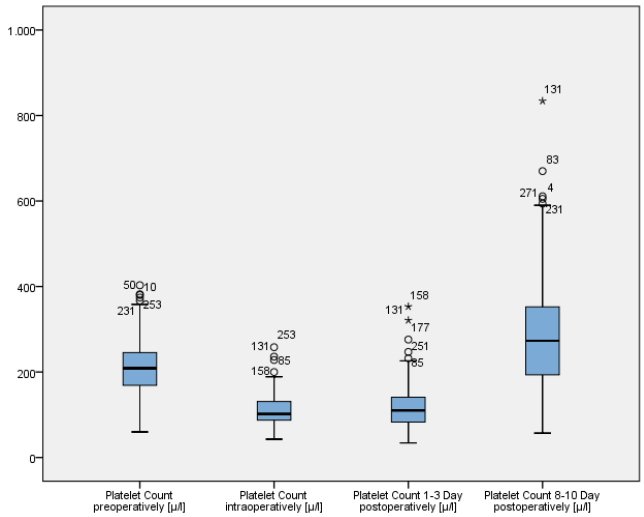

Figure 9) Platelet Count of Study Population over Time

258 (90,2%) of 285 patients had a physiologic platelet range preoperatively. 25 patients (8,7%) showed an unspecific low platelet count and two patients had a mild thrombocytopenia.

42 of 292 patients (14,4%) still had a physiologic range of thrombocytes intraoperatively. 124 patients (42,4%) showed an unspecific low platelet count and 120 ones (41,0%) a mild thrombocytopenia. Six patients (2,1%) had a moderate thrombocytopenia and one outlier (0,3%) showed a thrombocytosis intraoperatively. The intraoperative blood product use will be described later.

58 (of 292) of the patients (19,8%) recovered to a physiologic range of platelets on the first to third day postoperatively. 123 patients (42,1%) still had an unspecific low platelet count. 82 patients (28,1%) had a mild thrombocytopenia and 29 patients (9,9%) showed a moderate one.

133 (of 176) of patients (75,6%) had a physiologic range of platelets on the eighth to 10th day postoperatively. 19 patients (10,8%) still had an unspecific low platelet count and two patients (1,1%) a mild thrombocytopenia. Another two patients (1,1%) had a moderate

thrombocytopenia. However seven patients (3,9%) developed an unspecific high platelet count and 13 patients (7,4%) a thrombocytosis.

PreOP		Frequency	Percentage	Valid Percentage
	60-99,9	2	0,7	0,7
	100-149,9	25	8,5	8,8
	150-449,9	258	88,1	90,5
	Total	285	97,3	100,0
	Missing	8	2,7	/
	Total Number	293	100,0	/
IntraOP		**Frequency**	**Percentage**	**Valid Percentage**
	20-59,9	6	2,0	2,0
	60-99,9	120	41,0	41,0
	100-149,9	124	42,3	42,3
	150-449,9	42	14,3	14,3
	> 500	1	0,3	0,3
	Total	293	100,0	100,0
PostOP 1		**Frequency**	**Percentage**	**Valid Percentage**
	20-59,9	29	9,9	9,9
	60-99,9	82	28,0	28,1
	100-149,9	123	42,0	42,1
	150-449,9	58	19,8	19,9
	Total	292	99,7	100,0
	Missing	1	0,3	/
	Total Number	293	100,0	/
PostOP 2		**Frequency**	**Percentag**	**Valid Percentage**
	20-59,9	2	0,7	1,1
	60-99,9	2	0,7	1,1
	100-149,9	19	6,5	10,8
	150-449,9	133	45,4	75,6
	450-499,9	7	2,4	4,0
	> 500	13	4,4	7,4
	Total	176	60,1	100,0
	Missing	117	39,9	/
	Total Number	293	100,0	/

Table 13) Platelet Count of Patients over Time. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l]

Moreover there is a correlation with each other given. The platelet count is linear dependent on each other. The significance is p= 0,00 after Pearson.

	Pearson	PreOP	IntraOP	PostOP 1	PostOP 2
PreOP	Correlation	1	0,529	0,409	0,370
	Significance (two-sided)	/	*0,000*	*0,000*	*0,000*
IntraOP	Correlation	0,529	1	0,634	0,476
	Significance (two-sided)	*0,000*	/	*0,000*	*0,000*
PostOP 1	Correlation	0,409	0,634	1	0,632
	Significance (two-sided)	*0,000*	*0,000*	/	*0,000*
PostOP 2	Correlation	0,370	0,476	0,632	1
	Significance (two-sided)	*0,000*	*0,000*	*0,000*	/

Table 14) Correlation analysis of Platelet Counts. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l]

The age of the patient show no correlation regarding to the platelet count. It is an independent preoperative parameter.

	Pearson	PreOP	IntraOP	PostOP 1	PostOP 2	Age
Age	Correlation	0,005	0,014	0,063	-0,043	1
	Significance (two-sided)	0,951	0,858	0,413	0,573	/

Table 15) Correlation analysis of the patient´s age on day of surgical operation. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l]

The size of annulus does not have a significant correlation according to the platelet count.

	Pearson	PreOP	IntraOP	PostOP 1	PostOP 2	Size of Valve
Size of Valve	Correlation	-0,059	-0,013	-0,130	-0,063	1
	Significance (two-sided)	0,325	0,820	0,026	0,408	/

Table 16) Correlation analysis between Size of Valve and Platelet counts. Valve Size [mm], Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l]

The main major surgical procedure (MSP) carried out was AVR combined with CABG, either with saphenous or IMA as graft. There is no difference apparent between the major procedures according to thrombocyte count.

In the first group is the AVR combined with CABG made out of saphenous vein. These participants had a mean of 216 +/- 60 $\times 10^9$ µ/l preoperatively. During operation the mean was 113 +/- 38 $\times 10^9$ µ/l and 117 +/- 50 $\times 10^9$ µ/l. In the first three days after surgical treatment the mean was 117 +/- 50 $\times 10^9$ µ/l. On day eight to ten the mean of platelet count

was 276 +/- 124 $\times 10^9$ µ/l. In the second group is the AVR combined with a CABG made out of IMA. These participants had a mean of 208 +/- 51 $\times 10^9$ µ/l preoperatively. During operation was the mean 108 +/- 32 $\times 10^9$ µ/l and 121 +/- 48 $\times 10^9$ µ/l. In the first three days after surgical treatment was the mean 121 +/- 48 $\times 10^9$ µ/l. On day eight to ten the mean of platelet count was 332 +/- 137 $\times 10^9$ µ/l.

		PreOP			IntraOP		
		Mean	SD	Number	Mean	SD	Number
MSP	AVR+CABG	216	60	242	113	38	242
	AVR+CABG+IMA	208	51	51	108	32	51

Table 17) Frequency of Main Surgical Procedure according to Platelet Count. MSP= Main Surgical Procedure, Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], SD= Standard Deviation

		PostOP 1			PostOP 2		
		Mean	SD	Number	Mean	SD	Number
MSP	AVR+CABG	117	50	242	276	124	242
	AVR+CABG+IMA	121	48	51	332	137	51

Table 18) Frequency of Main Surgical Procedure according to Platelet Count. MSP= Main Surgical Procedure, PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l]SD= Standard Deviation

The operation duration has a linear dependency with the platelet count regarding to the preoperative (p= 0,43) and intraoperative platelet counts with p= 0,044. The other values showed no linear dependency. The CCT has a correlation to the 8th to 10th day postoperatively with p= 0,028. The other values do not have a linear dependency. In case of the Perfusion time of ECC is no dependency revealed and the total hours in ICU stay does not show a monotone dependency on platelet count.

	Pearson	PreOP	IntraOP	PostOP 1	PostOP 2	Duration
Duration	Correlation,	0,155	0,154	0,057	0,149	1
	Significance (two-sided)	*0,043**	*0,044**	0,461	0,051	/

Table 19) Correlation between Duration of surgical Operation and Platelet Counts. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l]Operation duration [min]

	Pearson	PreOP	IntraOP	PostOP 1	PostOP 2	CCT
CCT	Correlation,	0,022	-0,011	*0,028**	0,176	1
	Significance (two-sided)	0,774	0,892	0,714	0,022	/

Table 20) Correlation between CCT and Platelet Counts. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l], CCT= cross-clamping time [min]

	Pearson	PreOP	IntraOP	PostOP 1	PostOP 2	ECC Time
ECC Time	Correlation,	-0,010	-0,133	-0,114	0,142	1
	Significance (two-sided)	0,901	0,108	0,169	0,084	/

Table 21) Correlation between Perfusion time and Platelet Counts. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l], ECC time [min]

	Spearman-Rho	PreOP	IntraOP	PostOP 1	PostOP 2
ICU Hours	Correlation Coeffizient	0,085	0,055	0,075	0,071
	Significance (two-sided)	0,303	0,509	0,365	0,392

Table 22) Correlation between Stay in ICU and Platelet counts. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l], Total ICU Stay [hour]

The dependency is controlled between the intraoperative as well as the postoperative Blood Product Use and the platelet count. There is a correlation found between intraoperative Fresh Frozen Plasma treatments and the intraoperative platelet count with p= 0,173 after Pearson. Also correlating parameter are the intraoperative Cryoprecitipate Units and the platelet count on day one to third postoperatively. The correlation is p= 0,143. No other linear dependency is found in our data.

		PreOP	IntraOP	PostOP 1	PostOP 2
Blood Product Use	Correlation, Pearson	0,025	-0,008	-0,048	0,049
	Significance (two-sided)	0,698	0,897	0,445	0,55
Red Blood Cell Units	Correlation, Pearson	0,026	0,03	-0,051	0,03
	Significance (two-sided)	0,682	0,639	0,425	0,712
Fresh Frozen Plasma Units	Correlation, Pearson	-0,058	*0,173***	0,043	-0,003
	Significance (two-sided)	0,362	0,006	0,497	0,975
Cyroprecipitate Units	Correlation, Pearson	0,053	-0,042	*-0,143**	0,092
	Significance (two-sided)	0,409	0,51	0,023	0,256
Platelet Units	Correlation, Pearson	-0,037	0,018	-0,028	0,016
	Significance (two-sided)	0,568	0,777	0,663	0,84

Table 23) Correlation between intraoperative Blood Product Use and Platelet Counts. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l]

		PreOP	IntraOP	PostOP 1	PostOP 2
Blood Products Use	Correlation, Pearson	0,023	-0,056	0,006	-0,075
	Significance (two-sided)	0,718	0,374	0,928	0,359
Red Blood Cell Units	Correlation, Pearson	-0,059	-0,032	-0,032	-0,114
	Significance (two-sided)	0,354	0,614	0,609	0,159
Fresh Frozen Plasma Units	Correlation, Pearson	0,078	0,035	0,021	0,136
	Significance (two-sided)	0,223	0,585	0,743	0,093
Cryoprecipitate Units	Correlation, Pearson	-0,035	0,064	0,002	0,015
	Significance (two-sided)	0,588	0,313	0,973	0,851
Platelet Units	Correlation, Pearson	-0,039	-0,044	-0,031	-0,037
	Significance (two-sided)	0,541	0,485	0,626	0,652

Table 24) Correlation between postaoperative Blood Product Use and Platelet Counts. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l]

9.1.3 The correlation of HCT and Platelet count

The HCT shows a correlation in three points:

1. The preoperative HCT with the preoperative Platelet count with p= 0,033.
2. The intraoperative HCT with the intraoperative platelet count with p= 0,002.
3. The intraoperative HCT with the platelet count of the first three days postoperative with p= 0,043.

No further dependencies are detectable.

		PreOP	IntraOP	PostOP 1	PostOP 2
PreOP HCT	Correlation, Pearson	-0,127	-0,012	-0,006	0,005
	Significance (two-sided)	*0,033**	0,844	0,926	0,946
IntraOP HCT	Correlation, Pearson	0,029	0,183	0,119	0,071
	Significance (two-sided)	0,632	*0,002***	*0,043**	0,349
PostOP 1 HCT	Correlation, Pearson	0,009	-0,030	0,055	-0,088
	Significance (two-sided)	0,883	0,616	0,348	0,244
PostOP 2 HCT	Correlation, Pearson	0,088	0,098	0,038	0,141
	Significance (two-sided)	0,261	0,203	0,618	0,066

Table 25) Correlation analysis between Hematocrit and Platelet counts. Preop= preoperative platelet count [%], IntraOP= intraoperative platelet count [%], PostOP 1= postoperative platelet count on first three days [%], PostOP 2= postoperative platelet count on day 8-10 [%], HCT= Hematocrit

9.1.4 Subgroup Analysis

Three subgroups are created including AHV characteristics that might show a relation to the mysterious platelet loss:

1. The different bioprostheses designs.
2. Is a bioprosthesis stented or not. Stented designs are: Mosaic by Medtronic, Magna Ease by Edwards, Mitroflow and Perceval by Sorin, Epic and Trifecta by SJM. The stentless bioprosthesis is FS by Sorin.
3. Is the bioprosthesis made out of bovine pericardium or made of native porcine valves. Made out of bovine pericardium are Magna Ease by Edwards, Mitroflow, Perceval and FS by Sorin. The Mosaic by Medtronic and Epic by SJM are made of native porcine heart valve.

The first subgroup shall be statistical controlled in detail. The other two subgroups shall be checked whether a relation exists between the AHV characteristic and the platelet count.

9.1.4.1 Bioprostheses designs

The following graphics show the platelet curves for every bioprostheses over time. They have an analog trend like the platelet count itself. Noticeable is the lower platelet count in the subgroup of FS compared to the other subgroup.

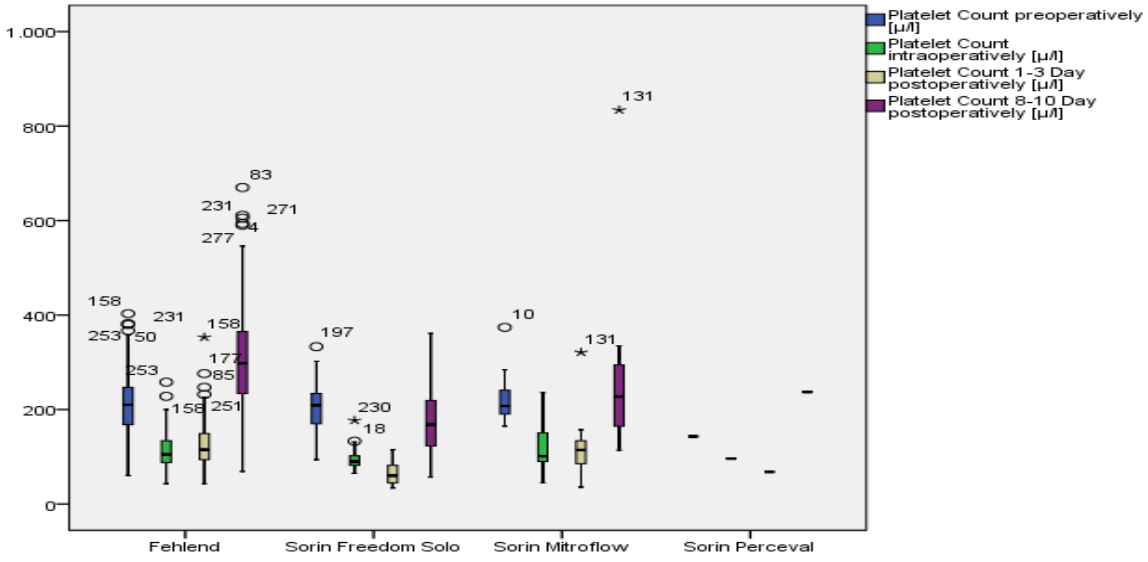

Figure 10) Platelet Count of Bioprostheses over time. Fehlend=Missing

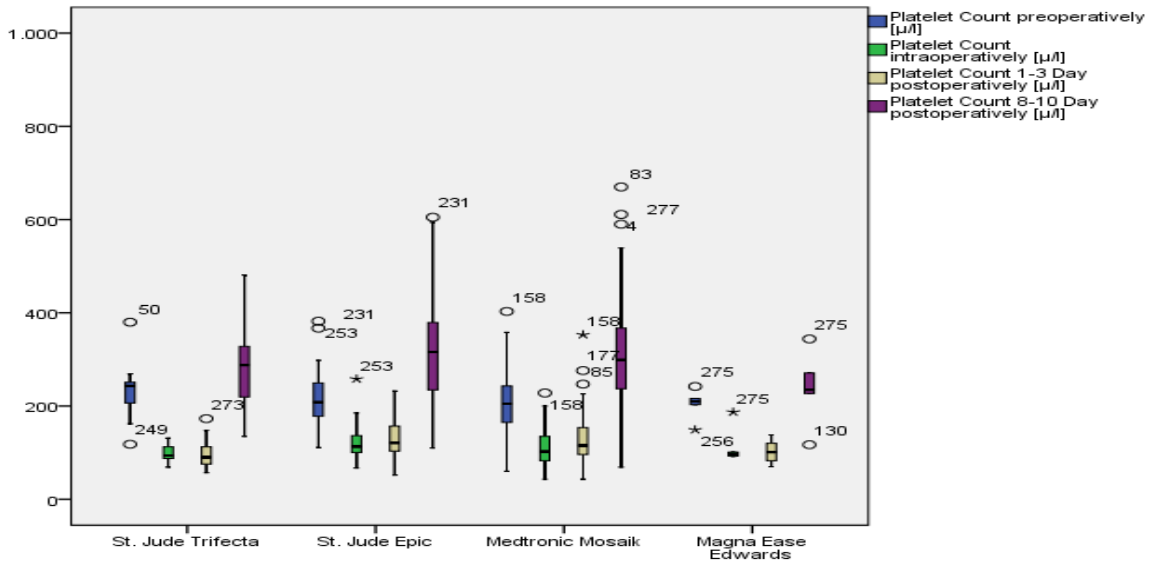

Figure 11) Platelet Count of Bioprostheses over time.

Preoperative 258 (90,5%) of 285 patients had a physiologic thrombocyte count. Just 27 patients (9,5%) showed lower values, two patients (0,7%) of them were in the FS group only. It is no difference between the subgroups obvious.

PreOP	60-99,9	100-149,9	150-449,9	Total
Magna Ease	0	2	8	10
Mosaic	1	12	113	126
FS	1	1	35	37
Mitroflow	0	1	20	21
Perceval	0	1	2	3
Epic	0	6	64	70
Trifecta	0	2	16	18
Total Number	2	25	258	285

Table 26) Preoperative Thrombocytopenia evaluation of bioprosthetic Designs.
FS= Freedom Solo

Intraoperative two patients (0,6%) of Magna Ease-subgroup still had a physiologic platelet range, four patients (1,2%) had an unspecific low platelet count and four patients (1,2%) had a mild thrombocytopenia. In the Mosaic-subgroup 19 patients had (6,4%) a physiologic range and one patient (0,3%) thrombocytosis. 53 patients (18,1%) showed an unspecific low platelet count as well as a mild thrombocytopenia (another 18,1%). Three patients (0,9%) had a moderate thrombocytopenia. In the FS-subgroup five patients (1,7%) still had a physiologic platelet range, ten patients (3,4%) had an unspecific low platelet count and 25 patients (8,5%) a mild thrombocytopenia. In the Mitroflow-subgroup five patients (1,7%) had a physiologic range, eight patients (2,4%) an unspecific low platelet

count, five patients (1,7%) a mild thrombocytopenia and three patients (0,9%) a moderate thrombocytopenia. In the Perceval-subgroup one patient (0,3%) had an unspecific low platelet count and two (0,6%) patients a mild thrombocytopenia. In the Epic-subgroup ten patients had (3,4%) a physiologic range, 40 patients (13,6%) an unspecific low platelet count and 23 patients (7,8%) a mild thrombocytopenia. In the Trifecta-subgroup one patient had (0,3%) a physiologic range, nine patients (3,0%) an unspecific low platelet count and eight patients (2,4%) a mild thrombocytopenia.

IntraOP	20-59,9	60-99,9	100-149,9	150-449,9	> 500	Total
Magna Ease	0	4	4	2	0	10
Mosaic	3	53	53	19	1	129
FS	0	25	9	5	0	39
Mitroflow	3	5	8	5	0	21
Perceval	0	2	1	0	0	3
Epic	0	23	40	10	0	73
Trifecta	0	8	9	1	0	18
Total Number	6	120	124	42	1	293

Table 27) Intraoperative Thrombocytopenia evaluation of bioprosthetic Designs. FS= Freedom Solo

On the first three days postoperative one patient had (0,3%) of Magna Ease-subgroup a physiologic platelet range, six patients (2,0%) had an unspecific low platelet count and three patients (1,0%) had a mild thrombocytopenia. In the Mosaic-subgroup 35 patients had (11,9%) a physiologic platelet range, 59 patients (20,2%) had an unspecific low platelet count, 31 patients (10,6%) had a mild thrombocytopenia and three (1,0%) patients a moderate thrombocytopenia. In the FS-subgroup one patient had (0,3%) a physiologic platelet range, two patients (0,6%) had an unspecific low platelet count, 16 patients (5,4%) had a mild thrombocytopenia and 20 patients (6,8%) a moderate thrombocytopenia. In the Mitroflow-subgroup three patients had (0,9%) a physiologic platelet range, nine patients (3,0%) had an unspecific low platelet count, seven patients (2,3%) had a mild thrombocytopenia and two patients (0,6%) a moderate thrombocytopenia. In the Perceval-subgroup one patient had (0,3%) a physiologic platelet range and two patients (0,6%) had a mild thrombocytopenia. In the Trifecta-subgroup three patients had (0,9%) a physiologic platelet range, six patients (2,0%) had an unspecific low platelet count, seven patients (2,3%) had a mild thrombocytopenia and two patients (0,6%) had a moderate thrombocytopenia.

PostOP 1	20-59,9	60-99,9	100-149,9	150-449,9	Total
Magna Ease	0	3	6	1	10
Mosaic	3	31	59	35	128
FS	20	16	2	1	39
Mitroflow	2	7	9	3	21
Perceval	0	2	0	1	3
Epic	2	16	41	14	73
Trifecta	2	7	6	3	18
Total Number	29	82	123	58	292

Table 28) Postoperative Thrombocytopenia evaluation of the first three days of the bioprosthetic Designs. FS= Freedom Solo

On day eight to ten postoperative four patients (2,2%) of Magna Ease-subgroup had a physiologic platelet range and one patient (0,5%) showed an unspecific low platelet count. In the Mosaic-subgroup 59 patients (31,8%) had a physiologic platelet range, four patients (2,2%) had an unspecific high platelet count and eight patients (4,4%) showed a thrombocytosis. Three patients (1,7%) had an unspecific low platelet count, one patient (0,5%) had a mild thrombocytopenia and one patient (0,5%) a moderate thrombocytopenia. In the FS-subgroup 13 patients had (7,3%) a physiologic platelet range, eleven patients (6,25%) had an unspecific low platelet count, one patient (0,5%) had a mild thrombocytopenia and another one (0,5%) had a moderate thrombocytopenia. In the Mitroflow-subgroup one patient had (0,5%) a thrombocytosis. Nine patients (5,1%) showed physiologic platelet range and two patients (1,0%) had an unspecific low platelet count. In the Perceval-subgroup one patient had (0,5%) with a physiologic platelet range. In the Epic-subgroup 38 patients had (21,5%) a physiologic platelet range, two patients (1,0%) had an unspecific high platelet count and four patients (2,2%) showed a thrombocytosis, one patient (0,5%) had a mild thrombocytopenia. In the Trifecta-subgroup nine patients had (5,1%) a physiologic platelet range, one patient (0,5%) had an unspecific high platelet count and another one (0,5%) an unspecific low platelet count.

PostOP 2	20-59,9	60-99,9	100-149,9	150-449,9	450-499,9	> 500	Total
Magna Ease	0	0	1	4	0	0	5
Mosaic	1	1	3	59	4	8	76
FS	1	1	11	13	0	0	26
Mitroflow	0	0	2	9	0	1	12
Perceval	0	0	0	1	0	0	1
Epic	0	0	1	38	2	4	45
Trifecta	0	0	1	9	1	0	11
Total Number	2	2	19	133	7	13	176

Table 29) Postoperative Thrombocytopenia evaluation on day 8-10th of the bioprosthetic Designs. FS= Freedom Solo

The mean age of the subgroups ranges from 75 to 81 years. FS subgroup had the youngest patients. The sex was distributed uniformly in all subgroups.

	Age		Sex			
			famale		male	
	Mean	SD	Number	Percentage	Number	Percentage
Magna Ease	77	7	3	2,4	7	4,1
Mosaic	76	5	47	38,2	82	48,2
FS	75	5	18	14,6	21	12,4
Mitroflow	78	4	16	13,0	5	2,9
Perceval	81	3	2	1,6	1	0,6
Epic	77	5	27	22,0	46	27,1
Trifecta	77	6	10	8,1	8	4,7

Table 30) Distribution of Age and Sex in Design-subgroup, FS= Freedom Solo, SD= Standard Deviation

Regarding to the EuroSCORE showed the Magna Ease-subgroup a median of 13,26, a minimum of 5,65 and a maximum of 33,80. The Mosaic- subgroup had a median of 8,38 with a minimum of 2,38 and a maximum of 55,25. The FS-subgroup had a median of 8,50 with an minimum of 2,38 and a maximum of 39,05. The Mitroflow-subgroup had a median of 10,74, a minimum of 3,51 and a maximum of 30,66. The Perceval-subgroup had median of 10,04 a minimum of 9,52 and a maximum of 13,80.The Epic-subgroup showed a median of 11,83, a minimum of 2,54 and a maximum of 76,84. The Trifecta-subgroup had median of 14,85 a minimum of 2,23 and a maximum of 24,79.

EuroSCORE	Median	Minimum	Maximum
Magna Ease	13,26	5,65	33,80
Mosaic	8,38	2,38	55,25
FS	8,50	2,38	39,05
Mitroflow	10,74	3,51	30,66
Perceval	10,04	9,52	13,80
Epic	11,83	2,54	76,84
Trifecta	14,85	2,23	24,79

Table 31) Distribution of EuroSCORE in Design-subgroup. FS= Freedom Solo

In the Magna Ease-subgroup AVR combined with a CABG made out of saphenous vein was performed in eight cases (80,0%), a AVR in combination with CABG using RIMA/LIMA as a graft was done in two cases (20,0 %). In the Mosaic-subgroup AVR combined with a CABG made out of saphenous vein was performed in 102 cases (79,1%), a AVR in combination with CABG using RIMA/LIMA as a graft was done in 27 cases (20,9%). In the FS-subgroup AVR combined with a CABG made out of saphenous vein was performed in 31 cases (79,5%), a AVR in combination with CABG using RIMA/LIMA as a graft was done in eight cases (20,5 %). In the Mitroflow-subgroup AVR

combined with a CABG made out of saphenous vein was performed in 19 cases (90,5%), a AVR in combination with CABG using RIMA/LIMA as a graft was done in two cases (9,5 %). In the Perceval-subgroup AVR combined with a CABG made out of saphenous vein was performed in 3 cases (100,0%). In the Epic-subgroup AVR combined with a CABG made out of saphenous vein was performed in 65 cases (89,0%), a AVR in combination with CABG using RIMA/LIMA as a graft was done in eight cases (11,0 %). In the Trifecta-subgroup AVR combined with a CABG made out of saphenous vein was performed in 14 cases (77,8%), a AVR in combination with CABG using RIMA/LIMA as a graft was done in four cases (22,2 %).

MSP	AVR+CABG		AVR+CABG+IMA	
	Number	Percentage	Number	Percentage
Magna Ease	8	80,0	2	20,0
Mosaic	102	79,1	27	20,9
FS	31	79,5	8	20,5
Mitroflow	19	90,5	2	9,5
Perceval	3	100,0	0	0,0
Epic	65	89,0	8	11,0
Trifecta	14	77,8	4	22,2

Table 32) Distribution of Major surgical Procedure in Design-subgroup. FS= Freedom Solo, MSP Major surgical Procedure. Table refers to the total number of patients in the different subgroups.

In the Magna Ease-subgroup one patient received a BHV with 19 mm annulus. Five patients received an 21 mm annulus and four patients an 23 mm annulus. In the Mosaic-subgroup six patients received an BHV with 19 mm annulus. 51 patients received an 21 mm annulus, 56 patients an 23 mm annulus, ten received an 25 mm annulus and six patients an 27 mm annulus. In the FS-subgroup have three patients received an 21 mm annulus, 14 patients an 23 mm annulus, 17 patients an 25 mm annulus and five patients an 27 mm annulus. In the Mitroflow-subgroup eleven patients received a BHV with 19 mm annulus. Eight patients received an 21 mm annulus and two patients an 23 mm annulus. In the Perceval-subgroup three patients received an BHV with 25 mm annulus. In the Epic-subgroup eight patients received a BHV with 19 mm annulus. 44 patients received an 21 mm annulus, 18 patients an 23 mm annulus and three patients an 25 mm annulus. In the Trifecta-subgroup four patients received an BHV with 19 mm annulus. Nine patients received an 21 mm annulus, four patients an 23 mm annulus and one patient an 27 mm annulus.

Size of Valve	19 mm	21 mm	23 mm	25 mm	27 mm
Magna Ease	1	5	4	0	0
Mosaic	6	51	56	10	6
FS	0	3	14	17	5
Mitroflow	11	8	2	0	0
Perceval	0	0	0	3	0
Epic	8	44	18	3	0
Trifecta	4	9	4	0	1

Table 33) Distribution of BHV Size in Design-subgroup. FS= Freedom Solo

For a cardiac surgery are the duration of surgical operation, the CCT and perfusion time important. Above it will be presented regarding to the different BHV. In the Magna Ease-subgroup was the mean of surgical operation duration 4:05 with a SD of 44 min. The mean of CCT was 110 min. with a SD of 32 min. The perfusion time lasted in mean 148 min. and had a SD of 34 min. In the Mosaic-subgroup the mean was 4:15 hours with SD of 54 min. regarding to surgical operation duration. The mean of CCT was 109 min. and the SD was 27 min. The mean of perfusion time was 153 min with a SD of 37 min. In the FS-subgroup was the mean 4:07 hours with SD of 1:02 min. regarding to surgical operation duration. The mean of CCT was 96 min. and with a SD of 21 min. The mean of perfusion time was 143 min and had a SD of 36 min. In the Mitroflow-subgroup was the mean 4:07 hours with SD of 45 min. regarding to surgical operation duration. The mean of CCT was 108 min. and the SD was 23 min. The mean of perfusion time was 148 min with a SD of 33 min. In the Perceval-subgroup the mean was 3:56 hours with SD of 40min. regarding to surgical operation duration. The mean of CCT was 102 min. and the SD was 4 min. The mean of perfusion time was 131 min and a SD was 7 min. In the Epic-subgroup the mean was 4:16 hours with SD of 1:07 hours regarding to surgical operation duration. The mean of CCT was 108 min. and the SD was 31 min. The mean of perfusion time was 155 min and a SD was 42 min. In the Trifecta-subgroup the mean was 4:15 hours with SD of 47 min. regarding to surgical operation duration. The mean of CCT was 115 min. and the SD was 22 min. The mean of perfusion time was 165 min and a SD was 46 min.

	DSO		CCT		ECC Time	
	Mean	SD	Mean	SD	Mean	SD
Magna Ease	04:05	00:44	110	32	148	34
Mosaic	04:15	00:54	109	27	153	37
FS	04:07	01:02	96	21	143	36
Mitroflow	04:07	00:45	108	23	148	33
Perceval	03:56	00:40	102	4	131	7
Epic	04:16	01:07	108	31	155	42
Trifecta	04:15	00:47	115	22	165	46

Table 34) Distribution of Duration of surgical Operation, CCT and Perfusion time with ECC. FS= Freedom Solo, SD= Standard Deviation, DSO= Duration of surgical Operation [hours], CCT= Cross-Clamping time [min], Perfusion time with ECC [min]

After surgical operation the patient must be monitored in ICU. The hours of ICU stay is an indirect parameter to assess the postoperative condition of patient. The Magna Ease-subgroup had a median of 50 hours, the minimum was 19 hours and the maximum 239 hours. The Mosaic-subgroup has a median of 68,3 hours, the minimum were zero hours and maximum were 937 hours. The FS-subgroup had a median of 61,3 hours the minimum were 10,5 hours and maximum were 771 hours. The Perceval-subgroup had a median of 26,5 hours, the minimum were 26,0 hours and maximum were 98,5 hours. The Mitroflow-subgroup had a median of 84,8 hours the minimum were 25 hours and maximum were 882 hours. The Epic-subgroup had a median of 72,8 hours, the minimum were zero hours and maximum were 1040 hours. The Trifecta-subgroup had a median of 99,5 hours, the minimum were 26 hours and maximum were 361,5 hours.

Total Hours in ICU	Median	Minimum	Maximum	Number
Magna Ease	50,0	19,0	239,0	10
Mosaic	68,3	0,0	937,0	129
FS	61,3	10,5	771,0	39
Mitroflow	84,8	25,0	882,0	21
Perceval	26,5	26,0	98,5	3
Epic	72,8	0,0	1040,0	73
Trifecta	99,5	26,0	361,5	18

Table 35) Distribution of Total Hours in ICU in Design-subgroup. FS= Freedom Solo

In this study population ten patients received a Magna Ease BHV, from which eight two patients (20%) suffered from complications. One died (10%) intraoperatively and one (10%) needed to be re-operated. In the Mosaic-subgroup were in total 129 patients, from which 13 patients (10%) developed complications (three patients died postoperatively(2,3%), one more patient (0,7%) died during surgical operation, six patients (4,6%) needed to be re-operated, one (0,7%) developed a heart block and one patient (0,7%) gastrointestinal complications and one patient (0,7%) was categorizes as others). 39

patients received a FS design. Around 28% (11n) were affected with complications. Two patients (5,1%) died intraoperatively and two patients (5,1%) needed a reoperation due to a hemorrhage or tamponade. In the Mitroflow-subgroup had two patients (9,5%) complications during their stay in hospital. One patient died and one needed to be re-operated. Patients which received a Perceval BHV did not suffer from complications. The Epic had 21 participants (28,8%) with complications. Two patients died (one (1,3%) during surgical intervention, one postoperatively (1,3%)) and in six cases (8,2%) was a reoperation necessary. One patient (1,3%) developed a tamponade and one patient (1,3%) was categorized as others. Three patients with the BHV Trifecta developed complications (16,6%). One (5,5%) died intraoperatively and one patient (5,5%) needed to be re-operated.

	Yes	Death	intraop Death	ReOP	Tam	HB	GI	Others	Total
Magna Ease	2	0	1	1	0	0	0	0	10
Mosaic	13	3	2	6	0	1	1	1	129
FS	11	0	2	2	0	0	0	0	39
Mitroflow	2	1	0	1	0	0	0	0	21
Perceval	0	0	0	0	0	0	0	0	3
Epic	21	1	1	6	1	0	0	1	73
Trifecta	3	0	1	1	0	0	0	0	18
Total	51	5	7	17	1	1	1	2	293

Table 36) Distribution of Complications in Design-subgroup. FS= Freedom Solo, intraop Death= intraoperative Death, ReOP= Reoperation due to Tamponade or Bleeding Complication, Tam= Tamponade, HB= Heart Block, GI= Gastrointestinal Complication

The multivariate analysis for variance shows no significance between the platelet counts regarding to FS and the other bioprostheses preoperatively. The significance is tested with Turkey, Scheffé and Bonferroni (Sig. for all more than p= 0,8).

In the intraoperative comparison a tendency is found. A difference of the platelet counts of the different BHV regarding to FS is possible.

In the first three days after surgical operation a significant difference is present in platelet count between FS and Mitroflow, Epic as well as Mosaic (p< 0,03 in Turkey, Scheffé and Bonferroni). The Trifecta has no significant difference in platelet count regarding to FS (p= 0,275 in Turkey; p= 0,414 in Scheffé and p= 0,481 Bonferroni).

In the 8-10th day postoperatively a significance is given between FS and Epic as well as Mosaic (p= 0,0 in Turkey, Scheffé and Bonferroni). For Mitroflow and Trifecta a strong tendency is given (Mitroflow: p= 0,13 Turkey; p= 0,294 Scheffé and p= 0,27 Bonferroni; Trifecta: p= 0,075 Turkey; p= 0,154 Scheffé as well as p= 0,101 Bonferroni).

				Mean Difference (I-J)	SD	Sig.	95%-Confidence Interval	
							Minimum Level	Maximum Limit
PreOP	Tukey-HSD	FS	Mitroflow	-14,67	21,294	*0,959*	-73,42	44,08
	"		Trifecta	-24,37	21,938	*0,801*	-84,90	36,15
	"		Epic	-8,11	15,250	*0,984*	-50,18	33,97
	"		Mosaic	-,87	14,026	*1,000*	-39,57	37,83
	Scheffé	FS	Mitroflow	-14,67	21,294	*0,976*	-81,03	51,69
	"		Trifecta	-24,37	21,938	*0,872*	-92,74	43,99
	"		Epic	-8,11	15,250	*0,991*	-55,63	39,42
	"		Mosaic	-,87	14,026	*1,000*	-44,58	42,85
	Bonferroni	FS	Mitroflow	-14,67	21,294	*1,000*	-75,28	45,94
	"		Trifecta	-24,37	21,938	*1,000*	-86,82	38,07
	"		Epic	-8,11	15,250	*1,000*	-51,51	35,30
	"		Mosaic	-,87	14,026	*1,000*	-40,79	39,06
IntraOP	Tukey-HSD	FS	Mitroflow	-19,35	12,544	*0,536*	-53,96	15,26
	"		Trifecta	-1,61	12,923	*1,000*	-37,27	34,05
	"		Epic	-23,50	8,983	*0,072*	-48,28	1,29
	"		Mosaic	-11,36	8,263	*0,645*	-34,16	11,44
	Scheffé	FS	Mitroflow	-19,35	12,544	*0,667*	-58,45	19,74
	"		Trifecta	-1,61	12,923	*1,000*	-41,89	38,67
	"		Epic	-23,50	8,983	*0,150*	-51,49	4,50
	"		Mosaic	-11,36	8,263	*0,756*	-37,11	14,39
	Bonferroni	FS	Mitroflow	-19,35	12,544	*1,000*	-55,06	16,35
	"		Trifecta	-1,61	12,923	*1,000*	-38,40	35,18
	"		Epic	-23,50	8,983	*0,098*	-49,07	2,07
	"		Mosaic	-11,36	8,263	*1,000*	-34,88	12,16
PostOP 1	Tukey-HSD	FS	Mitroflow	-55,20	16,620	*0,010*	-101,06	-9,34
	"		Trifecta	-34,11	17,123	*0,275*	-81,35	13,14
	"		Epic	-64,83	11,903	*0,000*	-97,67	-31,99
	"		Mosaic	-63,29	10,948	*0,000*	-93,50	-33,09
	Scheffé	FS	Mitroflow	-55,20	16,620	*0,030*	-107,00	-3,40
	"		Trifecta	-34,11	17,123	*0,414*	-87,47	19,25
	"		Epic	-64,83	11,903	*0,000*	-101,92	-27,73
	"		Mosaic	-63,29	10,948	*0,000*	-97,41	-29,18
	Bonferroni	FS	Mitroflow	-55,20	16,620	*0,011*	-102,51	-7,89
	"		Trifecta	-34,11	17,123	*0,481*	-82,85	14,63
	"		Epic	-64,83	11,903	*0,000*	-98,71	-30,95
	"		Mosaic	-63,29	10,948	*0,000*	-94,46	-32,13
PostOP 2	Tukey-HSD	FS	Mitroflow	-92,78	41,559	*0,173*	-207,45	21,89
	"		Trifecta	-111,46	42,816	*0,075*	-229,60	6,67
	"		Epic	-144,09	29,763	*0,000*	-226,21	-61,97
	"		Mosaic	-136,54	27,375	*0,000*	-212,07	-61,00
	Scheffé	FS	Mitroflow	-92,78	41,559	*0,294*	-222,30	36,74
	"		Trifecta	-111,46	42,816	*0,154*	-244,90	21,98
	"		Epic	-144,09	29,763	*0,000*	-236,85	-51,34
	"		Mosaic	-136,54	27,375	*0,000*	-221,85	-51,22
	Bonferroni	FS	Mitroflow	-92,78	41,559	*0,270*	-211,08	25,52
	"		Trifecta	-111,46	42,816	*0,101*	-233,34	10,41
	"		Epic	-144,09	29,763	*0,000*	-228,81	-59,37
	"		Mosaic	-136,54	27,375	*0,000*	-214,46	-58,61

Table 37) Analysis of Significance in Design-subgroup (Turkey, Scheffé, Bonferroni). FS= Freedom Solo, SD= Standard Deviation, Sig.=Significance

9.1.4.2 Bioprostheses stented or stentless

This subgroup distinguishes between stented BHV and stentless BHV. No stent have: Mosaic by Medtronic, Magna Ease by Edwards, Mitroflow and Perceval by Sorin, Epic and Trifecta by SJM.

The bioprosthesis without a stent is FS. All other bioprostheses are stented. The diagram illustrates the typical thrombocyte curve over time for both subgroups. It is obviously that the stentless-group has a lower platelet count, especially on the early postoperative days.

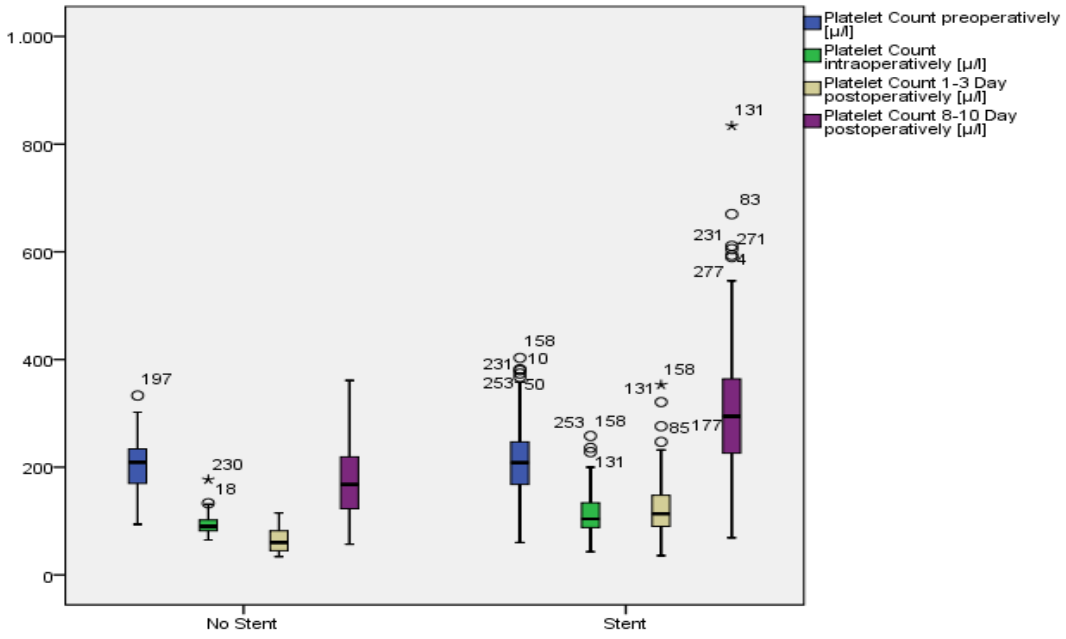

Figure 12) Comparison of Stented and Stentless BHV regarding to platelet count over time.

The platelet count was in physiologic ranges for 258 (90,53%) of 285 patients before surgery. 25 (8,77%) patients suffer from an unspecific low platelet count. Most of them received a stented bioprosthesis. Two patients (0,7%) had a mild thrombocytopenia.

PreOP	60-99,9	100-149,9	150-449,9	Total
Stentless	1	1	35	37
Stented	1	24	223	248
Total	2	25	258	285

Table 38) Distribution of platelet count in Stent-subgroup preoperatively.

Intraoperative the stentless valve subgroup developed in 9 (23,1%) cases an unspecific low platelet count and in 25 (64,1%) cases a mild thrombocytopenia. The rest kept its physiologic range (5n, 12,8%). The stent-subgroup had in a physiologic range 37 cases

(14,6%). 115 patients (45,3%) developed an unspecific low platelet count and 95 patients (37,4%) a mild thrombocytopenia. In six patients (2,0%) a moderate thrombocytopenia occurred.

IntraOP	20-59,9	60-99,9	100-149,9	150-449,9	> 500	Total
Stentless	0	25	9	5	0	39
Stent	6	95	115	37	1	254
Total	6	120	124	42	1	293

Table 39) Distribution of platelet count in Stent-subgroup intraoperatively.

In the stentless valve-subgroup one patient (2,6%) had a physiologic range in the first three days after surgical operation. Two patients (5,2%) had an unspecific low platelet count and 16 patients (41,0%) a mild thrombocytopenia. In 20 cases (51,3%) a moderate thrombocytopenia occurred. The stented valve-subgroup had 57 patients (22,5%) in a physiologic range and 121 (47,8%) patients with an unspecific low platelet count. In 66 patients (26,1%) a mild thrombocytopenia occurred and in nine patients (3,6%) a moderate one.

PostOP 1	20-59,9	60-99,9	100-149,9	150-449,9	Total
Stentless	20	16	2	1	39
Stent	9	66	121	57	253
Total	29	82	123	58	292

Table 40) Distribution of platelet count in Stent-subgroup on the first three days postoperatively.

Eight to ten days after surgical operation 13 patients (50,0%) had a physiologic range, eleven patients (42,3%) an unspecific low platelet count and one patient (3,8%) a mild thrombocytopenia. Another one patient (3,8%) had a moderate thrombocytopenia. In the stented valve-subgroup 120 patients (80,0%) had a physiologic range, seven patients (4,7%) showed an unspecific high platelet count and 13 patients (8,7%) had even a thrombocytosis. Eight patients (5,3%) still had an unspecific low platelet count, one patient (0,7%) a mild thrombocytopenia and another one (0,7%) a moderate thrombocytopenia.

PostOP 2	20-59,9	60-99,9	100-149,9	150-449,9	450-499,9	> 500	Total
Stentless	1	1	11	13	0	0	26
Stent	1	1	8	120	7	13	150
Total	2	2	19	133	7	13	176

Table 41) Distribution of platelet count in Stent-subgroup on day 8-10 postoperatively.

As a control of dependencies between the subgroup stentless/ stented BHV, a t-Test analysis on the base of dependent samples (platelet counts recorded on the different days) was performed. It shows the following significances:

	Correlation	Significance
PreOP	0,031	0,684
IntraOP	0,146	0,056
PostOP 1	0,409	*0,000*
PostOP 2	0,367	*0,000*

Table 42) t-Test analysis in stentless/ stented subgroup. Preop= preoperative platelet count [µ/l], IntraOP= intraoperative platelet count [µ/l], PostOP 1= postoperative platelet count on first three days [µ/l], PostOP 2= postoperative platelet count on day 8-10 [µ/l]

There reoperation due to tamponade or bleeding complication occurred in two cases (5,1%) in the stentless-subgroup. Compared to the stented-subgroup 15 patients (5,9%) needed a reoperation. In the stentless-subgroup two patients (5,1%) died intraoperatively. In the stented-subgroup fife patients (1,9%) died during their stay in hospital and fife more patients (1,9%) died intraoperatively. One patient (0,3%) developed a tamponade, one patient (0,3%) a heartblock, one patient (0,3%) gastrointestinal complications and two patients (0,6%) complications categorized as “others”.

	Stentless	Stented	Number
Yes Complications	11	40	51
Death	0	5	5
IntraOP Death	2	5	7
ReOP Bl/Ta	2	15	17
Tamponade	0	1	1
Heart Block	0	1	1
GI	0	1	1
Others	0	2	2
Total Number	39	254	293

Table 43) List of complications referring to stented/stentless-subgroup. In this list are only hemorrhagic complications shown. IntraOP= intraoperative, ReOP= reoperation, Bl= bleeding, Ta= Tamponade, GI= gastrointestinal

9.1.4.3 Bioprostheses made out of pericardium or porcine native valve

These BHVs are made out of bovine pericardium: Magna Ease by Edwards, Mitroflow, Perceval and FS by Sorin. The Mosaic by Medtronic and Epic by SJM are made of native porcine heart valves.

The platelet count of AHV made out of pericardium lead to a deeper drop of thrombocytes on day eight to ten and shows a more sluggished recovery compared to the porcine native valve.

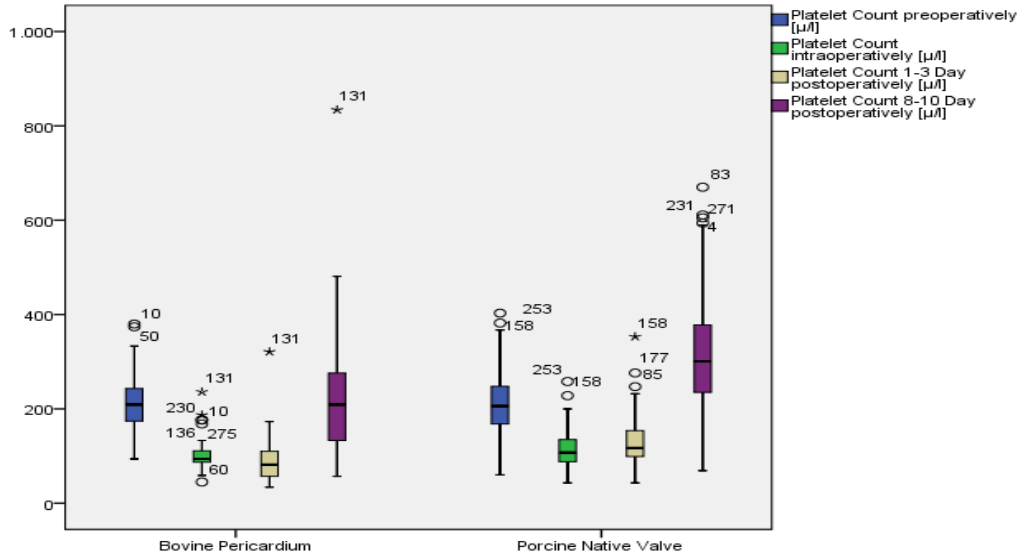

Figure 13) Comparison of platelet count over time in Material-subgroup.

Preoperative 81 patients in the Pericardium-subgroup had (91,0%) a physiologic range, seven patients (7,9%) had an unspecific low platelet count and one patient (1,1%) had a mild thrombocytopenia. In the Native valve-subgroup 177 patients (90,3%) had a physiologic range, 18 patients (9,2%) show an unspecific low platelet count and one patient (0,5%) had a mild thrombocytopenia.

PreOP	60-99,9	100-149,9	150-449,9	Total
Percardium	1	7	81	89
Native Valve	1	18	177	196
Total	2	25	258	285

Table 44) Distribution of platelet count in Material-subgroup preoperatively.

In the Pericardium-subgroup 13 patients (14,3%) showed a physiologic range, 31 patients (34,1%) an unspecific low platelet count and 44 patients (48,4%) a mild thrombocytopenia intraoperatively. Three patients (3,3%) had a moderate thrombocytopenia. In the native valve-subgroup 29 patients (14,4%) had a physiologic range and one patient (0,5%) a thrombocytosis. 93 patients (46,0%) had an unspecific low platelet count, 76 patients (37,6%) a mild thrombocytopenia and three patients (1,5%) a moderate thrombocytopenia.

IntraOP	20-59,9	60-99,9	100-149,9	150-449,9	> 500	Total
Percardium	3	44	31	13	0	91
Native Valve	3	76	93	29	1	202
Total	6	120	124	42	1	293

Table 45) Distribution of platelet count in Material-subgroup intraoperatively.

On the first three days after surgical operation nine patients (9,9%) had a physiologic range, 23 (25,3%) had an unspecific low platelet count, 35 patients (38,5%) a mild thrombocytopenia and 24 patients (26,4%) a moderate thrombocytopenia. In the native valve-subgroup 49 patients (24,4%) had with a physiologic platelet range, 100 patients (48,8%) with an unspecific low platelet count, 47 patients (23,4%) with a mild thrombocytopenia and fife patients (20,5%) with a moderate thrombocytopenia.

PostOP 1	20-59,9	60-99,9	100-149,9	150-449,9	Total
Percardium	24	35	23	9	91
Native Valve	5	47	100	49	201
Total	29	82	123	58	292

Table 46) Distribution of platelet count in Material-subgroup on the first three days postoperatively.

On the 8th to 10th day after surgical operation 36 patients (65,5%) of the pericardium-subgroup had a physiologic range. One patient (1,8%) had an unspecific high platelet count and another one (1,8%) a thrombocytosis. 15 patients (27,3%) had an unspecific low platelet count, one patient (1,8%) a mild thrombocytopenia and another one (1,8%) a moderate thrombocytopenia. In the native valve-subgroup 97 patients (80,2%) had a physiologic range, six patients (4,9%) an unspecific high platelet count and twelve patients (9,8%) a thrombocytosis. Four patients (3,3%) showed an unspecific low platelet count, one patient (0,8%) a mild thrombocytopenia and another one (0,8%) a moderate thrombocytopenia.

PostOP 2	20-59,9	60-99,9	100-149,9	150-449,9	450-499,9	> 500	Total
Percardium	1	1	15	36	1	1	55
Native Valve	1	1	4	97	6	12	121
Total	2	2	19	133	7	13	176

Table 47) Distribution of platelet count in Stent-subgroup on day 8-10 postoperatively.

10 Discussion

The bioprosthetic heart valve FS by Sorin was released in 2004 and has proven echocardiographic advantages in postoperative studies. Well hemodynamic results, a fast LV remodeling (LV mass diminishment after a year about 23%[28]) and a higher survival in patients[29]. The implantation of FS in supra-annular position with a single continuous suture line[12] leads to shorter CCT, ECC time and therefore shorter surgical operation duration. Furthermore the surgeons appreciate this simple technique of implantation. Hence many Departments of Cardiac Surgery decided to implant the FS design, but time brought an unspecific suspect of thrombocytopenia in patients after AVR with the FS. A first study in 2007 confirmed this suspicion. It recorded that platelet loss was more severe from day of surgical operation procedure until first two weeks afterward. The postoperative recovery documented to day 13 after AVR was more sluggished compared to the Mitroflow by Sorin[29]. Even in follow-ups of patients in later days with FS, the departments noticed a lower platelet count compared to other BHV. A lot of studies followed and certified this observation[30, 31], but some institutes did not find any differences in enrolled studies between FS and other BHV regarding to platelet count[32]. Many studies were provided to find a reason for this thrombocytopenia in the FS, but this mystery is not solved yet and is still ongoing until today.

Independent preoperative factors are the patient's age, sex and morbidity (scored with the EuroSCORE) and considered to be risk factors for thrombocytopenia after AVR. Our data cannot confirm this presumption. The age showed no linear dependency and the EuroSCORE no monotone dependency on platelet count. Hilker et al.[33] reported similar results. According to our data the sex of a patient does not affect the platelet count in any way.

The dependent preoperative parameters are the thrombocytes themselves. Our data showed that the platelet count is linear dependent on each other. The significance is p= 0,00 after Pearson. The blood product use does not have a monotone dependency on the platelet count with exception: on the one hand the intraoperative Fresh Frozen Plasma use correlates with a p= 0,173 with the intraoperative thrombocyte count, but this is a logical relation. On the other hand the intraoperative Cryoprecitipate Units correlates with the platelet count on day one to third postoperatively with p= 0,143. This is also a logical relation.

There are a lot of intraoperative parameters that might have effects on the platelet count. Although many of them have been controlled in other studies before, our cohort is controlled either.

The implantation technique of FS is accused to be a factor affecting platelet counts. In contrary, the same technique has been performed with o´Brien CryoLife valve 25 years ago. No postoperative thrombocytopenia has been recorded then[34].

The percentage of platelet count in patients with concomitant surgical procedures as CABG and mitral valve replacement did not differ significantly regarding to Yerebakan et al. study[28]. In our cohort every patient undergoing surgery with additional prostheses was excluded. More than one prostheses are expected to distort our findings because of additional platelet activating effects. Our cohort consists of patients with at least one additional CABG procedure made out of saphenous vein and/ or IMA. Further studies are going to be investigated to compare different surgical techniques to find the reason for the postoperative thrombocytopenia. Nevertheless our statistical analyses show no dependency and thus have these further techniques no effects on platelet count.

More characteristics of surgical procedure are considered to influence the platelets. Our survey showed that surgery duration correlates linear with the preoperative and intraoperative platelet count. This can be explained by the fact that less thrombocytes lead to more small bleedings. These bleedings need to be stopped which again needs time. The CCT correlates linear with the 8^{th} to 10^{th} day postoperatively. For the other values we did not find linear dependency regarding to thrombocyte levels. Yerebakan et al. did not find any correlations between the operation duration, CCT and platelet count[28].

Against all our expectations no correlation is found for perfusion time of ECC. We considered the HLM to traumatize platelets due to the contact with them and the plastic surface tubes. Moreover the hydrodynamic shearing in the roller pump of HLM harms thrombocytes as well and leads to stronger damage. These damages activate them and the complement system that responses with unspecific platelet consumption. Thus the thrombocyte function and its count are affected. Regarding to former studies the HLM leads to a distinct diminishment of around 50% compared to preoperative thrombocyte level[9].

Furthermore hypothermia is performed during surgical procedure. The HLM cools down the core temperature of the patient to 34°C. Many studies describe side effects of

hypothermia on the function of thrombocytes[35]. The hypothermia duration is dependent on the perfusion time of ECC. The longer the perfusion time, the longer hypothermia lasts. Nevertheless, our data show no linear dependency between perfusion time and thrombocyte level.

Postoperative parameter may also have influence on the platelet count. The postoperative procedure is the same for all cardiopulmonary stable patients. In the study of Yerebakan et al.[28] the whole postoperative management of his cohort was controlled, recorded and statistical analyzed. In his study the platelet count of FS was compared to the thrombocyte levels of Mitroflow. His study protocol included valve specific parameter (aortic stenosis, aortic regurgitation, arterial HTN) as well as morbidity parameters (diabetes mellitus, renal insufficiency). He also recorded the drug intake of the patients postoperatively (Heparin, Danapaoid, Beta-blocker, ACE-inhibitors, CSE-inhibitors, Calcium antagonists, Loop diuretics, Antibiotics (Fluorchinolon), ASS, Clopidogrel). He could not find any differences regarding to thrombocytes between these subgroups.

The FS has a significant higher incidence in patients who developed thrombocytopenia. After AVR the blood flow of heart is not physiological anymore. Hence the hemodynamic is evaluated routinely per echocardiograph periperatively. There is a consideration that this unphysiological hemodynamic changes lead to platelet activation. In the study of Yerebakan et al. no peak and mean gradient is found between the subgroups consisting of FS and Mitroflow perioperatively[28].

Therefore microhemodynamic effects were considered to cause platelet activation. They are not representable by echocardiograph any more. The prosthesis structure is assumed to cause microhemodynamic turbulences leading to a transient and unspecific activation of thrombocytes with a diffuse consumption [36]. Blood shear stress plays a significant role in blood element damage[37] resulting from velocity gradients. A difference of 0,25m/sec is enough to induce shear stress that lead to platelet damage if it is repeated frequently. Approximately 1.000 cycles are necessary for one thrombocyte to induce damage[37]. Thus even a little fold in BHV may cause a velocity gradient. First and foremost the bioprosthetic shape may be a reason for higher platelet activation.

Miceli et al. [31] recorded the Mean Platelet Volume (MPV) and Platelet distribution width (PDW) after FS implantation and compared it with other bioprostheses. At the third

postoperative day the FS group showed a higher MPV and PDW. Thus it is confirmed that higher platelet consumption occurs.

A discussion about a toxic effect caused by preparation solutions were lead. Especially the preparation of FS with homocysteic acid was a starting point. Homocysteic acid is activating the N-methyl-D-aspartate receptors that cause platelet aggregation[38]. This thesis was dropped down due to a concentration use of 10 µmol/l and the fact that toxic effects occur with concentration of 300-500 µmol/l. After treatment with homocysteic acid solution the FS valve was washed two times with a homocysteic acid free solution. Afterward it is stored and send in a homocysteic acid-free (and glutaraldehyde free) solution. In this store-solution the homocysteic acid is even lower than the physiologic range in humans[33]. Furthermore no rinsing with the storage-solution is necessary before surgical operation. And the AHV Freedom by Sorin is stored in same substance and does not have such a platelet suppressive effect postoperatively[38]. During premarket laboratory tests, no toxic effect was identified[39]. A tissue treatment analyses was carried out from Sorin Group international. These analyses did not reveal blood factor alterations and confirmed the valves biocompatibility with current ISO standards[34].

A HIT may occur in a patient with heparin treatment within the fifth to 10th day. The platelet count drops lower than 100.000/ µl and more than 50% of initial lab value. Around 50% of affected patients develop a thrombosis because of antibody induced platelet activation[23]. A HIT can be excluded with an enzyme immune assay. Unfortunately it is not possible to perform such an enzyme immune assay retrospectively. Our study population was screened for a sudden and deep drop in recorded platelet counts of the patients then. No drop was found. Yerebakan et al performed in 50% of patients with FS bioprosthesis an enzyme immune assay to detect suspected HIT. No HIT antibodies were found[28]. Thus HIT seems to be a seldom cause for thrombocytopenia after AVR.

A perioperative pseudothrombocytopenia may be another etiology for a sudden drop in thrombocyte levels. It develops due to an antibody inducing agglutination of thrombocytes. It occurs when the calcium level decreases in EDTA. The diagnosis is simple and done clinically. Any further reason for thrombocytopenia is excluded and the patient shows no petechial or gingival bleedings[23]. Unfortunately it is not possible to exclude a pseudothrombocytopenia for sure retrospectively. Our study population was screened for a sudden drop in recorded platelet counts of the patients. No drop was found.

There are no obvious differences between the platelet count and bioprostheses preoperatively. During surgical operation most patients develop at least an unspecific low platelet count. The percentage of the different designs with a platelet count lower than 150 $\times 10^9$ µ/l are as follow: Trifecta 94,4%; FS 87,2%; Mosaic 84,5%; Mitroflow 76,2%; Epic 55,3%. On the first three days after surgical procedure following picture emerge: FS 92,3% (5,1% have an unspecific low platelet count, 41,0% a mild thrombocytopenia and 51,3% a moderate thrombocytopenia); Trifecta 50,0%; Mitroflow 42,9%; Mosaic 26,6%; Epic 24,7%. And finally the distribution on day 8 to 10 postoperatively: FS 50,0%; Mitroflow 16,7%; Trifecta 9,1%; Mosaic 6,6%; Epic 2,2%. These data reveal very distinctly that the FS is a strong and independent risk factor for thrombocytopenia postoperatively.

Particular BHV characteristics are the material, the size of annulus and whether stented or stentless. In our data a slight tendency is recognizable that bovine pericardium leads to a deeper drop of platelets as well as to more sluggished recovery. This tendency is not significant and is confirmed by literature. By contrary it is reported that porcine valves induce more damage on blood elements[37].

Sizes smaller than 23 mm were less chosen for FS. For the other bioprostheses mostly smaller sizes were chosen (< 25 mm). Except the Mosaic, for this BHV no size preference is noticeable. Repossini et al. found a significant association between the larger valve sizes and higher drop of platelet count[39].

Regarding to the characteristic stented versus stentless a significant variance is given on day one to three (p=0,00) and on day eight to ten (p= 0,00). The subgroup-stentless consists of FS, the subgroup-stented consists of the other BHV. This significance should be considered with caution, because the FS-subgroup has a significant difference in platelet count compared to all other BHV. Therefore it must have a significant difference compared to stented-subgroup, which consists of all other BHV.

The FS causes a reduction in mean and peak gradient significantly 12 month after implantation. It has a superior hemodynamic performance remaining under exertion during stress echocardiography[40]. No adverse effects were found[31]. The LV mass is reduced significantly after implantation and the effective orifice areas are increased. Although exceptions are existing: some patients do not show the superior hemodynamic profile after FS implantation and some patients have higher mean and peak gradients under stress test echocardiography. A detailed evaluation of these patients showed an oversizing of the

valve, an aortic root calcifications and more rare a subaortic hypertrophic obstruction[40]. Thus it seems to be important to implant the FS in thoroughly selected patients.

The low platelet count in patients with FS replacement started already intraoperative and reaches a drop point on second and third day postoperatively[39]. This drop point disappears on fifth to seventh day postoperative and is replaced by slower recovery in platelet count compared to other bioprostheses. The platelet count is still low on 13th day postoperatively[29]. The study shows no association with hemorrhage complications afterward[29, 30, 39, 41]. These findings can be confirmed by our data. There are 5.000-10.000 functioning thrombocytes per µl necessary to avoid hemorrhagic complications. A severe thrombocytopenia is defined as a platelet count lower than 20.000/µl. No patient of our cohort developed such low thrombocyte levels. And the effects of FS on platelets affect their quantity, not quality. Therefore is it not surprising that no hemorrhagic complications occur.

Unless there are no proven doubts according to biocompatibility of FS, it can be implanted in thoroughly chosen patients. The advantages are clear and should not be ignored. The thrombocytopenia is a known side effect of FS nowadays. Patient should be monitored for 14 days after surgical operation. The therapy with coumarins should be controlled regularly by general practitioner in the first three month postoperatively. The therapy with aspirin lasts for the rest of patient´s life. Therefore the platelet count should be controlled regularly and the patient trained on petechial bleeding signs. For further therapy with drugs having thrombocyte suppressive side effects, the FS should bear in mind as risk factor. These therapeutics should be avoided if possible.

11 Limitations

Every retrospective study has its limitations due to a lack of standardization. In this study the main limitation is the impossibility to record all diagnoses of all patients of the last years as well as the patient´s drug intakes during the last three weeks before replacement.

- To draw a conclusion from a patient's therapy one has to record all known diagnoses from the last month. A cancer therapy for example might be treated with chemotherapeutic agents or radiation which has a long lasting effect on bone marrow cells. Furthermore the patient might suffer from an already diagnosed congenital type of thrombocytopenia. This influences the decision drawn on a low platelet count of the affected patient.
- Important would be a complete list of every patients drug intake and their dosage from the last three weeks before surgery. Many drugs have suppressive or stimulating effects on megakaryocytes, thrombopoiesis/ TPO or platelets. It takes in average of up to 21 days to normalize drug effects on megakaryocytes and thrombopoiesis. And it takes at least 10 days to stabilize the platelet count.

12 Summary

The first implantation of artificial heart valve prosthesis was performed in 1952. Since that time many ingeneurs have designed different models made out of different material and shapes with particular hemodynamic characteristics. There are two big groups available: mechanic artificial heart valves and biological prosthesis. Nowadays a lot of designs are established. The seven main implanted bioprostheses at Department of Cardiac Surgery in Graz are introduced in detail above. The names are arranged according to implantation frequency: Mosaic by Medtronic, Epic by SJM, FS by Sorin, Mitroflow by Sorin, Trifecta by SJM, Magna Ease by Edwards and Perceval by Sorin. In this study the platelet count after AVR is the main feature and will be controlled in detail. The main thrombocytes function is to prevent bleedings and the closure of wounds. Is the count or functioning of platelets affected a higher risk for hemorrhages is present. Regarding to patients after AVR it is a higher risk for bleeding complications intra-and postoperatively. A thrombocytopenia is defined as less than 100 $\times 10^9$ platelets per liter. The diagnosis is performed clinically. Petechial bleeding, a purpura and/or hemorrhages of mucosa are a distinct sign. In case of a sudden developed low platelet count in a patient but no clinical signs, one should keep pseudothrombocytopenia in mind. Around 50% of patients receiving heparin in hospital develop a HIT within 5-10 days. The platelet drop is more than 50% of initial lab value. For a clear diagnosis an enzyme immune assay is necessary. Further etiologies of thrombocytopenia are infectious-induced, congenital or drug-induced.

An aortic valve replacement with the bioprosthesis FS by Sorin is associated with a mild to severe thrombocytopenia and a sluggished recovery of platelet count postoperatively. It offers benefits according to left-ventricular function, left-ventricular mass reduction, low gradient and well hemodynamics. Long term evaluation of patients with a Freedom Solo show a lower complication rate compared to other bioprostheses.

These statistical analyses revealed no good idea for the cause of platelet drop after implantation of FS. Neither preoperative parameters nor intra-or postoperative parameters show significance that is a decisive input. Therefore the artificial heart valve itself is considered to cause postoperative platelet drop. Hemodynamic changes might lead to unspecific platelet activation with consumption, but no study found echocardiographic differences regarding to other bioprostheses. Although larger sizes of annulus leads significantly to higher drop in platelet than smaller sizes. A discussion was lead about

particular substances with which the FS was treated before storing in package. A tissue treatment analysis was carried out, but no blood factor alteration was found. And this analysis confirmed the biocompatibility of the valve.

After aortic valve replacement with FS a mild to moderate thrombocytopenia occurs with sluggished platelet recovery in patients. Nevertheless postoperative echocardiographic examinations and in later follow-ups show a fast LV remodeling and a higher survival in patients. The implantation of FS in supra-annular position with a single continuous suture line leads to shorter CCT, ECC time and therefore shorter operation duration. Adverse hemorrhagic effects are not recorded yet. Unless there are no proven doubts according to biocompatibility of FS there is no reason to avoid the implantation of this bioprosthetic heart valve. The advantages are clear and in thoroughly chosen patients a good choice. Patient should be monitored for 14 days after surgical operation. The therapy with coumarins and ASS controlled regularly. Moreover should the patient be trained on petechial bleeding signs. For further therapy with drugs having thrombocyte suppressive side effects, the FS should be beard in mind as a risk factor. These therapeutics should be avoided if possible.

13 List of References

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