Improving the treatment of HOCM

The investigation of a patient specific cutting mould and a 3D printed heart

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Abstract

Introduction: Hypertrophic obstructive cardiomyopathy (HOCM) affects 1 in 200 people. HOCM is a hereditary cardiac condition with asymmetric growth of the left ventricular wall, which results in left ventricle outflow tract obstruction (LVOTO). The hypertrophic tissue of severe symptomatic patients can be resected using a septal myectomy. However, there is a mismatch between the number of surgeries and the number of patients, due to the challenges and limitations of the septal myectomy treatment. The goal of this Bachelor's thesis is to improve the treatment of HOCM to produce a reliable treatment, which mitigates the challenges of the septal myectomy.

Methods: Four partial challenges in the treatment of HOCM are described, whereupon an extensive literature report is carried out in which current solutions and future solutions to the challenges are covered. Based on the literature study, a plan for further investigation is given. This includes making a 3D printed- and ballistic- model of the left ventricle and a patient specific 3D cutting mould with the CMR images of the patient in SolidWorks. The different components of the cutting mould are tested on pig hearts and ballistic heart models.

Results: The 3D prints and ballistic models visualize the size of the hypertrophic tissue and may help the surgeon during preoperative planning. The 3D cutting mould prototype is finalised and succeeds in resecting the ballistic model's hypertrophy. It was not clear if the visibility of the cutting mould on ultrasound was better in a fluid filled heart. A possible clinical implementation of the 3D heart and 3D cutting mould is described.

Conclusion: The cutting mould is a very promising solution to mitigate the described challenges of the septal myectomy. The knife slit and suction system require further development. Further research is required to verify if a fluid filled heart results in better imaging and if therefore an aorta-plug is necessary. When implementing the 3D printed heart and the cutting mould into the septal myectomy protocol it is likely to significantly enhance the number of positive outcomes.

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List of Abbreviations

AR	Augmented Reality
AP	Action potential
ASA	Alcohol Septal Ablation
AV	Atrioventricular
BT	Brachytherapy
CMR	Cardiac Magnetic Resonance imaging
CT	Computed Tomography
DTI	Diffuse Tensor Imaging
EBRT	External Beam Radiation Therapy
ECG	Electrocardiogram
FDM	Fused deposition modelling
HCM	Hypertrophic Cardiomyopathy
HDR	High Dose Rate
HIFU	High Intensity Focused Ultrasound
HOCM	Hypertrophic Obstructive Cardiomyopathy
ICS	Intercostal Space
IGRT	Image Guided Radiation Therapy
IMRT	Intensity Modulated Radiation Therapy
LAD	Left anterior descending
LBBB	Left bundle branch block
LCx	Left Circumflex Artery
LDR	Low Dose Rate
LV	Left Ventricle
LVOT	Left Ventricular Outflow Tract
LVOTO	Left Ventricular Outflow Tract Obstruction
MRI	Magnetic Resonance Imaging
MST	Medisch Spectrum Twente
OR	Operating room
PDR	Pulsed Dose Rate
PLA	Polylactic acid
RIC	Radiation induced cancer
RIHD	Radiation Induced Heart Disease
RT	Radiation Therapy
SABR	Stereotactic Ablative Radiotherapy
SAM	Systolic anterior movement
SBRT	Stereotactic Body Radiation Therapy
SD-card	Secure digital card
SLA-SMS	Stereolithography
TEE	Transesophageal echocardiogram
TPU	Thermoplastic polyurethane
TTE	Transthoracic Echocardiography

Chapter 1 – Main Introduction

Hypertrophic Cardiomyopathy (HCM) is a genetic cardiac condition which affects around 1 in 200 people [1]. In most cases the thickening, or hypertrophy, is located in the left ventricular wall, without the presence of any other cardiac or systemic condition which could cause the observed abnormality [2]. HCM is caused by an autosomal dominant mutation which affects the formation of sarcomere proteins. Histologically, this results in myocytes that will not be parallel to each other (myocyte disarray), fibrosis and small vessel disease. Macroscopically, this results in asymmetrical hypertrophy in the left ventricle (LV) which, if large enough and located on the septum, may result in left ventricular outflow tract obstruction (LVOTO), systolic anterior movement (SAM) of the mitral valve, arrhythmia and papillary displacement [3]. In the case of obstruction of the left ventricular outflow tract (LVOT), the condition is called Hypertrophic Obstructive Cardiomyopathy (HOCM). HOCM is the main problem on which this research is focussed, because it affects around two-thirds of HCM patients. The involved anatomy, physiology and pathophysiology are described in the next paragraphs as well as the current diagnostic techniques and the current treatments.

1.1 Anatomy

The LV is enclosed by the ventricular septum and part of the free wall [4,5]. The bundle of His runs through the interventricular septum and transmits impulses from the atrioventricular (AV) node to the ventricles. It branches into left and right bundle branches which eventually turn into the Purkinje fibres. The mitral valve allows blood to flow from the left atrium to the LV. This valve consists of two cusps and both cusps receive chordae from more than one papillary muscle. The chordae, along with their muscles, prevent the cusps from being forced into the left atrium during systole. The aortic valve allows blood to flow from the LV into the aorta and it consists of three semilunar cusps. The coronary ostia are found right above these cusps and supply blood to the coronary arteries.

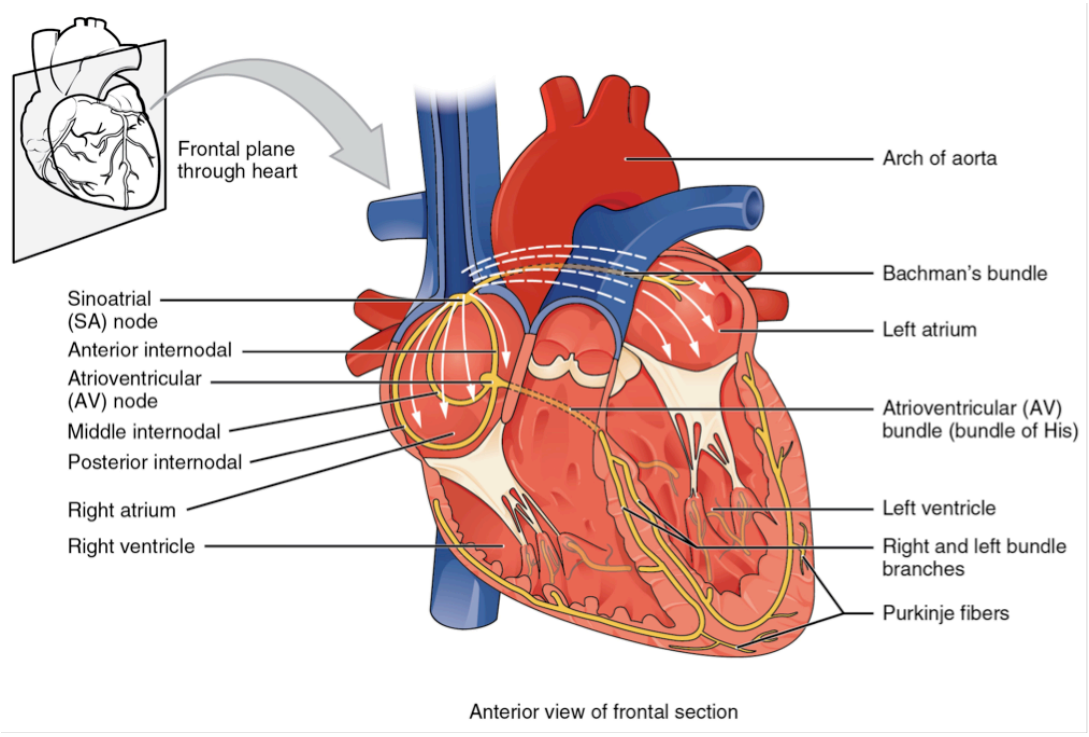

Figure 1: Anatomy of the heart.

1.2 Physiology

A healthy heart supplies the body of oxygen rich blood and the lungs of oxygen diluted blood [6,7]. It does so in two phases. The diastolic phase, in which the heart is in a resting state that allows blood to flow from the atria into the chambers. And the systolic phase, in which the heart is in a contracted state and pushes blood from the chambers into the aorta and pulmonary artery.

These phases are controlled by the sinus node, located at the top of the right atrium [6,7]. The sinus node sends an action potential (AP) through both atria. This AP causes the atria to contract and is received by the AV node. Which passes the AP down, with some delay, through the bundle of His to the Purkinje fibres in the walls of both chambers. This results in contraction of the chambers and papillary muscles.

The contraction is due to the shortening of the sarcomeres, which consist of actin and myosin filaments that are located in the myocardium [6,7]. The action potential is a sympathetic innervation that enlarges the permeability of Ca^+. This Ca^+ binds to troponin C, causing it to let go of troponin T and enabling it for myosin to react with the active elements of actin. This reaction causes the muscle to contract. The strength and contraction speed of the muscle depend on the pre- and afterload.

1.3 Pathophysiology

In patients with HCM the heart does not work like described in the previous paragraph. This is due to thickening of the myocardium. Usually this is an asymmetrical thickening of the LV, in which the interventricular septum is more thickened than the free wall. When the hypertrophy causes the LVOT to be obstructed, it is called HOCM.

HOCM has several causes, like high blood pressure, heart valve deviations. intensive sport activities and, probably the biggest cause, genetic disease [8,9]. The genetic disease is caused by an autosomal dominant mutation in the genes which encode for the sarcomere proteins. Due to these mutations myocyte disarray occurs, this will cause the HCM.

HOCM has three major pathological effects, namely SAM of the mitral valve, arrhythmias, and dislocation of the papillary muscles. With SAM, the anterior leaflet of the mitral valve is pulled towards the HOCM, due to the Venturi effect in the narrowed LVOT. The SAM can also be caused by hypertrophy of the papillary muscle, causing the chordae to hang loosely and allowing the anterior leaflet to move towards the LVOT [10].

HOCM causes arrhythmias that can result in sudden cardiac death (SCD). Arrhythmias are caused by the following mechanisms [2]: the LVOTO results in less blood flow to the aorta, thus less blood will enter the coronary arteries, thus the heart muscle will become ischemic and contract in an abnormal manner. Due to the HCM the tissue of the myocardium enlarges, and this results in compression of the coronary arteries, resulting in the same problem as with the LVOTO. At last, the myocyte disarray will change the way the action potential travels through the heart, inducing arrhythmias [2].

The last pathological effect is the thickening of the papillary muscle. As said before the thickening of the papillary muscle causes a more severe SAM, but it can also induce other flow changes in the LV, causing a more severe LVOTO [3].

1.4 Diagnostic Techniques

The diagnostic process typically starts with symptoms such as unexplained syncope, dyspnoea, and chest pain [11]. These symptoms may suggest HCM but must be distinguished from aortic stenosis and coronary artery disease. To diagnose HCM or HOCM, several diagnostic techniques are used as described below. An elaboration of these techniques is given in Appendix A.

1.4.1 Electrocardiogram

The electrocardiogram (ECG) provides a better understanding of the symptoms, however it does not provide a definitive diagnosis. The most common findings are T-wave abnormalities and deep septal Q waves [12]. A Holter monitor may provide more detailed information. This diagnostic tool is used to make an ECG for 24 to 48 hours. Along with a diary, describing the activities done in these 24-48 hours, the Holter monitor provides valuable information in the diagnosis of HOCM.

Another ECG based diagnostic tool is the stress test, which provides information about the cardiac function during exercise [13].

1.4.2 Echocardiogram

If HCM is still suspected after the ECG tests, an echocardiogram is used. M-mode echocardiography visualises the interventricular septum, the SAM of the mitral valve, the size of the LV and the closing of the aortic valve [14]. The diagnostic criterion for HCM requires a septum thickness that exceeds 15mm and a thickness ratio that exceeds a value of 1.3. HOCM is diagnosed by using doppler echocardiography. Colour doppler provides information about insufficiency of the mitral valve. A posterior backflow signifies SAM of the mitral valve. Continuous doppler is used to measure the LVOT-gradient. If this gradient exceeds 30 mmHg, HOCM is diagnosed.

1.4.3 Categorisation

With the diagnostic information HCM can be categorised into different classes [15]. These classes provide information about the treatment needed. This is described in Appendix B.

1.5 Current Treatments

Based on the classification, it is decided which treatment is best to perform. A distinction is made between asymptomatic patients and symptomatic patients. The classes, along with their treatments are described in Appendix B The different treatment strategies are discussed below.

1.5.1 Medication

Treatments for symptomatic patients are lifestyle changes. Based on the severity of the HOCM, patients are also treated with medication, to reduce the symptoms. Typical medicines used are beta blockers, verapamil, diuretics, intravenous phenylephrine, disopyramide, diltiazem and/or angiotensin blockers.

1.5.2 Invasive therapies

When medication does not suffice, invasive therapies are used to reduce the septal thickness in HOCM such as septal myectomy (Morrow Procedure) and Alcohol Septal Ablation (ASA). A septal myectomy is performed to cut away the hypertrophic tissue. With ASA however, alcohol is injected in a septal coronary artery. The tissue reduces in size due to necrosis.

1.6 Medical and technical challenges of the Septal Myectomy

The septal myectomy is the gold standard in the treatment of HOCM. However, this treatment is not perfect, as it has some limitations and challenges to overcome, listed below. A detailed elaboration is given in Appendix C.

- Invasive therapy [14]
- Limited visibility [16,17]
- Inaccurate determination of the resection size [18]
- Embolization of the myocardial tissue [19]
- Damaging important structures [19,20]
    - Aortic valve cusps
    - mitral valve
    - chordae
    - nerves, with a left bundle branch block (LBBB) as a result
- Septum, with a septal defect as a result
- Difficult procedure to perform[16]

1.7 Aims of this study

As described, the septal myectomy does not provide a perfect treatment of HOCM. The main goal of this research is to improve the treatment of HOCM. Therefore, a literature study is performed to get an overview of all the possible treatment strategies which may improve the current treatment. During this literature study, the following research question is kept in mind:

How can the treatment of HOCM be improved to realise an accurate treatment which minimizes the described challenges of the septal myectomy?

This main question is divided into several sub-questions, as described in Appendix D. An advice is given, based on the literature study. This advice describes a plan for further investigation and will be discussed in the second part of this research.

Chapter 2 – Literature Study

2.1 Introduction

The main goal of this bachelor thesis is to develop an improved and reliable treatment for patients with HOCM. As described in the main introduction, the current treatment has several limitations which makes the treatment hard to execute without inducing severe complications. To improve the current treatment, all aspects must be investigated. The exact strategy is described in Appendix E. The involved aspects are divided into four partial challenges. The answers to these challenges combined give a solution to the main goal. The four challenges are:

- Access routes to the heart
- Reduction of hypertrophic tissue
- Preoperative planning
- Intraoperative demarcation and localisation of the hypertrophic tissue

For each challenge, several solutions are presented. A detailed description of the methods, along with their advantages and disadvantages, is given in Appendix F. This appendix also provides information about researched techniques of which the authors think they are not useful in the treatment of HOCM.

In this chapter, the advantages and disadvantages are summarised in a table. Each partial challenge is provided with a sub-conclusion. This sub-conclusion contains two recommendations: both a recommend-dation from a technical-medical perspective as well as a recommendation which is achievable within the time given for this bachelor thesis. The technical-medical advice will be the ultimate solution the authors recommend as Clinical Technician students. However, these solutions deserve an elaborate investigation which is unachievable within the time-period of this bachelor thesis.

With these sub-solutions in mind, an overall conclusion is given. This conclusion contains solutions to the biggest limitations of the current treatment. Combined, these solutions open a door to a future treatment.

2.2 Challenge 1 - Access routes to the heart

To develop a reliable way of removing the outflow tract obstruction inside the heart, the access route to the heart needs to be assessed. The access way must provide enough space to reduce the hypertrophic tissue, without damaging surrounding tissue. Ideally, the procedure is minimally invasive with accurate visual sight. Fulfilling these requirements is a challenge. In this chapter a total of four entry ways are presented: surgical, endoscopic, endovascular, and extracorporeal. The method, its advantages and its disadvantages are extensively described in Appendix F.1. Below, a brief summary of the advantages and disadvantages of each entry way is given (Table 1). Thereafter, two recommendations (as described in Paragraph 2.1) for short- and long-term implementation are presented.

Access route	Advantages	Disadvantages
Surgical entryways	- Plenty of workspace and good vision[21] - Repair of the mitral valve is possible[21]	- Most invasive option - High change of postoperative complications[21]
Minithoracotomy	- Less invasive than a median sternotomy[22] - Faster recovery leading to a shorter hospitalisation[22]	- Small working space compared to a median sternotomy[21] - More time of cardiac pulmonary bypass needed[21] - Not suitable for every patient[22]
Endoscopic	- No median sternotomy required[23,24]	- Less visibility for the surgeon
Robot-assisted	- Accurate performing due to the more degrees of freedom and precise movements[23,24]	- Cannot be performed on a beating heart [25] - Surgeon needs excessive training [23,24]

Endovascular	- Shorter hospitalisation and recovery time leading to less postoperative discomfort[26]	- Need to be performed in experienced interventional cardiology centres - Relies on the coronary anatomy of the patient[27] - Risk on catheter-based complication such as retroperitoneal haemorrhage[28]
Extracorporeal	- Minimally invasive	
Needle		- Risk of major complications, such as ventricular arrhythmias, pneumothorax and hypotension[29]
Radiation		- Possibility of DNA mutations[30]

Table 1: This table shows the advantages and disadvantages of the four main entryways: surgical, endoscopic, endovascular, and extracorporeal. The pros and cons of these main entryways are summarised in their respective row. These advantages and disadvantages also apply to the more specific access routes listed below each main entryway. These are subcategories of the main entryways. The pros and cons of each specific access route are given in their respective rows.

2.2.1 Sub-conclusion

The goal is to remove hypertrophic tissue in the most effective and minimally invasive way. The endovascular route or the use of radiation will achieve this goal. Therefore, it is recommended to perform more research on these topics, based upon a technical medical perspective. The short-term advice, achievable within the terms of this bachelor thesis, is using the surgical entry way and improving the septal myectomy.

2.3 Challenge 2- Reduction of the hypertrophic tissue

To reduce the symptoms of a patient who suffers from HOCM, the size of the hypertrophic tissue must be decreased. Multiple ways to reduce a specific portion of the hypertrophic tissue are described in this paragraph. The four main possibilities are: septal myectomy, ablation, High Intensity Focused Ultrasound (HIFU) and radiation therapy. These techniques are excessively described in Appendix F.2, along with their advantages and disadvantages. Below, a brief summary of the advantages and disadvantages of each reduction method is given (Table 2). Thereafter, two recommendations (as described in in Paragraph 2.1) are presented.

Reduction method	Advantages	Disadvantages
Septal myectomy	- Immediate removal of hypertrophic tissue[23]	- Change of serious complications, such as coronary dissection, septum defect, permanent pacemaker implant, complete heart block and intraoperative death[31]
Ablation	- Less invasive thus a shorter hospitalisation[32]	
ASA	- Significant drop in LVOT gradient without the discomfort of a median sternotomy[33]	- High number of postprocedural temporary AV or RBB block[26] - Depends on coronary and septal anatomy of the patient[27]
Radiofrequency	- No use of chemicals that can-do unwanted damage to the myocardium - Not depended on coronary anatomy[32]	- Long ablation time[27] - Chance of complications e.g. LBB and total heart block[28]

Embolization	- Less complication than ASA in patients with a thinner HOCM (15-20mm)[34]	- Not suitable for every patient due to dependency on septal and coronary anatomy[27] - Outcome is unpredictable because of the fast adaption of the septum, e.g. collaterals could perfuse the ablatedsite[27]
HIFU	- Non-invasive[35] - Combined with MRI for anatomical guidance and precise ablation[36]	- Not yet used on humans, so complications are unclear[35]
Radiation Therapy		- Chance of cardiotoxicity or radiation-induced heart disease[37]
External beam	- Ability to compensate for moving organs such as lungs and the heart with IGRT[38] - High accuracy - Low dose delivery to healthy tissue by using IMRT[38] - Accurate high dose delivery and shorter radiation time using SBRT[38]	- Expensive - Usage of ionising radiation[38] - Accurate preprocedural planning asks for high resolution imaging[38]
Brachytherapy	- Minimal invasive implantation and short hospitalisation using permanent implants[39] - High dose delivery using temporary implants[39]	- Accurate dose calculation required using permanent implants - Low dose delivery thus longer radiation is required[39] - Long hospitalisation and high dose rate for medical personal using temporarily implants[39]

Table 2: This table shows the advantages and disadvantages of four main methods to reduce the size of the hypertrophic tissue: surgical septal myectomy, ablation, HIFU and radiation therapy. The pros and cons of these main methods are summarised in their respective row. These advantages and disadvantages also apply to the more specific reduction methods listed below each main method. The pros and cons of each specific reduction method are given in their respective rows.

2.3.1 Sub-conclusion

Radiation has great opportunities in the treatment of HOCM in the future. EBRT seems to be the most interesting radiation technique. With the use of the most modern techniques an accurate treatment can be composed. Risks of RIHD remain, however these risks are limited due to the high accuracy. More research must be done to assess the efficiency of this therapy, the best implementation, and the ethical challenges. The routing, dose planning and approval of the treatment will need a lot of new research and are therefore not achievable within the time of this bachelor thesis. Nevertheless, the main goal of this bachelor thesis is designing a new or improved protocol for the treatment of HOCM. For this reason, the feasible advice for the short term is improving the septal myectomy procedure.

2.4 Challenge 3 - Preoperative planning

To treat the obstructive hypertrophy, the surgeon has to know what the HOCM of the patient looks like. Based on preoperative measurements the surgeon composes a plan for resecting hypertrophic tissue. There are various possibilities to perform this preoperative planning. Both imaging modalities, such as MRI and Ultrasound, as well as the possibility of practicing on 3D models of the heart are described in this chapter. These techniques are described in detail in Appendix F.3, along with their advantages and disadvantages. Below, a brief summary of the advantages and disadvantages of each technique is given (Table 3). Thereafter, two recommendations (as described in Paragraph 2.1) are presented.

Method	Advantages	Disadvantages
MRI	- Non-invasive visualisation of the heart. - High resolution	- Expensive - Low availability [40]
Cardiac Magnetic Resonance Imaging (CMR)	- Specialised for cardiac imaging [41] - The use of 4D flow may enable modelling of the blood flow [42] - The use of LGE provides extra information about fibrosis [40]	- Less expensive ultrasound also suffices [40] - 4D flow MRI isn't integrated in the MST [40]
Diffuse Tensor Imaging (DTI)	- Visualisation of the cardiac conduction system and therefore better preoperative risk assessment[43,44] - Additional diagnostic information about myocyte disarray and arrhythmia. [43,44]	- Little research available - Not currently used as a medical tool. [43,44]
Ultrasound	- High availability and easy access - Non-invasive - Fast imaging - Integrated in current diagnostic process and treatment [40]	- Lower resolution
Transthoracic Echocardiogram (TTE)	- Most cardiac structures are visible [45] - Patient friendly, as the probe doesn't go through the throat [45]	- Difficult visualisation of posterior cardiac structures [45] - Structures closest to the skin are better visualised than deeper structures. [45] - TTE doesn't visualise the HOCM very well [45]
Transesophageal Echocardiogram (TEE)	- Imaging closer to the heart, which provides clearer images [46,47] - All cardiac structures are visualised [47] - Already used during surgery. It provides immediate intraoperative results. [40,48]	- Takes longer than TTE [49] - Uncomfortable for patient [49] - Sedation possibly required with the need of specialised medical staff [49]
3D printed Heart	- May provide better understanding of patient specific 3D anatomy and provides the opportunity to practice the surgery. - Easy future integration in treatment protocol as MRI images and software are available - Entire process from imaging to 3D heart takes a few hours [50]	- Hard to mimic the cardiac tissue due to its heterogeneity
Augmented Reality	- May provide better understanding of patient specific 3D anatomy during surgery and supports surgical training[51,52] - Increases visualisation of the heart in the OR [51]	- Hard to translate preoperative imaging with an active heart to the relaxed heart intraoperative - Reliable comparisons of distance and spatial relations is still an open request [51]

Table 3: This table shows the advantages and disadvantages of four main techniques and methods to improve the preoperative planning in the treatment of HOCM: MRI, Ultrasound, a 3D printed heart and Augmented Reality. The pros and cons of these main methods and techniques are summarised in their respective row. These advantages and disadvantages also apply to the more specific techniques listed below each main method. The pros and cons of each specific technique are given in their respective rows.

2.4.1 Sub-conclusion

All in all, 4D flow MRI is a very promising technique to preoperatively determine the amount of resection for the best result. In order to use this method a model needs to be designed that calculates the changes of the hemodynamic within the heart, when tissue is being resected. This is not achievable within the period of this bachelor thesis. A more achievable goals is designing a 3D printed 'practice' heart. This practice heart will provide the surgeon with insights regarding the hypertrophy and the sight through the aorta. Another possibility is the implementation of the 3D computer model (created from an MRI) into augmented reality, which can be used during the surgery.

2.5 Challenge 4 - Intraoperative demarcation and localisation

The fourth and last challenge describes the intraoperative demarcation and localisation of the hypertrophic tissue. One of the main problems of the current septal myectomy procedure is the inaccurate determination of the amount of tissue that must be resected. The amount of tissue that has to be removed is predetermined using the ultrasound imaging (thickness, length, width). The surgeon localises intraoperatively the area where the obstruction is, this procedure requires expertise of the surgeon and is hard to perform. Three improvements for localisation are: laser guided surgery, a 3D tracking system, and a cutting mould. Each of these techniques is explained in detail in Appendix F.4, including their advantages and disadvantages. Below, a brief summary of the advantages and disadvantages of each technique is given (Table 4). Thereafter, two recommendations (as described in Paragraph 2.1) are presented.

Method	Advantages	Disadvantages
Laser guided surgery	- Provides intraoperative information about the exact angle and depth of incision	- Preoperative imaging does not represent intraoperative anatomy of the heart due to relaxation of the myocardium. Therefore, additional intraoperative imaging is needed
3D Tracking system	- Provides an intraoperative guide for the placement of instruments [53] - Real-time feedback about the placement of instruments [53]	- Difficult within the complex surgical area - More research needed to integrate in cardiac surgery
Cutting Mould	- Exact patient specific volume and shape of hypertrophic tissue can be integrated [54] - Easy integration in current treatment - Could provide a standardised procedure in the future - No embolization of hypertrophic tissue particles	- Intraoperative relaxed heart differs from contracted preoperative heart - Hard to get correct placement over hypertrophy - Scattering and acoustic shadowing in intraoperative TEE
Aorta-plug	- The filling of the heart may provide better TEE imaging - Filling the heart may lead to a better representation of the active heart in its inactive state.	- Leakage

Table 4: This table shows the advantages and disadvantages of three main techniques and methods to improve the intraoperative demarcation and localisation of the hypertrophic tissue: laser guided surgery, 3D optical tracking system and the use of a cutting mould. The pros and cons of these main methods and techniques are summarised in their respective row. The aorta-plug is an important new component of the cutting mould and it is therefore provided with its own advantages and disadvantages.

2.5.1 Sub conclusion

The ideal solution would be the integration of a real time tracking system in the OR. This tracking system uses optical markers and could provide a surgical guide that helps with the optimal placement of the instruments. However, this is a completely new method and not achievable within the time of this bachelor thesis. An achievable goal is to develop a 3D cutting mould in combination with an aorta-plug. This has already been investigated within another bachelor's thesis [54]. However, several improvements must be made to use this tool in the OR.

2.6 Conclusion of literature study

Many recommendations are given, however, not all recommendations are feasible to investigate within the timeframe of this bachelor thesis. Therefore, two recommendations are further investigated: the use of a 3D practice heart and the improvement of the 3D cutting mould.

The next two chapters describe the research that is performed regarding these two topics. First, methods for 3D printing and casting of a realistic heart model are described in order to improve the preoperative planning (Chapter 3). The casted models are also used for experimenting with the cutting mould. Secondly, the making of the cutting mould, along with its improvements and experiments are described (Chapter 4)

Chapter 3 - Methods for 3D printing and casting a realistic heart model for preoperative planning and research purposes

3.1 Introduction

One of the challenges of the septal myectomy is the fact that the procedure is complex and difficult to perform, see Chapter 1. Solutions for this challenge are elaborated in Chapter 2.4. One of the best solutions is the use of a 3D heart which can preoperatively be used to practice the surgery. As described in the literature study, this practice heart may provide a better understanding of the complex anatomy of the hypertrophic tissue and it may provide an opportunity to practice the procedure.

Next to this, it is necessary to have a test subject for the cutting mould. Since testing on a living human with HOCM is unethical in this stage of the research. A ballistic heart provides researchers with a realistic testing subject to see whether the mould does what it is supposed to do. It provides a way to see if and how the cutting mould needs to be adjusted to provide proper functioning and positioning of the cutting mould.

The production of a ballistic heart is investigated in this chapter. The next paragraphs provide a description of designing the 3D heart, after which the conclusion of the method of making this 3D heart is given. All pictures referred to, can be found in Paragraph 3.2 and a discussion can be found in Subsection 5.1.2.

3.2 Designing the 3D 'practice' heart

3.2.1 Making of 3D printed heart using magnetic resonance imaging (MRI) and segmentation

3D segmentation

To create a realistic heart model, it is important to make cardiac magnetic resonance imaging (CMR) of the patient's heart. The CardioResearch department of the MST provided a CMR of a patient with HOCM. These images were segmented using the Philips IntelliSpace Portal vs. 10 software of the MRI system. This process took about one minute and made it possible to extract the left ventricular volume with the aorta attached, (Figure 2A), the myocardium of the LV (Figure 2B) and a segmentation of the entire heart (Figure 2C). It is also possible to use a program like 3D slicer 4.10.2. This is an open source 3D segmentation software. Nevertheless, it is advised to use the Philips software, because 3D slicer requires the user to have a lot of knowledge of the anatomy of the heart and is more time consuming.

Virtual 3D models

The segmentations made by the Philips software can be viewed using Windows 3D viewer. This makes for a nice visualization of the inside of the heart and the hypertrophic section of the septum. An even better view of this section is provided by Windows 3D Builder. The healthy half of the heart can be cut away to look into the LV from the left side. (Figure 2D) The virtual 3D models can therefore be used by the surgeon to get a good impression of the size of the hypertrophy and use it in the preoperative planning. Furthermore, it is possible to load the 3D models into Solid Works 2018 SP4 to make casting and cutting moulds. The casting moulds will be discussed in the next paragraph and the cutting mould will be discussed in Subsection 4.2.1 of this paper.

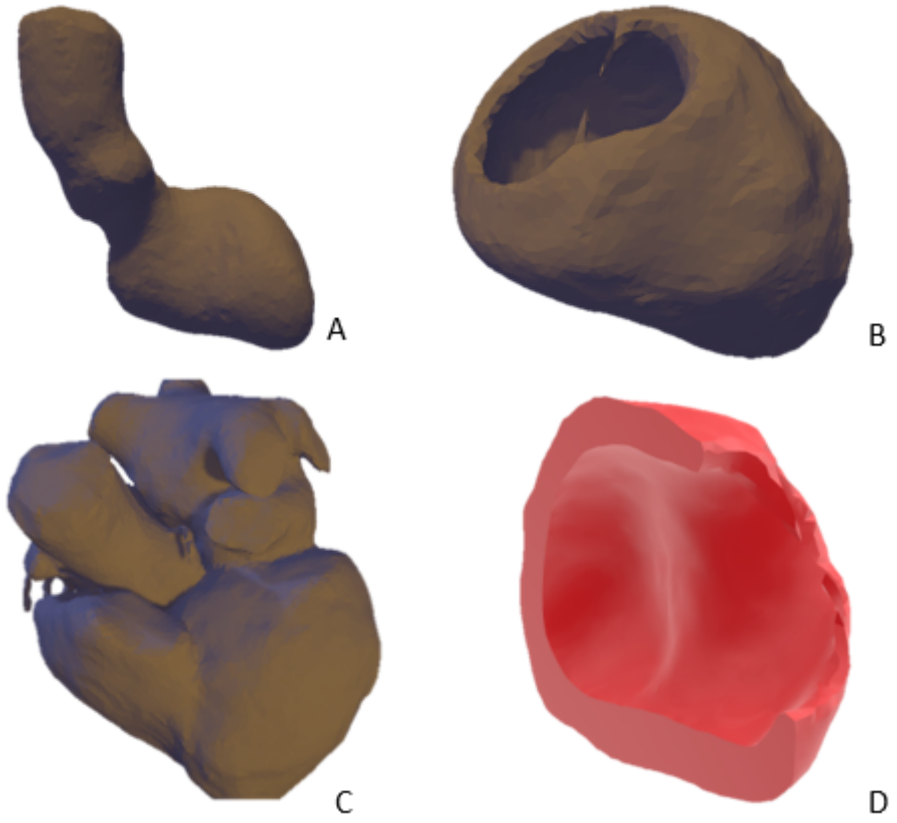

Figure 2: A) 3D segmentation of the volume of the LV and the aorta. B) 3D segmentation of the LV myocardium. C) 3D segmentation of the entire heart. D) The 3D segmentation of picture B cut in half to visualize the HOCM.

Figure 3: Ballistic model of the right side of the LV with the first prototype of the cutting mould inserted over the hypertrophic section.

Making a casting mould in SolidWorks

In this subsection the designing of the casting mould will be described. The design steps will be shown in figures with a brief explanation in the caption. For an extensive description of these steps please refer to Appendix L.

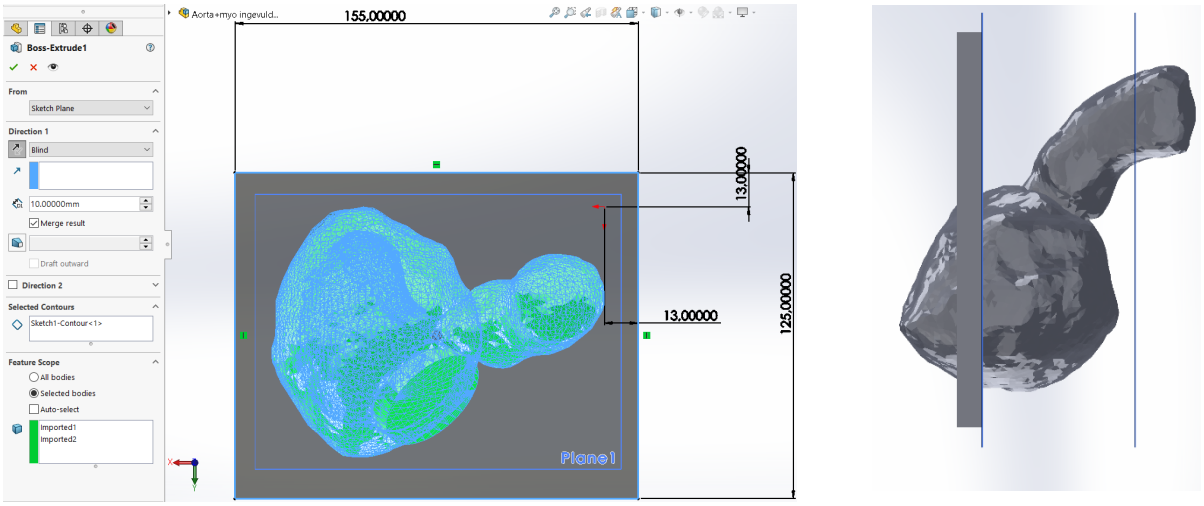

Figure 4: First a rectangle that includes the myocardium and LV volume is drawn. This rectangle is turned into a volume to create a stop for the up to next.

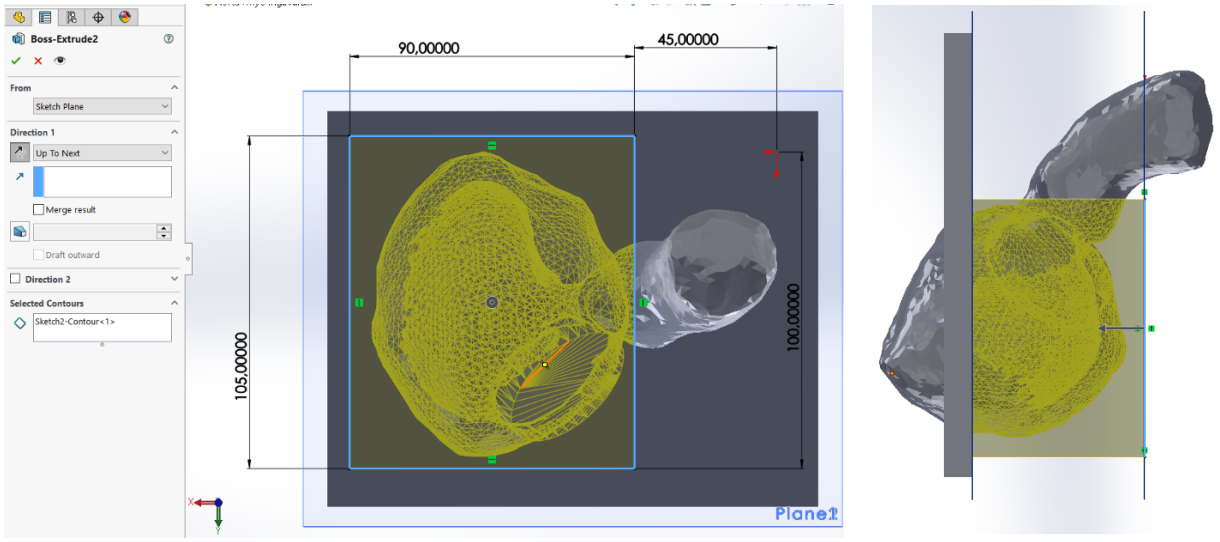

Figure 5: To complete the negative casting mould a rectangle including the myocardium is drawn under the solid body. Then the feature extruded boss/base and the option up to next are used to create a negative casting mould

3D printing the heart models

To print the virtual 3D models out of plastic the authors used Cura 4.1 software of Ultimaker to create printable files. These printable files were put on a Secure digital card (SD-card) and loaded into an Anycubic I3 Mega 3D printer equipped with black polylactic acid (PLA) filament of 123inkt.nl. PLA filament is a plastic material that simulates the shape of the heart but does not simulate the flexibility of the heart. Therefore, the hypertrophy does not change shape like it would in a cardioplegic state. Nevertheless, it still creates a tangible heart where the hypertrophic section can be felt and inspected by the surgeon. The 3D PLA heart sections can be used to cast more realistic models made out of ballistic gel.

3.2.2 Making of the 3D ballistic mould & 3D ballistic heart

Method: making ballistic heart models

After the 3D PLA models were printed, the casting process started. At first plaster was used to create negative impressions of the LV myocardium. This turned out to be a real challenge and resulted in only one usable mould. This mould was used to create one ballistic model of the right half of the LV myocardium. (Figure 3) In the plaster mould, the 3D print of figure 2A was inserted and in between the plaster and the 3D print the ballistics gel was poured. The model of the one half of the heart felt like human tissue and was very flexible.

This flexibility was achieved by using Dr. Oetker professional gelatine with a high bloom of 250 and mixing this with water. The ratio was 13 parts gelatine to 87 parts water [55]. Care had to be taken not to stir too hard, because this would make the mixture foam. To continue with this batch first the foam had to be removed. After pouring the gel into the desired cast it had to cure inside a fridge at 2 °C for about 8 hours.

3.3 Conclusion

All in all, the 3D prints and ballistic models gave the authors a better interpretation of the hypertrophy than the imaging. Seeing and feeling the hypertrophy in real life adds a new dimension to the understanding of an individual patient's hypertrophy. Furthermore, the ballistic moulds lend themselves very well for testing the cutting mould. Therefore, it is believed the models will be of value in the pre-operative evaluation of the individual patients' hearts.

Chapter 4 - Creating the cutting mould and experiments

4.1 Introduction

There are several challenges when performing a septal myectomy. One of these challenges is resecting the right amount of tissue, described in Chapter 2.3 and Chapter 2.5. When too much tissue is resected a LBBB can occur, or even a ventricular septal defect, but when too little tissue is resected, the obstruction together with its symptoms remains. Other challenges are not damaging the aortic valve, mitral valve, chordae and making sure no embolisms arise. By designing a perfect and personalised cutting mould for each patient the exact amount of tissue can be resected, there will be minimal damage to important anatomical structures and embolisms will not arise. This chapter describes the design of the cutting mould in SolidWorks and the purpose of the different components. Thereafter, the method and results of the experiments with the cutting mould are described. Improvements of the experiment are described in the discussion section of this report.

4.2 Designing of the cutting mould

In this paragraph the designing of the cutting mould and the imprint of the LV volume will be described. The design steps will be shown in figures with a brief explanation in the caption. For an extensive description of these steps refer to Appendix L.

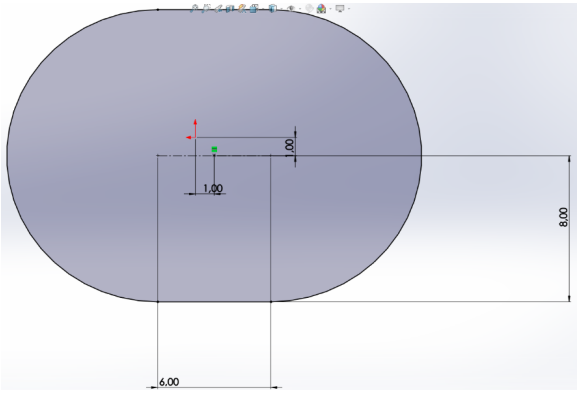

Figure 6: This is a straight slot with a radius of 8mm and a straight of 6mm, sketched in the top plane.

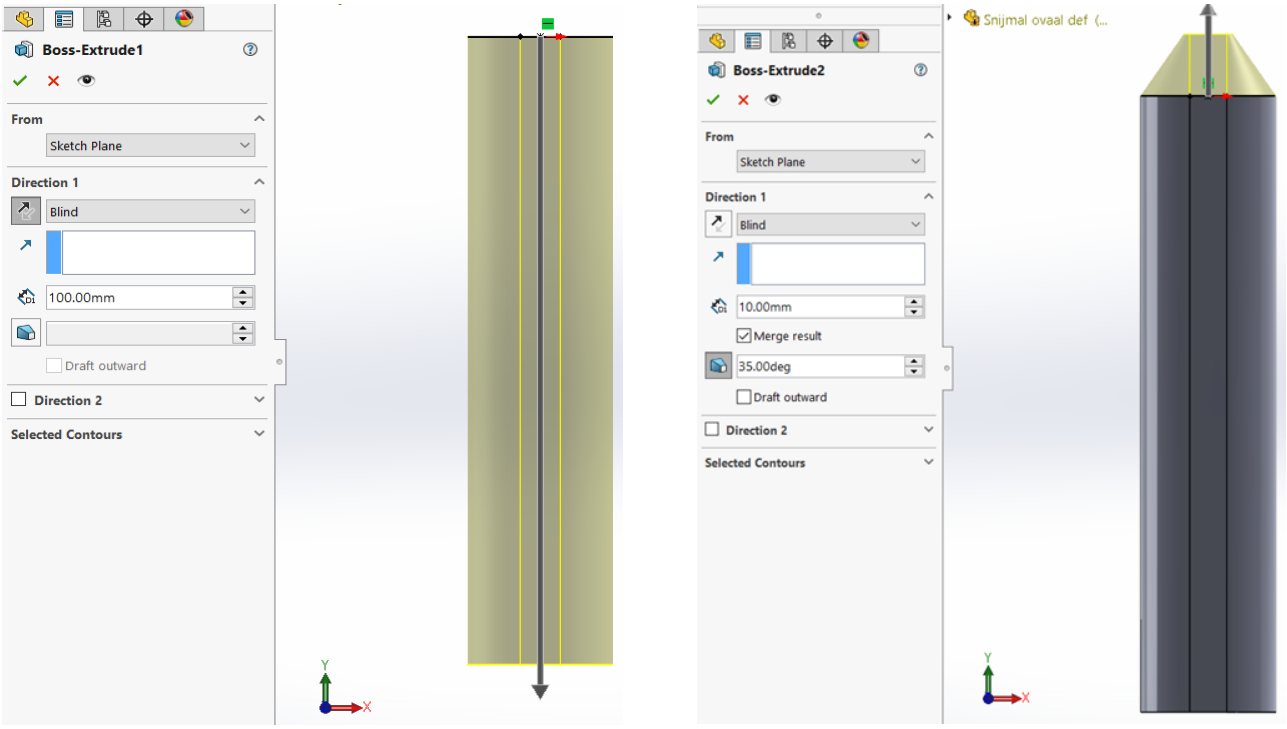

Figure 7: In this image is shown how the sketch is turned into a 3D volume. The straight slot is extruded 100mm in the negative-Y direction to make the mould and 10mm in the positive-Y direction, with a draft of 35° to make the tip.

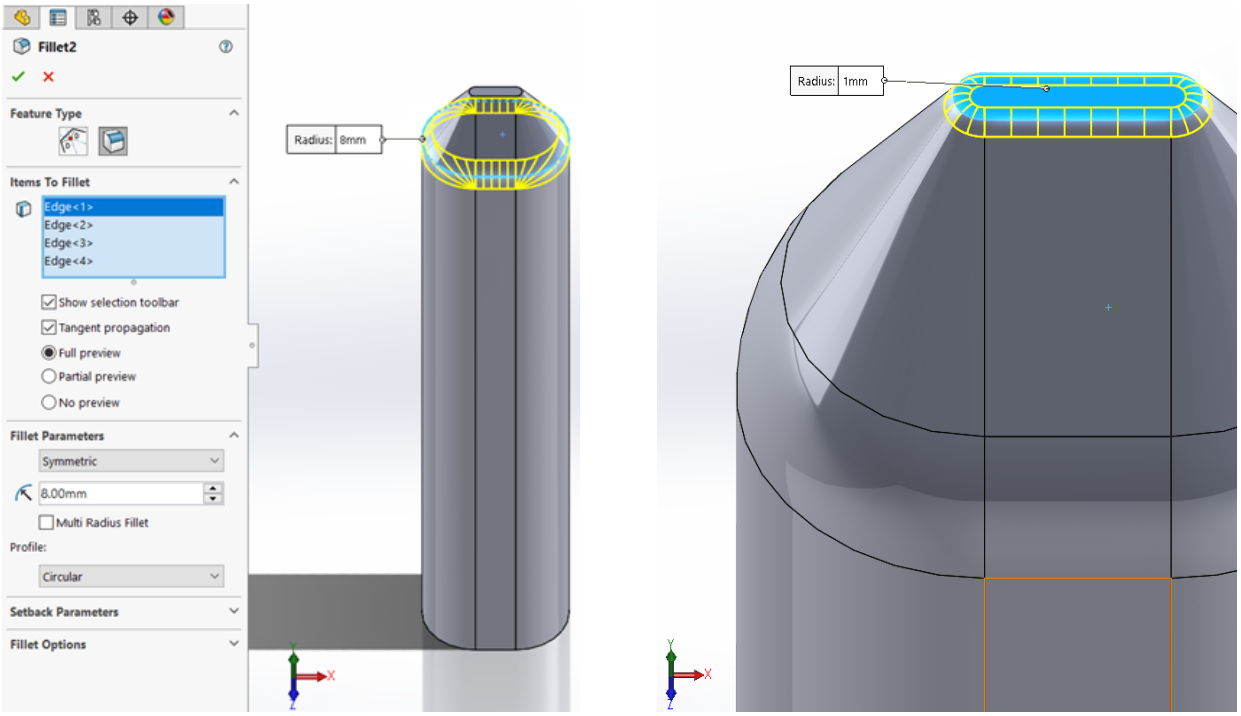

Figure 8: The sharp edges of the mould are smoothed, using the feature fillet. The edge between the tip and the rest of the mould uses a radius of 8mm and the end of the tip a radius of 1mm.

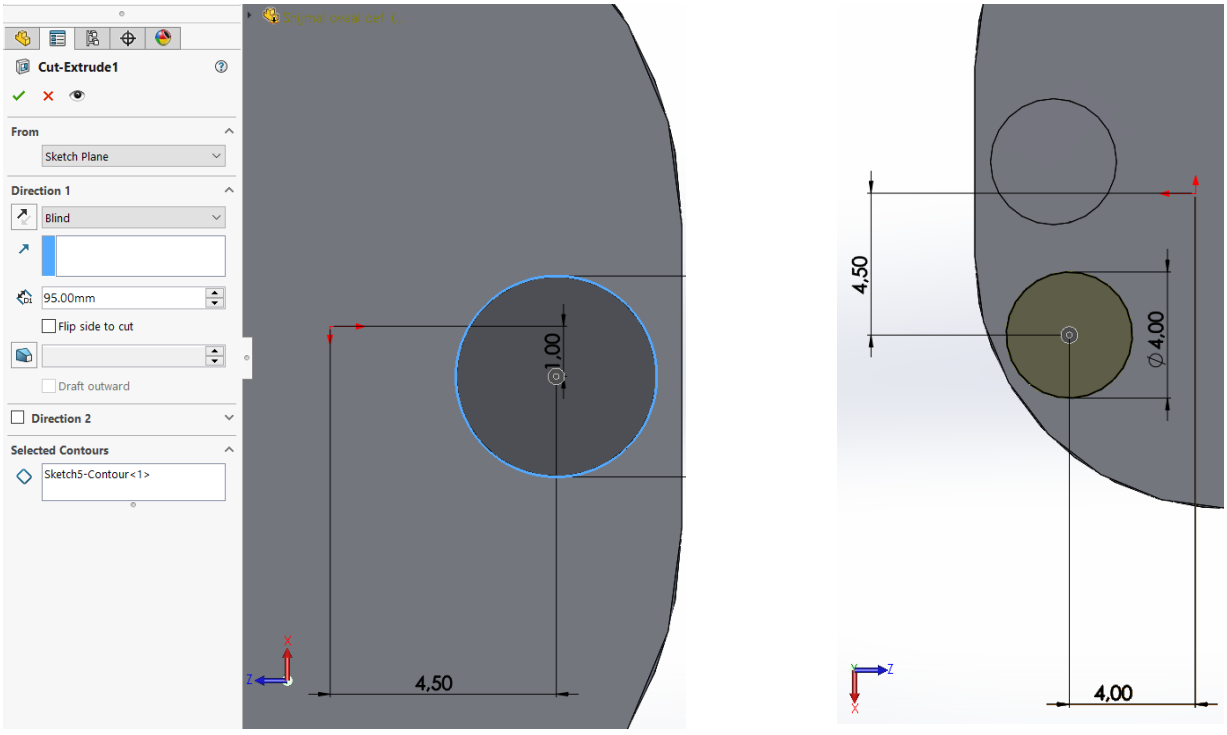

Figure 9: The main suction duct and the fluid duct are constructed in the top plane using the feature extruded cut. Both circles are 4mm in diameter and the suction duct reaches 95mm into the mould and the fluid duct 115mm, which means it comes out of the other side.

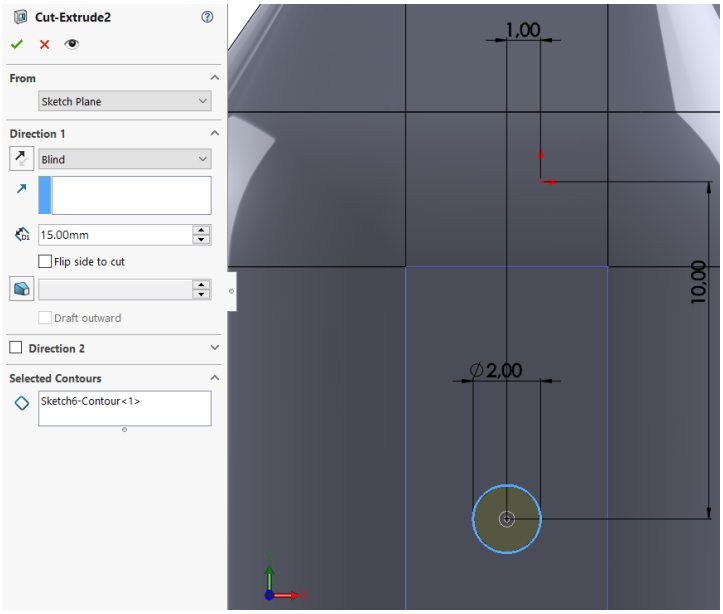

Figure 10: The straight centre ducts are constructed in the front plane, the xy-plane, the radius is 1mm and the extruded cut is 15mm deep. Six centre ducts are constructed, beginning at 10mm above the origin reaching up to 35mm. Each centre of the ducts is separated by 5mm.

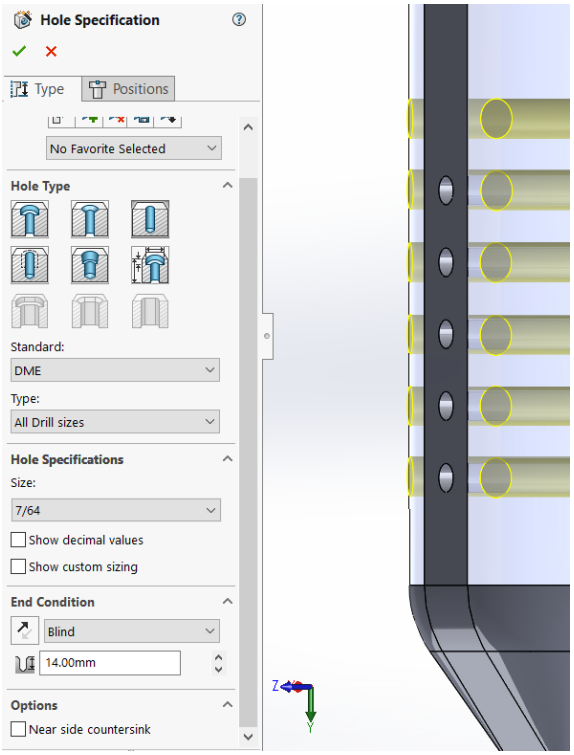

Figure 11: The side ducts were placed at both sides of the centre ducts. These side ducts were made using the feature 'Hole Wizard', with a radius of 2.78mm. The centres of the centre ducts and side ducts separate 6mm.

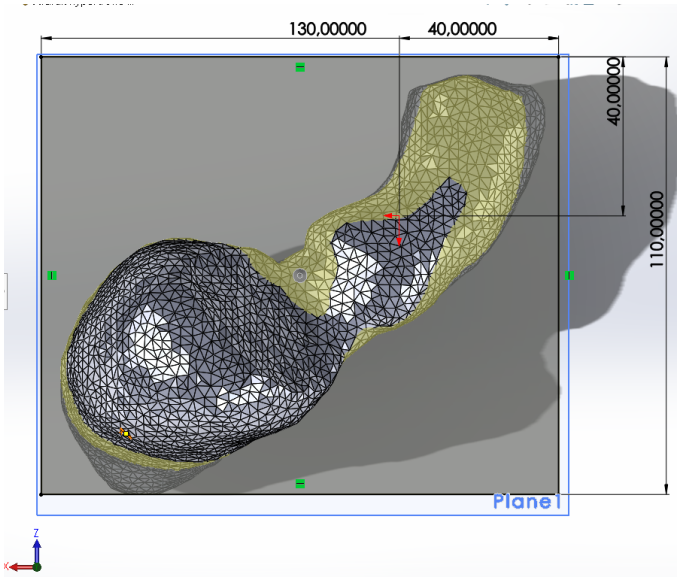

Figure 12: For the negative mould of the hypertrophy the LV volume was loaded into Solidworks. A plane is created above the hypertrophic region and a rectangle is drawn in this plane. In this picture you the dimensions of the extruded boss/base so the function up to next can be used for the negative mould.

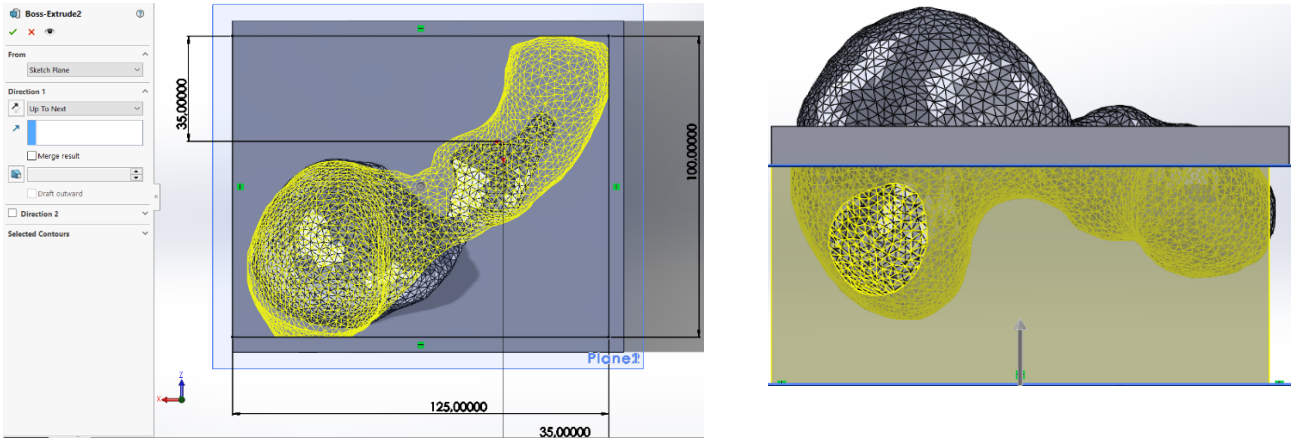

Figure 13: A plane is created beneath the solid body of the LV volume and in this plane a rectangle is sketched. Using the feature extruded boss/base and the option up to next a negative mould of the LV volume is created.

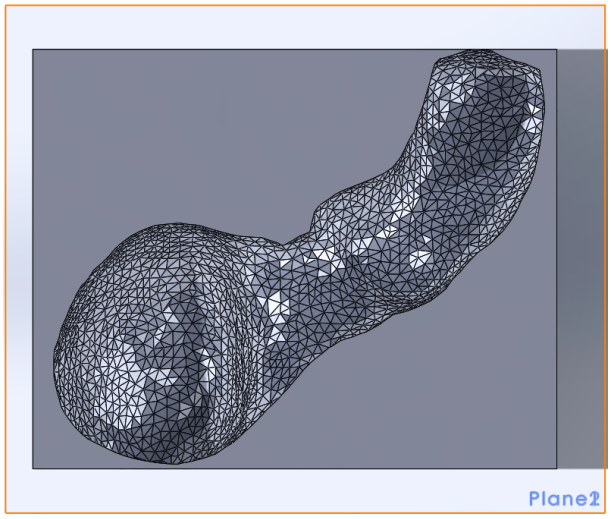

Figure 14: The final product of the negative mould design

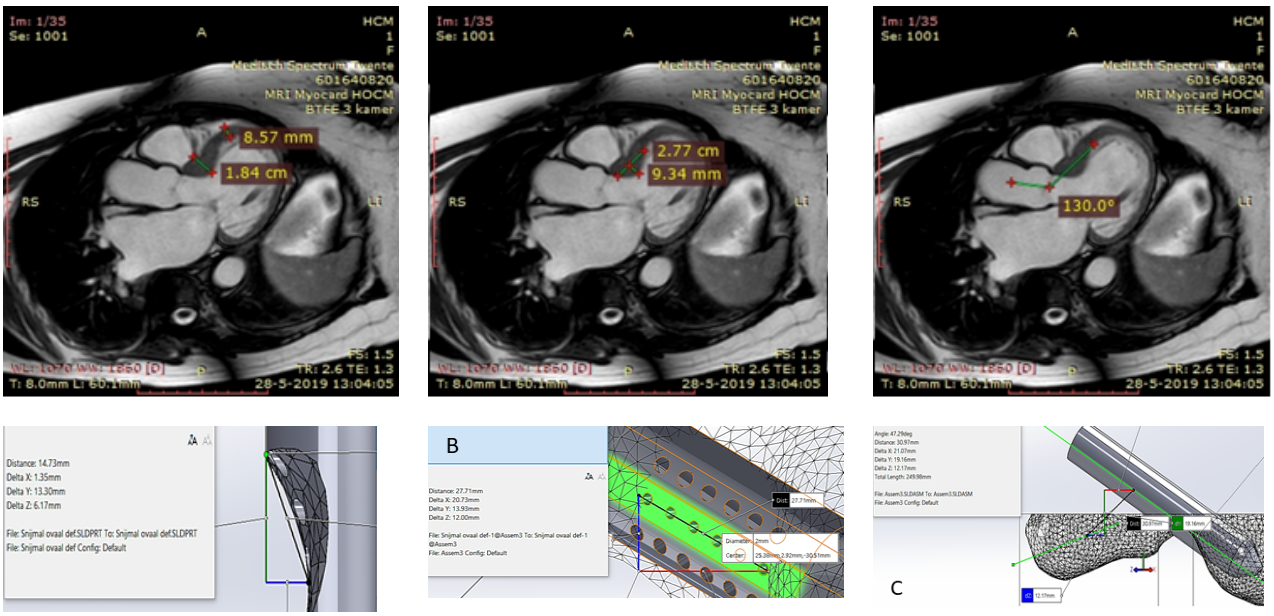

Figure 15: CMR parameters as input for SolidWorks design.
A: The septal thickness reduction
B: The length of the hypertrophic region
C: The angle between the mould and the aorta

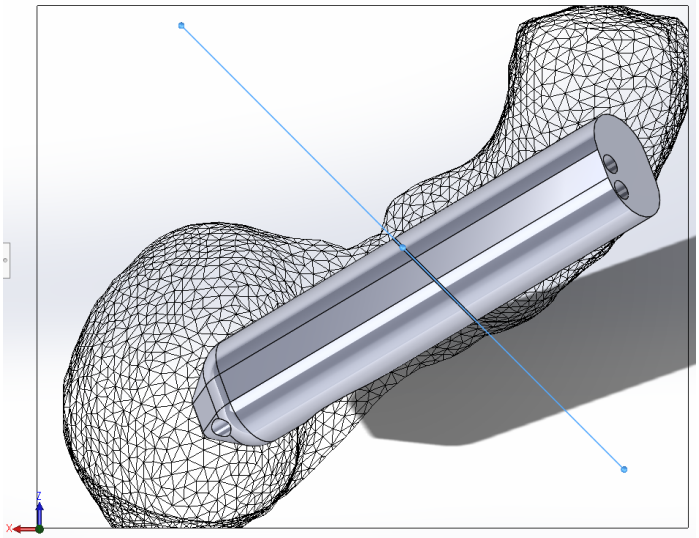

Figure 16: Placement of the Aorta plane in order to easily create the reference ring

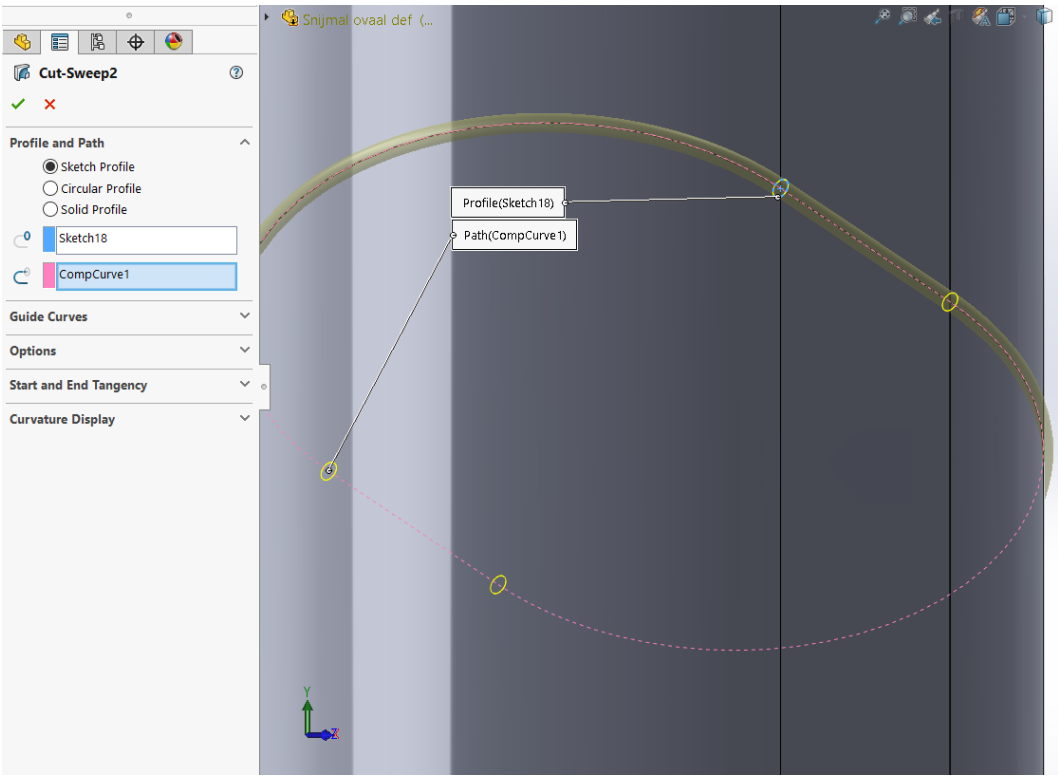

Figure 17: This ring is constructed to use as a reference for the aorta's fibrous ring. The reference ring is place according to a split line at the intersection of the aortic plane and the cutting mould, during assembly. Then a CompCurve and a circle perpendicular to the CompCurve are sketched. Using the feature swept cut these components come together as the reference ring.

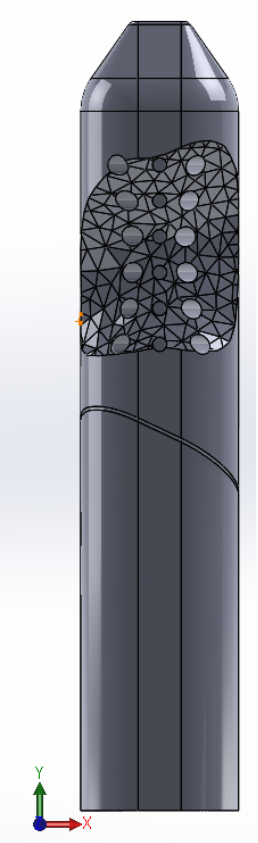

Figure 18: The final prototype design

4.2.1 Components of the cutting mould

The cutting mould consists of several components, which are all designed for optimal use, see figure 19. The utility of each of the components is described in this subsection. First the components that are designed by the previous MDO-group are described. Hereafter, the new or improved components that were integrated are described.

Pointed end

The pointed end of the cutting mould ensures an easier placement through the aortic valve. One of the problems of the septal myectomy is the risk of damaging the aortic valve (see chapter 1). This damage is caused by inserting instruments, such as a scalpel, through the aortic valve. The pointed end may prevent this damage by pushing away the cusps to the aortic wall.

Hypertrophic cutout

The hypertrophic cutout makes the cutting mould patient specific. The cutout is obtained from the MRI images made before surgery, and therefore it is an exact negative of the hypertrophic tissue. This may provide a more accurate resection which solves the inaccuracy involved in the septal myectomy.

Knife slit

The knife slit is not shown in figure 19. The previous group experienced difficulties printing the cutting mould with this knife slit. The slit collapsed and therefore was not usable. In order to test the cutting mould, the knife slit was not integrated to prevent this collapsing. Instead, a knife was made which surrounds the outside of the cutting mould.

Suction system

The suction system ensures the fixation of the hypertrophic tissue into the cutting mould. The hypertrophy is sucked into the cutout and can therefore be cut by the knife. The suction system consists of a main branch with several side branches. These side branches cover the surface of the hypertrophic cutout. They do not cover the surface outside the cutout. This differs from the cutting mould made by the previous group. The suction may cause damage to the myocardium which must be prevented. Therefore, the side branches are only integrated in the hypertrophic cutout, because this tissue will be removed anyways. Besides, as described in the next paragraph, the heart will be filled with a fluid. To prevent leakage of this fluid into the suction system, all of the side branches have to be enclosed by tissue. This was not the case for the cutting mould of the previous group.

Fluid channel

Another new addition to the cutting mould is the fluid channel. This fluid channel makes it possible to inject a physiological saline, which fills the LV. The shape of the heart changes during the surgery, because of cardioplegia. This also changes the shape of the hypertrophy which is a challenge. In order to solve part of this challenge, the LV is filled with physiological saline, to build op pressure, to try and restore the shape of the heart. The fluid channel provides the passageway of the saline solution. Besides, by filling the heart with a fluid, the ultrasound images could be improved. This is also tested in the experiments.

Aorta-plug

In order to fill the heart with a fluid, it must be sealed. This is ensured by the aorta-plug, which is not shown in figure 19. The aorta-plug consists of a donut shaped balloon which surrounds the lower part of the cutting mould. This balloon barricades the aorta and prevents leakage of fluid outside the LV.

Shape of the cutting mould

In comparison with the previous cutting mould the shape has also changed. The shape used to be circular, however, this enables unwanted rotation of the cutting mould. Therefore, the shape is changed to an oval, in order to minimise the rotation and to ensure a better fit on the hypertrophic tissue.

Reference ring

The last component of the cutting mould is the reference ring. This also differs from the previous cutting mould. The previous cutting mould used an oblique edge (as shown in figure 20) as a reference point. However, this oblique edge makes it hard to connect the fluid and suction tubes. Therefore, this oblique edge is removed and replaced by a reference ring. During the placement of the cutting mould onto the hypertrophic tissue, this reference ring must be at

the height of the fibrous ring of the aortic valve (figure 21). This fibrous ring provides an easy reference point for the surgeon. The reference ring has an advantage over the oblique edge. The reference ring surrounds the entire cutting mould which also provides information about the correct angle of the cutting mould. If the reference ring follows the fibrous ring on all sides, the cutting mould is not only at the correct height, but also in the correct angle.

4.2.2 Printing and material of the cutting mould

Cura 4.1 software of Ultimaker was used to create printable files of the cutting mould. These printable files were put on a SD-card and loaded into an Anycubic I3 Mega 3D printer. The material used was black PLA filament, because of its availability. A table with the material requirement for the cutting mould can be found in Appendix G.

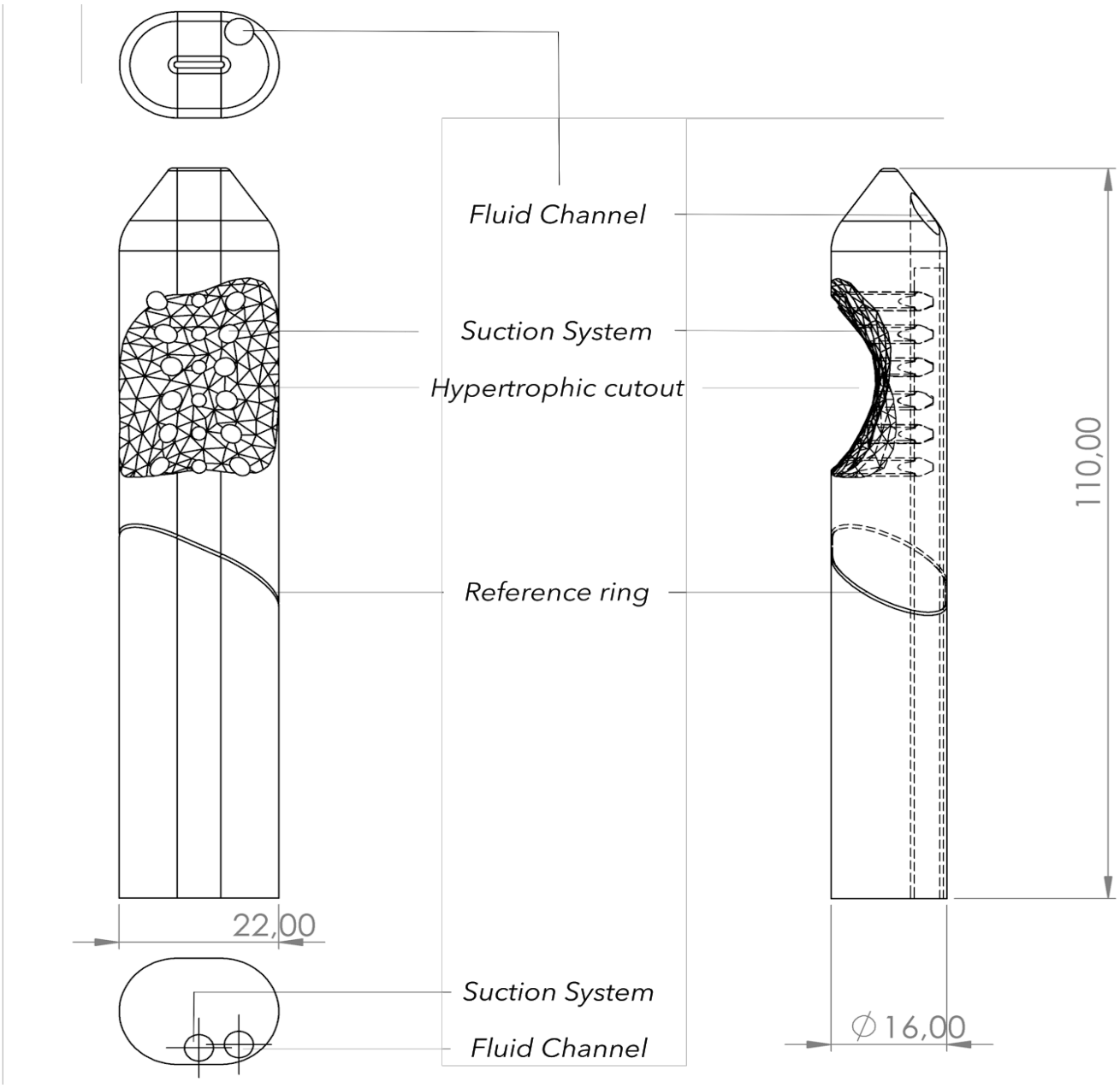

Figure 19: Technical drawing of the cutting mould.

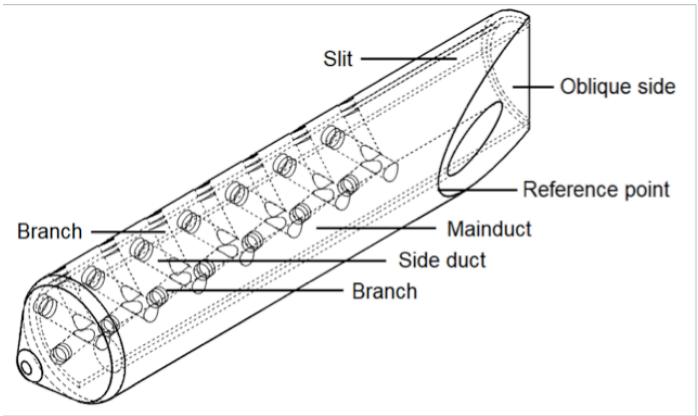

Figure 20: Cutting mould of the previous group [54].

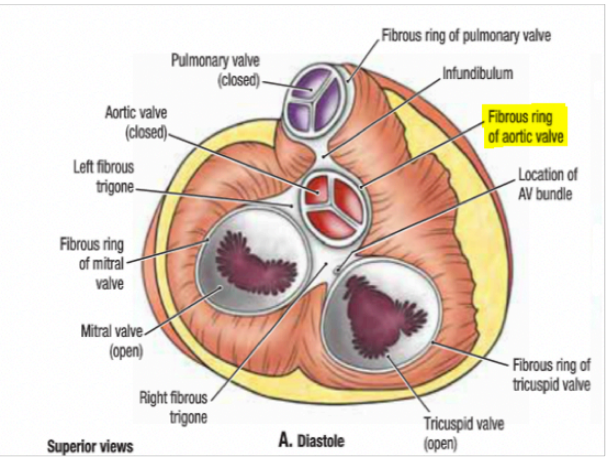

Figure 21: Fibrous ring of the aortic valve [5].

4.3 Experiment with the cutting mould

The experiment had three goals:

1. Test if the suction system of the cutting mould works.
2. Test if filling the heart with a fluid improves the ultrasound imaging.
3. Test the cutting of the cutting mould.
   a. Test the accuracy of the placement of the cutting mould.
   b. Test the resection of the hypertrophic tissue made by the cutting mould.

In this chapter a description of the method and the findings of the experiment are given. The limitations and improvements (future perspectives) of the experiment can be found in Chapter 5.

4.3.1 Description of experiment

The questions of the experiment were:

1. *Does the suction system of the cutting mould work?*
2. *Does filling the heart with a fluid improve the ultrasound imaging?*
3. *To what extent is the cutting mould able to cut away the hypertrophic tissue accurately?*
   a. *How accurate is the placement of the cutting mould? (Using the ballistic mould)*
   b. *How hard / easy is the cutting? (using the pig's heart?)*

The brief method for answering each of these questions is described below. We used both a ballistic mould and a pig's heart to test on. The elaborate test protocol of the experiment can be found in Appendix H.

Suction system

The suction system was tested on the outside of the pig's heart. A syringe was used to provide the suction. The cutting mould was placed on the outside of the LV, the handle of the syringe was pulled back. Next, the razor blade was pushed over the tissue to test the cutting in combination with the suction system.

Filling the heart with a fluid

To test if filling the heart with a fluid improves ultrasound imaging, the ultrasound images of an empty and a water-filled pig's heart were compared. Both with and without the cutting mould inside the pig's heart. A tie wrap was placed around the pig's aorta and the cutting mould, to prevent water from leaking out via the cutting mould. This tie wrap replaces the aorta plug.

Cutting with the cutting mould

To test the accuracy of the placement of the cutting mould, a ballistic model of the LV was used. The cutting mould was placed inside the ballistic mould on top of the hypertrophy. A video was made with the improved oval cutting mould (Video 10, Appendix M). During this video, the hypertrophic ballistic part was resected with the cutting mould. This process was repeated on the other ballistic cutting mould. The volume of both resections was measured.

The pig's heart was used to test the cutting of the cutting mould. The cutting mould was tested on both the outside of the right ventricle (Video 11, Appendix M) and the septum inside the LV. The resected tissue was inspected, and the damage of other structures was examined.

4.3.2 Results (with images of experiment)

In this subsection the answers to the questions of this experiment are described, based on the findings of the experiment. The extensive lab report can be found in Appendix I. In Chapter 5 an explanation about the outcome, the limitations of this experiment and the improvements (future perspectives) for a better outcome are given.

1. Does the suction system of the cutting mould work?

The suction system of the cutting mould works to some extent. When using the suction system on the pig's heart 2cm^3 tissue was resected, the required amount was 3cm^3 (based on the measurement of resection on the ballistic model).

2. Does filling the heart with a fluid improve the ultrasound imaging?

Filling the heart with water made the LV slightly bigger, however no major differences were seen. Figure 22 shows the ultrasound planes. Figure 23 shows the pig's heart without water with the cutting mould. The sides of the cutting mould are shown at the top and bottom of the yellow line. Figure 24 shows the pig's heart filled with water with the cutting mould. The sides of the cutting mould are shown along the orange lines. This figure is greyer than Figure 23. Video 9 (Appendix M) shows how the LV is successfully filled with water. No conclusion can be made if filling the heart with a fluid improves the ultrasound. When filling the heart with water, it is necessary to use an aorta-plug to prevent the water from leaking alongside the cutting mould.

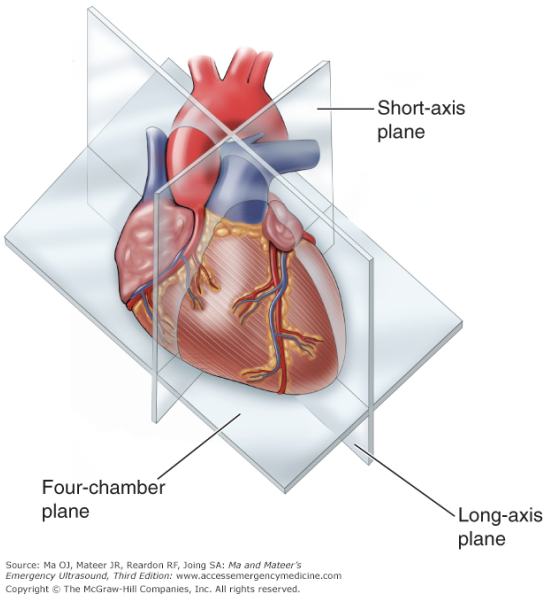

Figure 22: Explanation of ultrasound planes[56].

3. To what extent is the cutting mould able to cut away the hypertrophic tissue accurately?

a. How accurate is the placement of the cutting mould? (Using the ballistic mould)

When using the ballistic mould, the cutting mould is placed accurately and cuts away the hypertrophic tissue accurately. Figure 25 shows the ultrasound image of the cutting mould (marked in red) with the razorblade inside the ballistic mould, no major artefacts were created by the mould. In the green square the suction canals are visible. Video 3 (Appendix M) is a movie of the cutting mould inside the ballistic mould, the movie shows the resection of the hypertrophic ballistic tissue. Figure 26 shows the ballistic mould with the resected tissue; the resected tissue lays on top of the cutting mould and fits the recess in the cutting mould. The cut out fits the hypertrophic recess in the cutting mould. (the 3cm^3 was resected).

b. How hard / easy is the cutting? (using the pig's heart?)

Using the pig's heart, the cutting is harder. The cut out did not fit the hypertrophic recess in the cutting mould. (2cm^3 was resected). Cutting with the cutting mould inside the pig's heart also damaged the aortic valve.

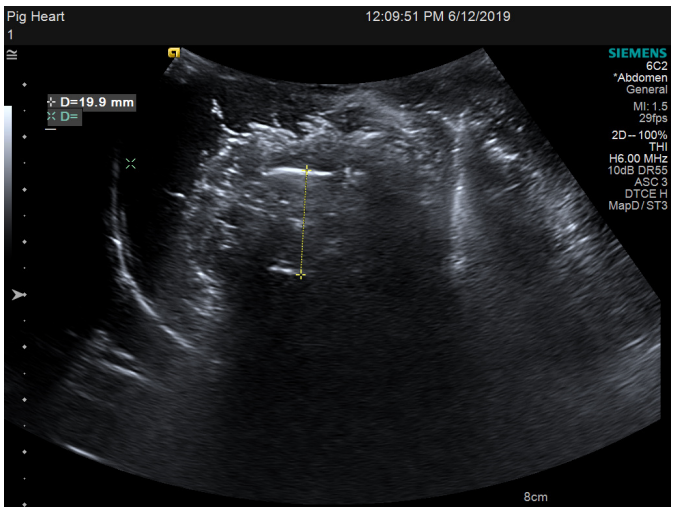

Figure 23: Measurement of the cutting mould inside the pig's heart: short axis plane.

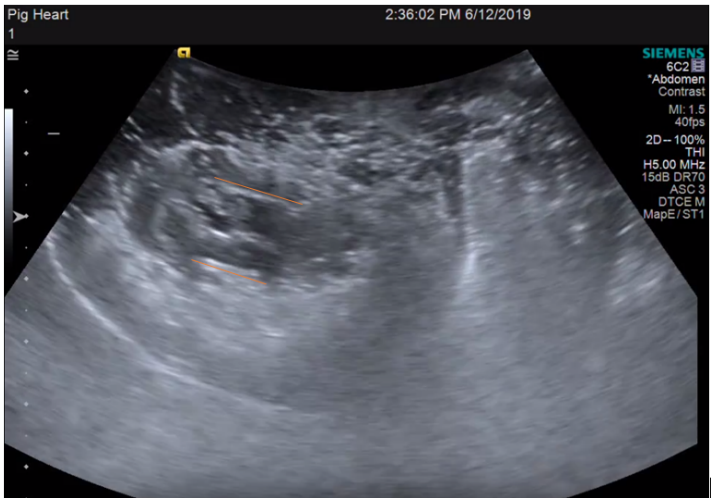

Figure 24: Heart filled with water and cutting mould, short axis plane.

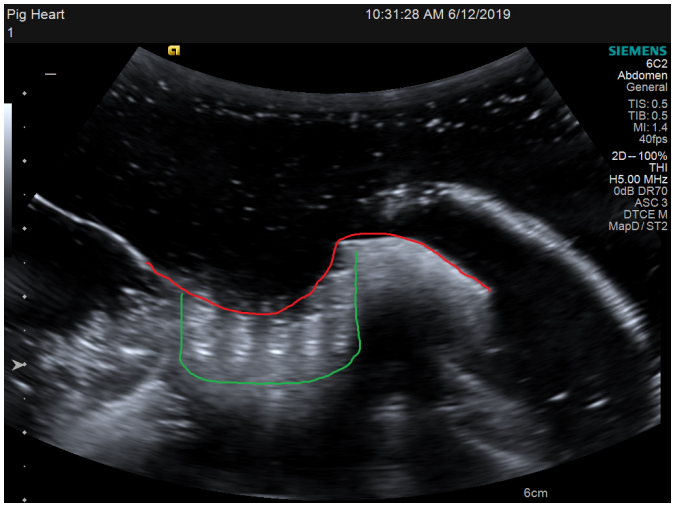

Figure 25: Cutting mould in the ballistic mould, marked in red. The suction canals are visible in the green square.

Figure 26: Ballistic mould with the resected hypertrophy. Cutting mould with the resection and the razor blade.

4.4 Conclusion

All in all, the cutting mould succeeds in its job to resect the ballistic hypertrophic tissue. The oval shape results in better placement, the reference groove adds a reference point and the fluid channel allows filling the heart with water. However, the suction system requires further development and further research is required to verify if a fluid filled heart results in better imaging and if therefore an aorta-plug is necessary. Limitations and improvements of the research are given in Subsection 5.1.3 of this report.

Chapter 5 - Discussion

In this chapter the discussion of Chapter 2, Chapter 3 and Chapter 4 is described and the future perspectives are given.

5.1 Discussion: explanation of results and limitations

The goal of this discussion is to provide the reader with explanation and clarification of the research. For chapter 2, 3 and 4 a discussion will be formulated to reflect on the process, describe what should be kept in mind when redoing this study and report on the things that should be done to finalize this research.

5.1.1 Discussion Chapter 2 - The literature study

The literature study provides a thorough investigation of four challenges involved in finding a better treatment for HOCM. For each of these challenges, two advices are given: both a recommendation from a technical-medical perspective as well as a recommendation which is achievable within the time given for this bachelor thesis. The advices are discussed in this subsection.

The first challenge involves the access routes to the heart. Several access routes are investigated, as described in Appendix F.1. From a technical-medical view, the least invasive access route is preferred because this causes the least harm to the patient. The endovascular and the extracorporeal approach are the least invasive ways to get access to the heart and are therefore preferred. The endovascular approach only requires a small incision and the extracorporeal approach requires nothing at all. The current endovascular techniques are highly developed, as well as the radiation techniques. Therefore, it is recommended that either of these access routes is used in the future. However, these approaches are not possible to investigate within the time-period of this bachelor thesis. Therefore, this research focuses on the development of the current access route, the surgical approach with the use of a sternotomy.

The second challenge describes several ways to reduce the size of the hypertrophic tissue, in order to resolve the LVOTO, as described in Appendix F.2. Several solutions are given, such as ablative therapies and radiation therapy (RT). Based on the findings, it is recommended to further investigate the use of RT in cardiac surgery. The use of RT may be controversial, however, with the current techniques the dose delivery is highly focused and limited to the target area. These techniques reduce the risk of radiation induced heart disease (RIHD) and cardiotoxicity which make the use justified. However, many researches must be performed to use RT as a replacement of cardiac surgery. Therefore, it is not possible to further investigate this treatment within the timeframe of this thesis. It is recommended to deliver an improved protocol that could help patients in the nearby future. For this reason, it is recommended to improve the septal myectomy. This procedure is widely used, and small improvements can already make a difference.

The third challenge is all about improving the planning of the treatment and the preoperative localisation of the hypertrophic tissue, see Appendix F.3. Mainly imaging techniques are investigated, as well as the preoperative practice by using a 3D heart. The futuristic recommendation includes the use of advanced MRI techniques such as 4D flow MRI. These techniques improve the understanding of the difficult anatomy and it may help defining the exact amount of tissue that must be resected. Moreover, with the use of 4D flow MRI, there is a possibility to predict the change in blood flow after resection. This may provide a prediction of the changes in blood flow after resection. Based on the non-invasiveness and the advanced techniques of MRI, it is recommended to further investigate the use of MRI in the future. However, the implementation of these techniques is hard to achieve within the time frame of this bachelor thesis. Therefore, it is recommended to further investigate the use of a 3D model of the heart. The MRI images of a HOCM heart are already available in the MST and therefore the printing is possible to achieve within the timeframe.

The fourth challenge seeks for an improvement of the intraoperative demarcation and localisation of the hypertrophic tissue (Appendix F.4). Based on these findings, the futuristic recommendation comprises the use of a 3D optical tracking system. This can provide an intraoperative guide which can give feedback about the placement of the instruments. In the septal myectomy, it is hard for the surgeon to make an accurate incision. With the feedback of a tracking system, this problem could be solved. However, integrating this into the OR requires more research. The short-term recommendation is to further investigate the use of the cutting mould made by our predecessors. This can be used in the current septal myectomy procedure and therefore it could be easily integrated when perfected.

Limitations of literature study

The literature study provides a thorough and in-depth analysis of the current and newly devised techniques used in and around the treatment of HOCM. As said, this literature report was based on four challenges. These challenges provided a good foundation to start with and it helped to study all the aspects involved in finding a better treatment. However, other researchers may think other challenges are more important, based on their perception. This could provide different findings.

Another limitation of the literature study could be the optimism of some articles. Some articles show promising results of their technique, however, after interviewing the experts in the MST, these techniques have quite a few limitations. These limitations make it hard to implement these techniques into the daily practice. So, the promising results are less promising in practice.

5.1.2 Discussion Chapter 3

During the experimental phase representative models of the patient's heart were conceived using the methods explained in Chapter 3. A 3D printable "STL"-file can be conceived in 15 to 30 minutes, when using MRI software that can segment the different anatomical structures of the heart. The segmenting will take less than a minute, so the extra time is added due to loading the file into the 3D-printing software and making it printable.

Due to shortness of time the ballistic model could not be evaluated by a surgeon. Some studies showed promising results on using 3D models as preoperative practice [50]. However, the benefit is plausible to differ per surgeon due to experience. Creating a ballistic model would take longer than a 3D-printed model. The preparation and pouring of the gel will last 30 minutes, but the gel needs 8 hours to harden.

At first the casting mould was made out plaster, this turned out to be a less ideal possibility with respect to a 3D-printed mould designed in SolidWorks.

5.1.3 Discussion chapter 4

Limitations of the experiment

In this subsection the limitations of the experiment (Chapter 4.3) are described per sub-question (Subsection 4.3.1). Advices for the improvement of the experiment are given in the future perspective.

Suction system

The suction system should be improved. During the experiment, the cutting mould did stuck on the pig's heart tissue, but it was not secured entirely, resulting in an incomplete resection. Explanation for this poor suction could be the fact that the cutting mould does not have enough suction holes, that there was no continuous pressure suction (suction was obtained by pulling a 20mL syringe back) and that pulling the razor blade over the suction holes interrupted the suction.

Filling the heart with a fluid

It cannot be concluded if filling the heart with water leads to better imaging, since it is not clear if the heart was filled with water or if all the water dripped out because of potential problems with the pig's heart. It is also not possible to conclude whether filling the heart with water restores the original shape of the heart, since the original shape of the heart was not known. It should also be kept in mind that the authors of this report, as technical medical students, are no ultrasound experts and do not have the required skills to interpret the ultrasound images.

Cutting with the cutting mould

The ballistic mould is slightly softer than human tissue, however due to its ability to make realistic models of, and pour into specific moulds, the ballistic gel was very usable during the experiments. The pig's heart represents human tissue, however the pig's hearts that were used had been frozen and were a bit stiff. Cutting on the ballistic mould went smoothly without any problems, cutting on the pig's heart did not go as smoothly. It cannot be concluded whether cutting on human tissue will be easy or hard, since the ballistic mould is softer, and the pig's heart is stiffer. Furthermore, the blade used was blunt and not as sharp as a scalpel. Moreover, the aortic valve was damaged during the resection because the razor blade was shoved along the cutting mould and the cutting mould did not have a knife duct. The razor blade was lost inside the LV after resecting the tissue, because the razor blade was not attached to the cutting mould.

5.2 Future Perspectives

During the search for an improved and reliable treatment for patients with HOCM, a lot of promising techniques and improvements for the future were found. In this chapter opportunities and advice for further research, the 'future perspectives', are described.

5.2.1 3D heart - Preoperative planning

3D printed heart/ ballistic models

During this research 3D printed hearts and ballistic models were created. A 3D printed heart/ ballistic model may help the surgeon in the visualisation and determination of the size of the hypertrophic tissue. However, the authors were not able to prove if the models help the surgeon in the preoperative planning. In different studies a 3D model was used to perform a septal myectomy, both for visualising and training. The studies showed good results [50,57].

The authors suggest to research if the 3D printed hearts and ballistic models help the surgeon in the preoperative planning. The surgeon can practice resecting on the ballistic mould and visualize the hypertrophic tissue with both the ballistic mould and the 3D printed heart. Afterwards, the surgeon can denote if the model was of any use. Results of a septal myectomy with and without a 3D model can be compared to prove if the 3D models contribute to a better septal myectomy.

Materials used for 3D printing and ballistic casting.

In this research two 3D models of the heart were created: a 3D printed heart of PLA filament, and a ballistic heart. The 3D printed heart of PLA is not as flexible as a human heart, the ballistic heart is as flexible as the human heart but is a bit too flexible and the production process is more time consuming. The advice is to find a more flexible 3D printing material, so it is more realistic for the surgeon and takes less time to produce. The material needs to fulfil the requirements written down in Appendix J. Appendix K conducts a table with the possible flexible materials to print the 3D heart of. Another advice is to print a dual 3D heart model; A model printed out of different materials. The hypertrophic tissue can be printed of a more flexible material, while the other parts can be printed of a less flexible material. In this way, the surgeon can practice the resection on the 3D printed heart.

There is also an option to print a porous structure of the heart out of a more rigid material [57]. This porous structure can be filled with a combination of silicone and two hydrogels. This results in a heart with a structure like the patient's heart and which can be used as a practice heart for the surgeon. The surgeon can cut away the HOCM and compare the resected volume with the volume found on the MRI imaging.

Realistic heart model of ballistic gel

To produce a real copy of the LV myocardium out of ballistic gel, one of the 3D printed LV's with aorta has to be printed using PVA+ from Primaselect. This printing material can dissolve in water. To make this realistic ballistic version of the heart the authors plan to put two 3D printed negatives of the LV myocardium together (Figure 27), with this soluble print wrapped in clinging foil. The ballistic gel can be poured between the negatives and the soluble 3D print. After this hardened, the two negative halves can be taken of and the soluble part can be dissolved using water. The clinging foil ensures the PVA+ does not dissolve when the ballistic gel is poured and that the ballistics gel does not dissolve when water is injected into the PVA+ mould to remove

is. The clinging foil can also be used to take all the dissolved PVA+ out to ensure nothing is left inside the realistic ballistic heart. Now, the only thing left is a ballistic version of the LV myocardium.

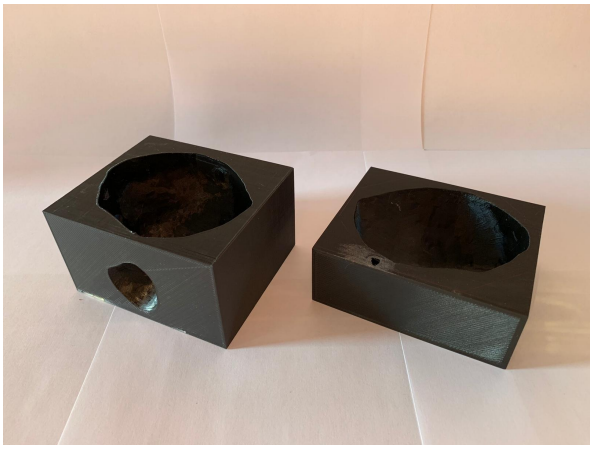

Figure 27: picture of the left and right halves of the negatives of the LV myocardium.

5.2.2 Cutting mould – Intraoperative Demarcation

Knife duct

Implementation of a 'knife duct' with a sharp knife is necessary to prevent the cutting mould from harming other anatomical structures and prevent the knife from falling into the LV. The predecessors of this paper had trouble constructing this duct, due to it collapsing while printing the cutting mould. In the tests performed for this paper a knife duct was not used, to prevent the 3D prints from failing and to see if it is even necessary. As described the knife damaged some of the anatomical structures of the pig's heart, the aortic valves. Some suggestions for constructing the knife duct are:

- Add sufficient supports to prevent it from failing.
- Measure the width of the duct and develop a knife that fits the duct.
- The knife should be as sharp as possible to ensure it does slide through the tissue. without resistance and no embolisms will occur.
- Make sure that the function of other ducts in the mould are not compromised.
- Make sure the mould still fits through the aorta.

Suction system

The currently integrated suction system sucked the mould to the ballistic model and pig's heart, but the suction was far from secure. The slightest movement of the cutting mould and the suction system would fail. To overcome this problem, several upgrades are necessary:

- Increase the number of small holes to increase the suction surface area. Make sure not to make them too small. This will not be 3D printable.
- In this research a syringe of 10ml was used. Ideally the mould should be connected to a continuous suction system to ensure stable suction.

Next to this solution, it is also possible to add suction pods like the octopus tissue stabilizer uses [58]. However, it should be kept in mind that these pods are quite big. Implementing them in the cutting mould is only possible if the pods can be produced in a smaller version.

Filling the heart with a fluid

To check if filling the heart with water improves the ultrasound imaging it is recommended to fill an alive cardioplegic heart with a fluid during surgery and compare the ultrasound images with the images of the non-filled heart. If the imaging improves, this technique can be used when checking the placement of the cutting mould, by using the fluid canal inside the cutting mould.

'Aorta- plug'

If filling the heart indeed results in better imaging, a system needs to be designed to prevent the water from leaking out. In the experiments in this research a tie wrap was used as a solution on pig's hearts. A more elaborate system needs to be created for the alive heart. It is recommended to create an 'aorta- plug' around the cutting mould. This plug could be a rubber plug around the cutting mould, which seals the aorta in the small space between the cutting mould. To design this, the measurements of the aorta need to be obtained, to create a rubber plug with the right dimensions. Figure 28 shows a sketch of the aorta-plug drawn by the authors of this report.

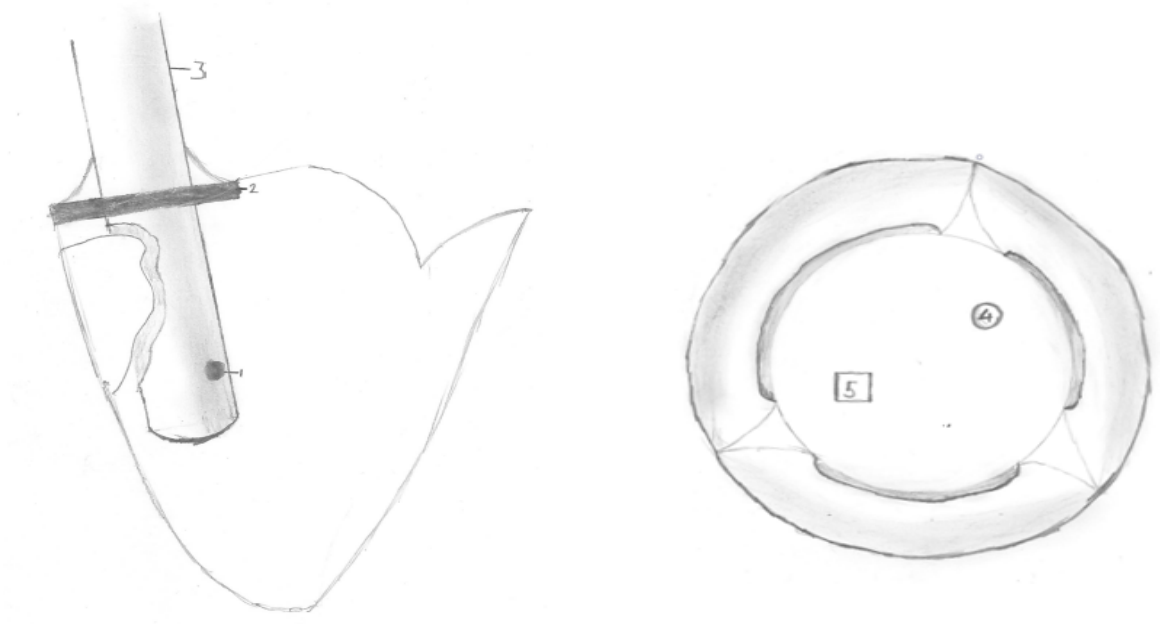

Figure 28: sketch of the 'aorta-plug'
1. Fluid exit
2. Rubber plug
3. 3D-cutting mould
4. Suction opening
5. Fluid exit

Another possibility to seal the aorta, is using an inflatable donut shaped balloon around the cutting-mould. The balloon should be attached to the cutting mould at the right height. When the cutting mould is placed at the right position, the surgeon can inflate the balloon by using the air canal which is implemented inside the cutting mould and connected to the balloon. When the balloon is inflated, and the aorta sealed, the surgeon can fill the heart with water via the water canal in the cutting mould. Thereafter, the surgeon can check the positioning of the cutting mould with ultrasound and use the cutting mould to resect the hypertrophic tissue.

Positioning

To ensure a perfect fit of the hypertrophic cutout over the hypertrophic septum, it is important to make sure the positioning of the mould is perfect. It is possible to determine the location of the aortic valve leaflets compared to the hypertrophic septum. The authors believe the shape of the leaflets can be integrated on the outside of the cutting mould. As the surgeon inserts the mould through the aorta, it gets stuck behind the three leaflets. This way the mould is in a fixed position and the aortic valve leaflets are protected from the knife.

5.2.3 Imaging models

Non-beating heart

The shape of the heart differs in the non-beating situation. It is not yet predictable how the heart will collapse when connected to the heart lung machine. It would be useful to create a model that visualizes the collapse of the heart and the visual change of structures. If the 3D model of the beating heart (from using the MRI images) could be transformed into a 3D model of the non-beating heart, the surgeon could use this during the preoperative planning. It is not known how the shape of the hypertrophic septum changes in a non-beating heart. The current cutting mould is not adapted to the possible changes of the hypertrophic septum in the non-beating heart. By creating a model of the changes, the hypertrophic recess inside the cutting mould could be adapted to the non-active situation, so the exact right amount of tissue can be cut away. The feasibility of this concept is a concern, since no literature about the subject can be found.

5.3 Clinical implementation of the cutting mould

So far, a lot of recommendations concerning the improvement of the septal myectomy are given. This paragraph explains how these recommendations, especially the cutting mould, can be implemented in the current treatment protocol.

A patient is diagnosed with HOCM. The gradient exceeds 50 mmHg and the septal wall thickness exceeds 15 mm. This means that the septal myectomy is the best treatment option. The first step after concluding the best treatment, is making a CMR. The radiologist segments the CMR imaging of the heart and isolates two components: the LV myocardium and the content of the LV with the aorta attached. This segmentation is converted into a 3D printing file. Preferably, this is printed with a flexible material that simulates the flexibility of a real heart. However, a non-flexible printed heart also suffices. These 3D prints can be evaluated by the surgeon preoperatively to improve the anatomical understanding.

The segmented components made by the radiologist are used by the clinical technician to develop the 3D cutting mould. The cutting mould is then printed, the knife is assembled, and the entire setup is sterilised. Now, the cutting mould is ready to be used by the surgeon. It might not be possible to do this in the hospital. If so, an external partner can produce the cutting mould.

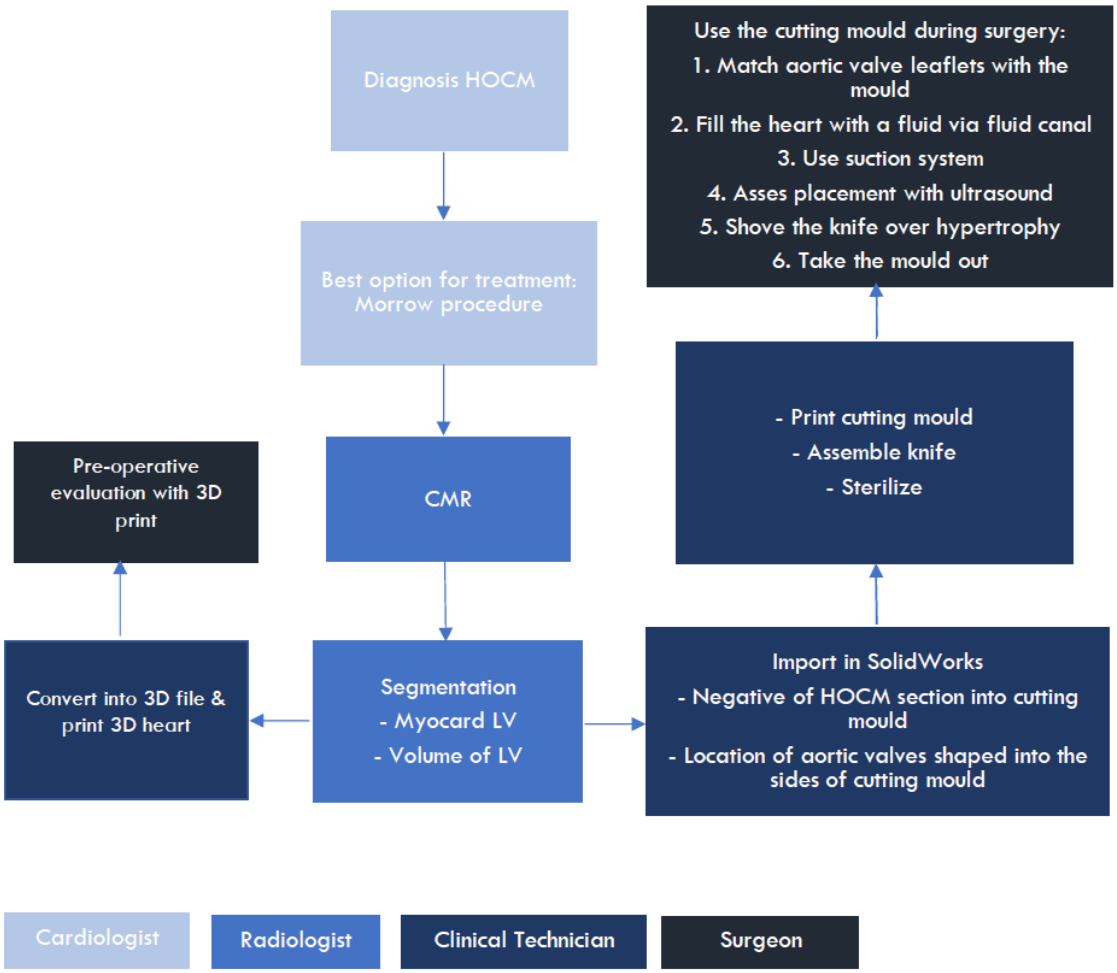

Figure 29: Flowchart of clinical implementation of the cutting mould and 3D printed heart. The Flowchart shows which steps need to be taken when the cutting mould is implemented in the treatment of HOCM. It shows the process from diagnosing HOCM, until the surgical procedure of resecting the tissue. This flowchart applies when the initial best treatment for the patient is a septal myectomy.

Chapter 6 – Main Conclusion

The cutting mould is a very promising solution to mitigate the described challenges of the septal myectomy. The 3D printed and ballistic heart models can be used to pre-evaluate the individual patients' hearts before surgery. When implementing the 3D printed heart and the cutting mould into the septal myectomy protocol it is likely to significantly enhance the number of positive outcomes.

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Appendix A – Plan of Approach

Nieuw myectomie protocol bij Hypertrofische Cardiomiopathie

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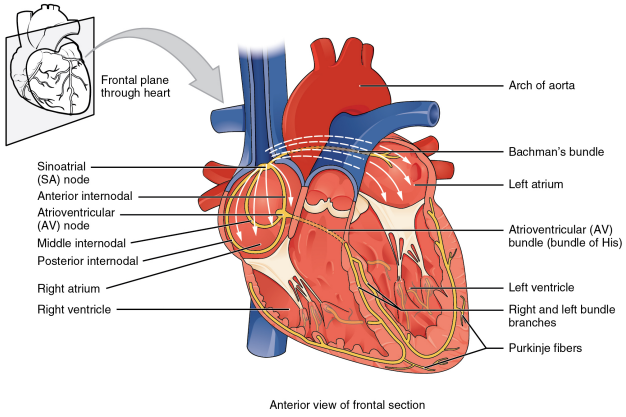
Samenvatting

1 op de 500 mensen lijdt aan hypertrofische cardiomyopathie (HCM). HCM kan worden opgedeeld in twee varianten: de obstructieve variant (HOCM), welke voorkomt bij tweederde van de patiënten, en de non-obstructieve variant (HNCM). Voor HOCM zijn er verschillende behandelmethoden: in eerste instantie bestaat de behandeling uit medicatie, maar bij ernstige klachten kan er voor gekozen worden om de hypertrofie operatief te verwijderen. Momenteel bestaan er twee operatieve methoden: alcoholablatie en septale myectomie. In deze opdracht zal er op de myectomie worden gefocust, aangezien dit de gouden standaard is. Helaas kent myectomie nog wel een aantal uitdagingen. De grootste uitdaging bij deze behandelmethode is het exact bepalen van de hoeveelheid hypertroof weefsel dat moet worden weggesneden. Dit komt doordat het hart tijdens de operatie aan de hart-longmachine ligt en zich niet meer contraheert. De vorm van het hart tijdens de operatie verschilt dus van de pre-operatieve beeldvorming. Door onnauwkeurigheid komt er op dit moment vaak over- of onderbehandeling voor. Naast dit probleem kent de behandeling nog een aantal complicaties, zoals: onregelmatige hartritmes door hartblok, infecties, bloedingen, vorming van een bloedprop die kunnen leiden tot een hersen- of hartinfarct, insufficiëntie van de aortaklep en een ventrikelseptumdefect. Vanwege deze uitdagingen en mogelijke complicaties wordt de behandeling maar zeer beperkt toegepast, terwijl voor een grote groep patiënten een behandeling wel noodzakelijk is.

1 Anatomie

Het linker ventrikel van het hart wordt omsloten door het ventriculaire septum en een deel van de vrije hartwand. In het ventriculaire septum loopt de bundel van His, deze splitst zich in linker en rechter bundels en gaat in de vrije wanden over in de Purkinje vezels zie figuur 1. De doorgang naar het linker atrium wordt afgesloten door de mitralis klep en de doorgang naar de aorta door de aortaklep. De mitralisklep zit vast aan papillairspieren in de ventrikel door middel van chordae tendinae. Deze pees-achtige structuren beperken de beweging van de klep tijdens de systole, zodat er geen bloed terug het atrium in stroomt. Direct boven de aortaklep bevinden zich de coronaire ostia, die de toegang verschaffen tot het coronaire vaatsysteem. Zo wordt het myocard van bloed voorzien.[1][2]

Een uitgebreide beschrijving van de anatomie is te vinden in bijlage C



Figuur 1: *Anatomie van het hart [3]*

2 Fysiologie

In de onderstaande paragrafen wordt er verder ingegaan op de werking van het gezonde hart. De fasen van de hartslag, de geleiding van het actiepotentiaal en de contractie van het myocard worden toegelicht.

2.1 Diastole en systole

De hartslag bestaat uit 2 verschillende fasen: de diastole en de systole. Tijdens de diastole is het hart in rust en worden de atria gevuld. De mitralis- en tricuspidalisklep worden niet actief gesloten, waardoor de ventrikels passief gevuld worden. Aan het einde van de diastole trekken de wanden van de atria samen, waardoor de atria geleegd worden in de ventrikels. Na de diastole begint de systole, waarbij de ventrikelwanden samentrekken en het bloed de aorta en de longslagader instroomt. [4] [5]

De systole en diastole worden gereguleerd door de sinusknoop, die een actiepotentiaal door het hart stuurt. Deze actiepotentiaal verplaatst zich eerst over beide atria, waardoor deze zich samentrekken. In de wand van het rechter atrium bevindt zich de atrioventriculaire knoop, deze vangt het signaal van de sinusknoop op en propageert deze met een vertraging naar de bundel van His. De bundel van His loopt door het septum richting de apex en vertakt zich in linker en rechter bundels, die op hun beurt via Purkinje vezels het hele myocard, waaronder de papillair spieren, voorzien van een actiepotentiaal. [4] [5]

2.2 Contractie van het myocard

Het myocard contraheert door de verkorting van sarcomeren, die bestaan uit actine- en myosinefilamenten. De contractie wordt gecontroleerd door sympatische innervatie, waarbij de permeabiliteit van Ca^+ kan worden verhoogd. De binding van Ca^+ aan troponine C zorgen ervoor dat uiteindelijk de filamenten, die zijn gebonden aan troponine T, loslaten en myosine kan reageren met de actieve gebieden van actine.

De kracht en contractiesnelheid van het myocard hangt af van 2 factoren: de pre- en de afterload. De preload heeft effect op de sarcomeerlengte, een hogere preload zorgt namelijk voor een langere sarcomeerlengte. Een langere sarcomeerlengte heeft op zijn beurt een hogere contractiekracht als gevolg. Daarnaast heeft de afterload, die te definiëren is als arteriële druk, of de te overkomen kracht, ook effect op de contractie kracht. Een hogere druk vergt meer kracht om hetzelfde bloedvolume de periferie in te pompen. [4] [5]

3 Pathofysiologie

De pathologie die centraal staat in dit verslag is Hypertrofische Obstructieve Cardiomyopathie (HOCM). In onderstaande paragrafen wordt deze pathologie en de bijbehorende oorzaken en gevolgen toegelicht.

3.1 Hypertrofische Cardiomyopathie

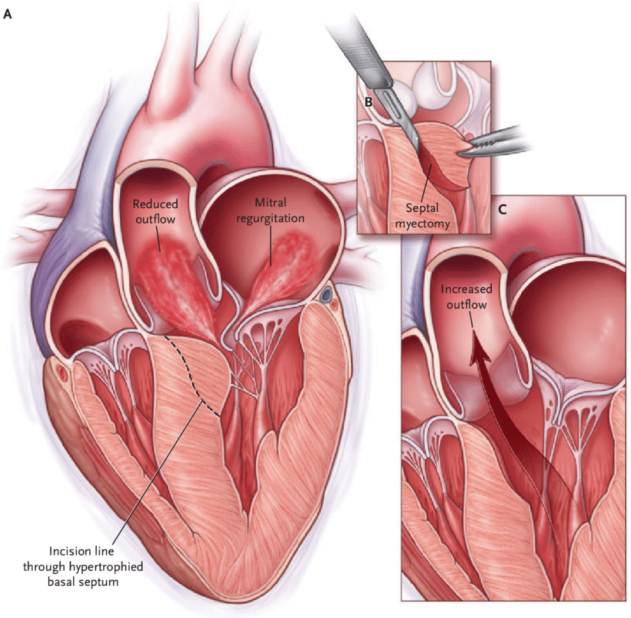
Hypertrofische Cardiomyopathie (HCM) is een cardiale aandoening waarbij het myocard is verdikt. Het betreft vaak een asymmetrische verdikking in het linker ventrikel, waarbij het interventriculaire septum sterker verdikt is dan de vrije wand. Afhankelijk van de mate van hypertrofie kan het hart het bloed nog goed rondpompen. Echter, bij sterke hypertrofie ontstaan er twee problemen:

1. De hartspier neemt veel ruimte in;
2. De hartspier kan slecht ontspannen en wordt stijf.

Deze problemen zorgen ervoor dat er minder bloed vanuit het atrium het ventrikel in kan stromen tijdens de diastolische fase, waardoor uiteindelijk de cardiac output wordt verminderd. Het kan zijn dat deze verminderde cardiac output asymptomatisch is, maar bij sterke vermindering kunnen er verschillende symptomen ontstaan, zoals [6]:

- Vermoeidheid;
- Dyspneu;
- Oedeem;
- Pijn op de borst;
- Syncope.

Als de hypertrofie zodanig is dat de uitstroom van het bloed vanuit het linker ventrikel richting de aorta belemmerd wordt, dan spreken we van HOCM, zoals is weergegeven in figuur 2. De sterke verdikking van het septum kan zich op verschillende hoogtes ontwikkelen, wat van invloed is op de stroming van het bloed. Hierover meer in paragraaf 3.3.



Figuur 2: *A: Anatomie van een hart met HOCM. De stippellijn geeft de resectielijn aan van het weg te snijden weefsel. B: Eenvoudige weergave van de septale myectomie, waarbij het hypertrofe weefsel wordt weggesneden. C: Het hart na de operatie, waarbij het bloed weer vrij richting de aorta kan stromen.[7]*

3.2 Oorzaken

HCM kent verschillende oorzaken, waaronder een hoge bloeddruk, hartklepafwijkingen of intensief sporten. Echter, in de meeste gevallen wordt HCM veroorzaakt door een genetische afwijking. Het betreft vaak een autosomaal dominante mutatie in de genen die coderen voor sarcomeer eiwitten, zoals [6][8]:

- het MYH7 gen wat codeert voor β-myosine;
- het MYBPC3 gen wat codeert voor het myosine bindende eiwit C;
- het TNNT2 gen wat codeert voor cardiaal troponine T.

Mutaties in de beschreven genen kunnen zorgen voor structurele afwijkingen van de myocyten. Waar normaal gesproken de myocyten parallel naast elkaar liggen, zal dit bij HCM niet of minder te herkennen zijn (*myocyte disarray*), wat hypertrofie als gevolg heeft.

3.3 Pathologische gevolgen

De beschreven hypertrofie in het ventriculaire septum heeft drie belangrijke pathologische gevolgen:

- Systolic Anterior Motion (SAM) van de mitralisklep;
- aritmie;
- verplaatsing papillairspier.

3.3.1 SAM van de mitralisklep

Zoals in figuur 2 te zien is, kan het hypertrofe weefsel de bloedstroom in de linker ventrikel beïnvloeden. Als de hypertrofie zich in de buurt van het *Left Ventricle Outflow Tract* (LVOT) bevindt, dan zal de stroomsnelheid van het bloed daar toenemen. Dit leidt tot het zogeheten Venturi-effect waarbij door het creëren van een zuigkracht het anterior klepblad van de mitralisklep richting het septum wordt getrokken. Dit effect veroorzaakt dus deels de SAM. SAM wordt niet alleen veroorzaakt door de Venturi krachten. Bij HCM kan er namelijk ook sprake zijn van hypertrofie van de papillairspier (zie paragraaf 3.3.3) die hierdoor richting anterior verplaatst. De chordae tendineae komen vervolgens losser te zitten, waardoor de anterior klep van de mitralisklep zich richting het septum zal bewegen. De LVOT obstructie wordt hierdoor versterkt. Daarnaast kan ook mitralisklepinsufficiëntie ontstaan. [9]

3.3.2 Hartritmestoornis

De meest voorkomende doodsoorzaak van HCM is een acute hartstilstand. Deze hartstilstand is het gevolg van hartritmestoornissen die vaak worden waargenomen bij mensen met HCM. Deze hartritmestoornissen worden veroorzaakt door verschillende factoren[10]:

Ten eerste is er door de LVOT obstructie een verminderde bloedstroom richting de aorta. Dit betekent ook dat er minder bloed wordt vervoerd naar de coronairen, waardoor het myocard minder zuurstof ontvangt. Dit kan ischemie en fibrose veroorzaken, waardoor de elektrische geleiding van het hart wordt verstoord.

Ten tweede is het myocard sterk verdikt, waardoor de coronairen krachtiger worden dichtgedrukt tijdens de systolische fase. De bloedstroom is dus al verminderd door de LVOT obstructie en daarnaast worden de coronairen ook nog dichtgedrukt door de hypertrofie, waardoor het myocard te weinig zuurstof krijgt.

Ten derde is er bij HCM sprake van myocyten wanorde, waarbij de myocyten niet parallel naast elkaar liggen. Dit levert ook veranderingen op in de elektrische geleiding waardoor hartritmestoornissen worden geïnduceerd.

3.3.3 Verplaatsing papillairspier

Zoals eerder genoemd is een derde gevolg van de hypertrofie de verplaatsing van de mitralisklep papillairspier. Bij HOCM is er sprake van asymmetrische hypertrofie, wat ook betrekking kan hebben op de papillairspier.[11] Hierdoor wordt deze niet alleen verdikt, maar kan deze zich ook naar verhouding richting anterior verplaatsen. Dit zorgt voor extra stromingsveranderingen in de linker ventrikel en versterkt de LVOT obstructie.

4 Huidige Diagnostiek

Er worden verschillende diagnostische technieken gebruikt om tot de diagnose HCM te komen en de ernst ervan in te schatten. De verschillende diagnostische technieken worden in de onderstaande paragrafen kort besproken.

4.1 Elektrocardiogram

Het elektrocardiogram (ECG) wordt met name gebruikt om meer inzicht te krijgen in de klachten van de patiënt, maar er kan geen definitieve diagnose voor HCM mee worden gesteld. Bij een verdikking van de linker ventrikel ziet de cardioloog een verhoogde precordiale spanning, niet specifieke ST-segmenten en T-golf abnormaliteiten. Wanneer het septum verdikt is worden er diepe, slanke Q-golven geregistreerd in de laterale en onderste afleiding van het ECG. Dit heeft veel weg van een Q-piek bij een myocardinaal infarct, maar bij HCM duren ze doorgaans korter dan 40ms en bij een infarct juist langer. Apicale HCM, een zeldzame vorm, gaat gepaard met gigantische T-golf inversie in de pre-cordiale leads.[12] Aangezien de veranderingen in de ECG's van HCM ook verklaard kunnen worden door andere hartaandoeningen is het nodig om verdere diagnostische middelen in te zetten.

Dit ECG kan worden uitgebreid tot een holteronderzoek. Hierbij draagt de patiënt gedurende 24 tot 48 uur een mobiel ECG kastje bij zich en houdt hij of zij een dagboek bij van de activiteiten die gedurende

de dag worden uitgevoerd. De cardioloog beoordeeld aan de hand van de ECG uitslagen en het dagboek of HOCM inderdaad de passende diagnose is.[13]

4.1.1 Inspanningstest

Tijdens de inspanningstest wordt een ECG gemaakt die inzage geeft in de reactie van het hart op inspanning. De patiënt wordt gevraagd om plaats te nemen op een hometrainer en gedurende 3 minuten langzaam te fietsen. Hierna volgen een aantal opdrachten als harder fietsen of fietsen met meer weerstand, waardoor de hartslag toeneemt. De cardioloog breekt de test af als de patiënt een te hoge hartslag bereikt, de patiënt pijn op de borst krijgt, uit de ECG blijkt dat het hart niet genoeg zuurstof krijgt of de patiënt te vermoeid is om door te gaan.[14]

4.2 Echocardiogram

4.2.1 Traditionele echocardiogram technieken

Na het constateren van een verdachte ECG is het maken van een echocardiogram de eerstvolgende stap in het diagnostische proces. Er kunnen verschillende typen echografie worden gebruikt:

M-Mode echocardiografie is de eerst gebruikte techniek en brengt de wanddikte, de kleppen en het septum in beeld. Verschillende indicatoren voor HCM zijn: asymmetrische hypertrofie van het septum, SAM van de mitralisklep, kleine linker ventrikel ruimte, septale immobiliteit en premature afsluiting van de aortaklep. Het linker ventrikel mag niet dikker zijn dan 15mm en de ratio tussen de wanddikte van het septum en het linker ventrikel moet buiten de 1.3 en 1.5 liggen. Als dit wel het geval is kan men al spreken van HCM. [15]

Doppler echografie kan nu worden ingezet om te bepalen of er sprake is van HOCM. Drie typen doppler worden gebruikt en allemaal leveren ze andere relevante informatie om de meest passende diagnose te stellen: [15]

Color doppler wordt gebruikt om te bepalen of er insufficiëntie is van de mitralisklep. Hierbij stroomt bloed terug van het linker ventrikel naar het linker atrium. De richting van deze terugstroom levert informatie voor de cardioloog of deze enkel te maken heeft met een patiënt met SAM (terugstroom in de posterieure richting) of dat de patiënt naast HCM ook nog een pappilair defect of obstructie heeft (terugstroom in de anterior richting).[15]

Continue doppler gebruikt men om het ontstane drukverschil te bepalen door een obstructie, dit noemt men ook wel de gradiënt. Patiënten met linker ventrikel obstructie hebben vaak een drukgradiënt van meer dan 30mmHg. Men moet hierbij wel opletten dat niet de terugstroom gemeten wordt die door de insufficiëntie veroorzaakt wordt. Voornamelijk bij een terugstroom in anterior richting kan dit erg lastig zijn. [15]

Pulsed doppler wordt gebruikt om de aanwezigheid en mate van diastolische disfunctie te bepalen. [15]

4.2.2 Nieuwe echocardiogram technieken

Er zijn een aantal nieuwe technieken, zoals contrast echocardiografie, tissue doppler imaging, strain rate imaging, real time 3D imaging en coronaire flow reserve. Deze verhogen allen het contrast van de traditionele technieken.

4.3 Indicaties

Er wordt in 4 klassen onderscheid gemaakt tussen patiënten met HCM. Deze klassen zijn met hun indicaties en diagnostische technieken opgenomen in tabel 1 van appendix E. [16]

5 Huidige Behandelmethoden

Op basis van de eerder genoemde indicatie worden hieronder de behandelmethodes besproken en contra-indicaties uitgelicht. Er wordt een onderscheid gemaakt tussen de asymptomatische patiënt en de symptomatische patiënt.

5.1 Asymptomatische patiënten

Bij patiënten met HOCM zonder symptomen worden de behandelingen aangeraden die in tabel 2 van appendix E zijn opgenomen. [16]

5.2 Symptomatische patiënten

5.2.1 Medicatie

Bij patiënten waarbij HOCM wel tot symptomen leidt, wordt begonnen met medicatie. Deze medicatie kan bestaan uit: Béta blokkers, verapamil, diuretica, intraveneuze phenylephrine, disopyramide, diltiazem en/of angiotensine blokkers. Het hoofddoel van deze medicamenten is om klachten als kortademigheid, hartkloppingen en pijn op de borst te verminderen. Indicaties per risicoklasse zijn in appendix D opgenomen.

5.2.2 Invasieve therapieën

Wanneer medicatie onvoldoende werkt zijn er twee invasieve therapieën mogelijk om de ernstige symptomen van HOCM te behandelen: een myectomie en alcoholablatie. Bij een myectomie wordt het hypertrofe weefsel weggesneden om zo de obstructie te verminderen. Bij alcoholablatie wordt door middel van een minimaal invasieve ingreep alcohol ingespoten in het hypertrofe weefsel. Hierdoor zal het weefsel afsterven en neemt de dikte van het specifieke segment in het hart af. Om als patiënt in aanmerking te komen voor één van deze invasieve therapieën moet hij of zij aan de volgende

eisen voldoen: de patiënt blijft symptomatisch bij gebruik medicatie, de symptomen moeten veroorzaakt worden door een combinatie van hypertroof weefsel en verplaatsing van de mitralisklep en een gradiënt van tenminste 50 mmHg bij rust of inspanning. Wanneer hieraan voldaan wordt volgt een advies per risicoklasse, zoals opgenomen in tabel 3 van appendix E. [16]

6 Uitdagingen Myectomie

De meest toegepaste chirurgische behandelmethode van HOCM is momenteel een septale myectomie. Hoewel dit momenteel de gouden standaard is, kent de behandeling nog een aantal tekortkomingen. Uit de literatuur blijkt dat er verschillende uitdagingen en verbeterpunten zijn:

- invasief;
- slecht zicht tijdens operatie;
- onnauwkeurige bepaling mate van resectie van het myocard;
- embolisatie van stukjes myocard;
- beschadiging van weefsel/structuren;
  - aortaklepbladen;
  - mitralisklep;
  - chordae;
  - zenuwen, met linkerbundeltakblok als gevolg;
  - septum, met septum defect als gevolg.
- lastige procedure.

6.1 Invasief

Aangezien het hart een zeer belangrijk orgaan is, wordt deze ook goed beschermd door het lichaam. Dit heeft een groot evolutionair voordeel, maar het maakt operaties aan het hart een stuk lastiger. Om het hart te bereiken moet de ribbenkast geopend worden middels een mediale sternotomie, wat als zeer invasief wordt beschouwd. [17]

6.2 Slecht Zicht

Om na de mediale sternotomie toegang tot het hart te krijgen wordt de aorta geopend middels een aortatomie. Vervolgens kan door retractie van het rechter aortaklepblad de linker ventrikel worden bereikt. Het zicht wordt dus beperkt tot een kleine opening in de aortaklep, waar tevens de instrumenten voor de resectie doorheen moeten. Structuren zoals de mitralisklep, de chordae en de papillairspier zijn dan ook lastig te zien. [18] [19]

6.3 Onnauwkeurige bepaling mate van resectie

De hoeveelheid weg te snijden weefsel wordt vooraf bepaald met behulp van de verkregen CMR beelden. Deze beelden worden preoperatief gemaakt, wanneer het hart nog klopt en zich aanspant. Tijdens de operatie wordt het hart stilgelegd en bevindt het hart zich in ontspannen toestand. Prof. dr. Jan Grandjean, thoraxchirurg aan het MST en hoogleraar aan de Universiteit Twente, gaf aan dat hierdoor niet alleen de vorm van het hart, maar ook de vorm van het hypertrofe weefsel veranderd, waardoor het lastig is om te bepalen wat er exact moet worden weggesneden [20]. Hierdoor kan er enerzijds te veel weefsel worden weggesneden, waardoor een linkerbundeltakblok ontstaat of zelfs een septum defect. Anderzijds kan er te weinig weefsel worden weggesneden, waardoor de obstructie niet volledig wordt verholpen en een reïnterventie nodig is.

6.4 Embolisatie

Tijdens het wegsnijden van het hypertrofe weefsel kan het voorkomen dat er kleine stukjes weefsel achterblijven in het hart. Na de operatie kan dit zorgen voor embolieën, doordat kleine vaten verstopt raken. [21]

6.5 Beschadiging Weefselstructuren

Zoals vermeld in paragraaf 6.2 vormt de aortatomie de toegangsweg tot het hart, waarbij door de aortaklep het linkerventrikel kan worden bereikt. De benodigde instrumenten voor de resectie zullen via de aortaklep het hart in worden geleid, waardoor er een kans is op beschadiging van deze klep. Daarnaast is er mede door het slechte zicht een kans dat andere structuren per ongeluk worden geraakt tijdens de resectie. De mitralisklep en de chordae zijn hier voorbeelden van.[21] Verder blijkt uit paragraaf 6.3 dat de hoeveelheid weg te snijden weefsel lastig te bepalen is. Hierdoor zijn beschadigingen aan de zenuwbanen of aan het septum goed mogelijk. Met als mogelijke gevolgen een linkerbundeltakblok en een septum defect. [22]

6.6 Complexe procedure

Tot slot is de procedure erg complex. De behandeling kent een lange leercurve, waardoor enkel de ervaren thoraxchirurgen het uit kunnen voeren. Daarnaast zorgen de benodigde sternotomie en de aortatomie ervoor dat behandeling niet uitgevoerd kan worden door andere specialisten. [19]

6.7 Conclusie

Hoewel HCM een prevalentie kent van 1 op 500, wordt de chirurgische behandeling van HOCM (een myectomie) in het MST in Enschede slechts 10 keer per jaar uitgevoerd [20]. Hieruit blijkt dat er een mismatch is tussen de hoeveelheid patiënten enerzijds en de hoeveelheid behandelingen anderzijds. Dit zal waarschijnlijk deels te wijten zijn aan de beschreven uitdagingen die deze behandeling erg onvoorspelbaar en onnauwkeurig maken. De huidige gouden standaard voor de

behandeling van HOCM vraagt dus om verbetering, waardoor patiënten sneller en vaker geholpen kunnen worden.

7 Technisch Geneeskundige vraagstelling

Met behulp van de gegeven informatie en de uitdagingen is het mogelijk om het klinische probleem om te zetten tot een Technisch Geneeskundige uitdaging. Hierin zal centraal staan dat HOCM een veelvoorkomende aandoening is, maar dat er nog geen nauwkeurige en voorspelbare behandelmethode is. De **hoofdvraag** is dan ook:

Hoe kan het huidige protocol voor septale myectomie worden aangepast om een nauwkeurige behandeling van HOCM te realiseren die het effect van de beschreven uitdagingen minimaliseert?

De bijbehorende **deelvragen** die opgelost moeten worden zijn:

- Wat zijn de uitdagingen voor de behandeling van HOCM?
- Wat zijn de mogelijke oplossingen van de uitdagingen voor de behandeling van HOCM?
  - Hoe opereert men op een kloppend hart?
  - Hoe worden minimaal invasieve hartoperaties uitgevoerd?
  - Zit er een verschil tussen het volume van actief en inactief spierweefsel?
- Welke (gecombineerde) oplossing voldoet aan de eisen voor de behandeling van HOCM en neemt de uitdagingen voor een groot deel weg?
- Hoe kan de oplossing worden geïmplementeerd in het protocol voor de behandeling van HOCM?

8 Methode

Het hoofddoel van deze MDO-opdracht is het ontwikkelen van een verbeterd en betrouwbaarder protocol voor een septale myectomie bij patiënten met HOCM. Om tot dit einddoel te komen, zullen wij stap voor stap de uitdagingen onderzoeken, zoals zal blijken uit de onderstaande methode.

8.1 Literatuurstudie

Een literatuurstudie levert de benodigde kennis over de klinische problemen. Deze problemen worden gedocumenteerd en besproken met experts. Wanneer de problemen zijn geïdentificeerd wordt er gekeken naar de verbeteringen en oplossingen van deze problemen. Dit wordt vervolgens meegenomen in het protocol. Hiervoor worden maximaal 2 weken uitgetrokken waarin 4 mensen fulltime de problemen in de huidige behandelmethode onderzoeken. Om deze problemen op te lossen wordt tegelijkertijd gezocht naar nieuwe, veelbelovende technieken. Voor dit onderzoek worden de volgende zoektermen gebruikt:

- myectomy
- myectomie challenges
- minimal invasive heart surgery
- surgery on beating heart
- volume of active muscle tissue
- volume of inactive muscle tissue
- catheter for removing tissue
- repairing secundary septum defect
- heart pacing
- mitral valve repair
- pappilary muscle correction

Aan de hand van de literatuur die met bovenstaande termen is gevonden, kan de lijst worden aangevuld.

In hoofdstuk 6 worden al een aantal uitdagingen geformuleerd die de basis vormen voor de oplossingsrichting. Het literatuuronderzoek zal zich dus focussen op documenten die een oplossing kunnen bieden voor deze uitdagingen.

8.2 Uitwerken oplossingsrichting

De problemen en oplossingen die zijn gevonden worden na deze 2 weken besproken met de opdrachtgevers. Hier wordt vanuit de technisch geneeskundigen een aanbeveling gedaan voor de meest geschikte oplossingsrichtingen, met daarbij de eigen voorkeur voor de beste optie. Aan de hand van het advies van de begeleiders en een eigen beargumentatie wordt een beslissing gemaakt voor de beste oplossingsrichting. Bij deze beargumentatie staan de uitdagingen centraal zoals beschreven in paragraaf 6. Uit de literatuurstudie zal blijken welke oplossingsrichting de uitdagingen het beste zou kunnen verhelpen.

Na een keuze voor een oplossingsrichting dient deze uitgewerkt te worden. Voor de uitwerking van de oplossingsrichting worden 5 weken uitgetrokken. De gekozen oplossingsrichting dient naar verwachting in die tijd uitgewerkt te kunnen worden. Wanneer besloten is wat de oplossingsrichting wordt, zullen er direct nieuwe deelvragen voor de oplossingsrichting worden opgesteld. De beantwoording van de deelvragen wordt in de planning opgenomen. Gezien de oplossingsrichting nog niet bekend is kunnen we alleen nog maar speculeren over een invulling van deze 5 weken.

8.3 Presentatie en afronding

In de laatste anderhalve week zullen de eindproducten in de vorm van een verslag en presentatie worden uitgewerkt. Het verslag zal zijn geschreven in de Engelse taal en de presentatie wordt gehouden in de Nederlandse taal.

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Appendix

A Tijdsplanning

Week 1	
Di 23 april	Planning maken & Samenvatting MDO/ Workshops
Wo 24 april	Inlezen onderwerp, samenvatting en begin plan van aanpak
Do 25 april	Afspraak met inhoudelijk begeleiders en tutor. Samenvatting MDO afmaken en insturen. Voortgang plan van aanpak bespreken.
Vr 26 april	Plan van aanpak. Klinisch belang, anatomie, pathofysiologie, klinische gevolgen, huidige diagnose en behandelmethodes, vraagstelling, methode en planning af.
Zo 28 april	Deadline insturen samenvatting MDO
Week 2	
Ma 29 april	Ochtend: Niewe behandelmethoden onderzoeken en voorbereiden 'meet the expert.' Middag: behandelmethoden verder uitzoeken en pp meet the expert maken
Di 30 april	Ochtend: Meet the Expert (9:00-10:30). Brainstorm naar problemen en oplossingsrichtingen. Middag: Verwerken in plan van aanpak
Wo 1 mei	Ochtend: Plan van aanpak af. 12:00 Deadline Plan van aanpak naar begeleiders versturen. Middag: presentatie PvA maken.
Do 2 mei	9:00 Bespreking begeleiders. Plan van aanpak presenteren. Feedback plan van aanpak verwerken en aanvullingen. Tijdsplanning invullen aan de hand van het plan van aanpak en de nieuwe oplossingsrichting.
Vr 3 mei	Plan van aanpak
Week 3	
Ma 6 mei	09:00 Groepsreflectie moment. Rest van de dag: Plan van aanpak
Di 7 mei	12:00 Deadline Plan van aanpak naar begeleiders en inleveren. Literatuuronderzoek
Wo 8 mei	literatuuronderzoek
Do 9 mei	Literatuuronderzoek. 11:00 Go/no-go bespreking begeleiders. Literatuuronderzoek
Vr 10 mei	Literatuuronderzoek
Week 4	
Ma 13 mei	09:00 Groepsreflectiemoment Literatuuronderzoek
Di 14 mei	Literatuuronderzoek
Wo 15 mei	Literatuuronderzoek
Do 16 mei	Literatuuronderzoek Onder voorbehoud: Gesprek begeleiders over voortgang literatuuronderzoek
Vr 17 mei	Literatuuronderzoek
Week 5	
Ma 20 mei	09:00 Groepsreflectiemoment Literatuuronderzoek
Di 21 mei	Literatuuronderzoek uitwerken tot voorstel
Wo 22 mei	Literatuuronderzoek uitwerken tot voorstel
Do 23 mei	09:00 Brainstorm begeleiders: Voorleggen voorstel en andere gevonden opties bespreken. Middag: Begin uitwerken gevonden oplossingsrichting
Vr 24 mei	Uitwerken oplossingsrichting

Week 6	
Ma 27 mei	09:00 Groepsreflectiemoment
	Uitwerken oplossingsrichting
Di 28 mei	Uitwerken oplossingsrichting
	Tussenevaluatie met tutor
Wo 29 mei	Uitwerken oplossingsrichting
Do 30 mei	Hemelvaartsdag
Vr 31 mei	Bridgeday

Week 7	
Ma 3 juni	09:00 Groepsreflectiemoment
	Uitwerken oplossingsrichting
Di 4 juni	Uitwerken oplossingsrichting
Wo 5 juni	Uitwerken oplossingsrichting
Do 6 juni	Uitwerken oplossingsrichting
	Onder voorbehoud voortgang overleg begeleiders
Vr 7 juni	Uitwerken oplossingsrichting

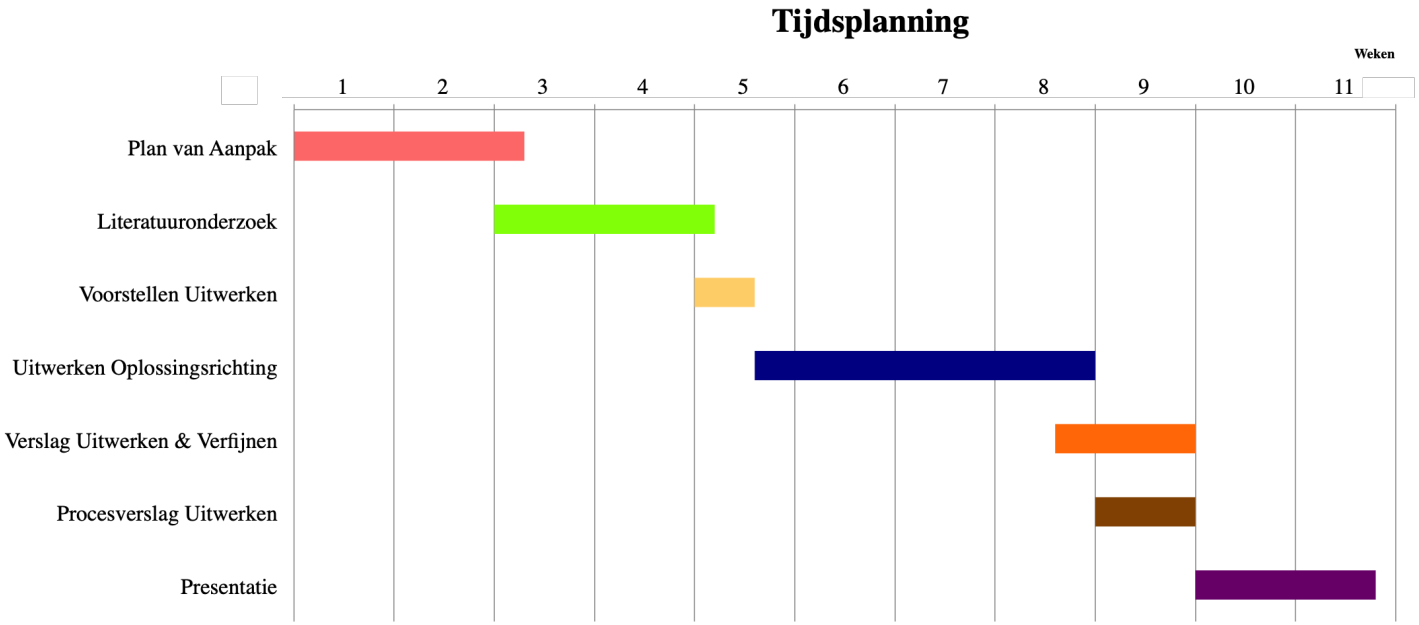
Week 8	
Ma 10 juni	Tweede Pinksterdag
Di 11 juni	09:00 Groepsreflectiemoment
	Uitwerken oplossingsrichting
Wo 12 juni	Masterclass presenteren
	Uitwerken oplossingsrichting
Do 13 juni	Uitwerken oplossingsrichting
	verslag uitwerken
Vr 14 juni	Uitwerken oplossingsrichting
	Verslag uitwerken

Week 9	
Ma 17 juni	09:00 Groepsreflectiemoment
	Groepsdeadline wetenschappelijk verslag
Di 18 juni	Verslag verfijnen
	Inhoudelijk procesverslag
Wo 19 juni	Verslag verfijnen
	Inhoudelijk procesverslag
Do 20 juni	09:00 Gesprek begeleiders
	Verslag verfijnen op basis van feedback
Vr 21 juni	Verslag verfijnen
	Inhoudelijk procesverslag

Week 10	
Ma 24 juni	09:00 Groepsreflectiemoment
	13:00 Deadline wetenschappelijk verslag
Di 25 juni	13:00 Deadline inhoudelijk procesverslag. 17:00 geprint inleveren bij docent professioneel gedrag.
	Presentatie maken
Wo 26 juni	Presentatie maken
Do 27 juni	Presentatie maken
Vr 28 juni	Presentatie maken

Week 11	
Ma 1 jul	09:00 Groepsreflectiemoment
	Presentatie maken en oefenen
Di 2 jul	Presentatie maken en oefenen
Wo 3 jul	Presentatie maken en oefenen
Do 4 jul	Eindpresentatie

B Tijdsplanning Gantt-Diagram



Figuur 3: *Tijdsplanning weergegeven in een Gantt-Diagram*

C Anatomie

Het hart bestaat uit twee atria en twee ventrikels, welke op hun beurt zijn onderverdeeld in een linker en een rechter variant. De atria en ventrikels zijn beide gescheiden door een septum. In het ventriculaire septum loopt de bundel van His, deze splitst zich in linker en rechter bundels en gaat in de vrije wanden over in de Purkinje vezels. Deze structuren zorgen voor een goede elektrische geleiding voor de propagatie van de contractie.

De rechter harthelft krijgt zuurstof-arm bloed aangevoerd uit het lichaam en pomp dit naar de longen, zodat zuurstof opgenomen kan worden en CO_2 kan worden afgegeven. Hierna stroomt het zuurstofrijke bloed in de linker harthelft, die op zijn beurt weer het bloed de periferie in pompt. De atria en ventrikels zijn gescheiden door hartkleppen.

Tussen de atria en ventrikels bevinden zich links de mitralis- en rechts de tricuspidalisklep, tussen de ventrikels en de grote en kleine bloedsomloop bevinden zich respectievelijk de aorta klep en pulmonalisklep. De mitralisklep en tricuspidalisklep zitten beide, door middel van chordae tendineae, vast aan de papillairspieren van het hart, waardoor de kleppen openen tijdens de diastole.

Vanuit het linker ventrikel wordt het bloed de aorta ingepompt. Direct boven de aortaklep bevindt zich de coronaire ostia. Dit is de ingang naar het coronair systeem wat bestaat uit de rechter coronaire arterie en de linker coronaire arterie. De linker splitst vrijwel direct op in de linker arterie descendens (LAD) en de linker arterie circumflex (LCx). Het bloed uit de coronaire arteriën wordt weer opgevangen door de cardiale venen, de linker atrium vene en de linker ventrikel vene. De coronaire venen monden uit in de coronaire sinus, die in verbinding staat met het rechter atrium.[2]

De wand van het hart is op te delen in 3 stukken: Het endocard, het myocard en het epicard.[1] De ventrikels, atria en alle kleppen zijn bekleed met endotheel, dit heeft een anti stollende werking in het hart. De wanden van de atria en de ventrikels en het onderste deel van het ventrikelseptum, bevatten voor een groot deel myocard. Het myocard bestaat uit hartspierweefsel, wat zich onderscheidt van skelletspierweefsel door grotere mitochondriën, minder en centraal gelegen celkernen en de aanwezigheid van intercalaire schijven.[4]

D Medicatie

Patiënten die symptomen vertonen door de HOCM wordt begonnen met medicatie. Béta blokkers, verapamil, diuretica, intraveneuze phenylephrine, disopyramide, diltiazem en angiotensine blokkers behoren tot de opties van de cardioloog. Het hoofddoel van deze medicamenten is om klachten als kortademigheid, hartkloppingen en pijn op de borst te verminderen. Indicaties per risicoklasse zijn als volgt[16]:

- Klasse I: Bèta-blokkers (contra-indicaties: sinus bradycardia of ernstige geleiding aandoening), verapamil bij uitblijven verbetering bij gebruik bèta-blokkers (contra-indicaties: hoge druk gradiënten, ver gevorderde hartfalen of sinus bradycardia). Intraveneuze phenylephrine als er acute

hypotensie optreed en er geen reactie is op toedienen van vocht.
- Klasse IIa: Bèta-blokkers of verapamil. Bij uitblijven effect kan disopyramide of orale diuretica worden gebruikt.
- Klasse IIb: Bèta-blokkers met screening op bijwerkingen. Bij uitblijven effect kan orale diuretica worden toegediend. De werking van angiotensine receptor blokkers en angiotensine omzettend enzym inhibitoren is nog niet echt bewezen. Diltiazem kan worden gebruikt als de patiënt verapamil niet goed accepteert.
- Klasse III: Als er bij gebruik van medicatie contra-indicaties zijn voor patiënten dienen deze niet te worden toegediend, omdat ze schade kunnen toebrengen.

E Tabellen

Klassen HCM	Indicaties	Diagnostiek
Klasse I	Profijt veel groter dan het risico. Voor dit type HCM toont onderzoek aan dat behandeling uitgevoerd moet worden.	12-lead ECG, herhaald bij verergerde klachten. 12-18 maandelijkse ECG screening als er op de echo geen HCM kon worden vastgesteld. 1e-graads familieleden screenen met een 12-lead ECG. Deze patiënten krijgen ook een holteronderzoek en een trans oesophagaal echocardiogram (TEE). De TEE dient om de 12-18 maanden herhaald te worden. Bij deze patiënten wordt geen inspanningstest gedaan. Een MRI is mogelijk als op de TEE niks gevonden wordt.
Klasse IIa	Profijt groter dan het risico. Er zijn onderzoeken beschikbaar over dit type HCM, maar die dienen nog met gerichte onderzoeken aangevuld te worden.	Holteronderzoek en bij bekende HCM een 12-lead ECG. Iedere 1-2 jaar een TEE en inspanningstest. MRI als TEE niet voldoende is en er apicale hypertrofie en/of een verdenking op een aneurysma is.
Klasse IIb	Profijt bijna gelijk aan het risico. Er zijn al onderzoeken beschikbaar, maar die dienen nog met breed onderzoek aangevuld te worden.	Holteronderzoek, MRI alleen als er indicatie is dat de patiënt een dodelijke hartstilstand kan krijgen.
Klasse III	Geen profijt of zelfs schade. Er is bekend dat een behandeling niet werkt of zelfs schade aan kan brengen.	Geen onderzoeken.

Tabel 1: *Klassen HCM met bijbehorende indicaties en diagnostiek[16]*

Klassen HCM	Behandeling
Klasse I	Comorbide hartaandoeningen behandelen.
Klasse IIa	Gezonde levensstijl aanhouden. Veel bewegen en gezond eten.
Klasse IIb	Geen behandeling of bèta-blokkers. De werking van bèta-blokkers is nog niet goed gedefinieerd.
Klasse III	Therapie ter verkleining van het septum, vasodilatoren of diuretica kunnen schade toebrengen aan deze patienten.

Tabel 2: *Behandeling Asymptomatische patiënten[16]*

Klassen HCM	Behandeling
Klasse I	Reductie van het septum.
Klasse IIa	Overleg met ervaren centra over septale myectomie en alcoholablatie. Septale myectomie kan worden uitgevoerd bij ongevoeligheid voor medicatie. Als de patiënt erg oud is of de operatie brengt een onacceptabel risico met zich mee kan alcoholablatie als therapie worden ingezet.
Klasse IIb	Septale myectomie of alcoholablatie zijn beiden een optie. De voorkeur ligt bij myectomie, omdat bij patiënten met een gradiënt van meer dan 30mmHg alcoholablatie niet effectief is gebleken. Echter, kan alcoholablatie wel uitgevoerd worden als de patiënt hier een duidelijke voorkeur aan geeft.
Klasse III	Contra-indicatie voor myectomie: asymptotische patiënten. Contra-indicaties voor alcoholablatie: Ingrepen voor andere hartaandoeningen, waardoor er ook meteen een myectomie uitgevoerd kan worden. Patiënten jonger dan 21. Daarnaast luidt het advies om alcoholablatie te voorkomen bij patiënten jonger dan 40.

Tabel 3: *Behandeling Symptomatische patiënten[16]*

Appendix B – Table of treatments of HOCM based on classification

RISK CLASSES	INDICATIONS	DIAGNOSTIC INTERVENTIONS
CLASS I	Profit from treatment significantly out ways the risks. For this type of HOCM literature supports executing treatment.	- 12- lead ECG, repeated when complaints get worse. - 12-18 months ECG follow up when ultrasound does not confirm HCM. - Holter monitor examination - Screening of 1st degree family members with 12-lead ECG. - TEE, 12-18 months follow up. - Endurance test - MRI when TEE is inconclusive.
CLASS IIA	Profit from treatment probably out ways the risks. Literature for this type of HCM misses answers to small research questions.	- Holter monitor examinations - 12-lead ECG when diagnosed with HCM - Every 1-2 years TEE and endurance test - MRI when TEE is inconclusive and apical HCM and/or aneurism is suspected
CLASS IIB	Profit from treatment almost the same to the risk. Little literature is available and great research questions remain to be answered.	- Holter monitor - MRI on indication of possible sudden cardiac death
CLASS III	No profit or even harm from treatment. It is known that treatment doesn't work.	- No diagnostic tests.

Table B.1: Treatment of asymptomatic patients.

RISK CLASSES	TREATMENT OPTIONS
CLASS I	Treat comorbid heart diseases
CLASS IIA	Lifestyle changes , e.g. healthy diet and exercise daily.
CLASS IIB	No treatment or beta-blockers. Effects of beta-blockers are not well defined.
CLASS III	Therapy to reduce HCM. No vasodilators or diuretics, as they can cause harm to the patient.

Table B.2: Treatment of asymptomatic patients.

RISK CLASSES	TREATMENT OPTIONS
CLASS I	Reduction of the septum
CLASS IIA	- Inform specialized centres about the best treatment: Septal myectomy or ASA - Preferably septal myectomy, if the patient is too old or surgery causes unacceptable risks, ASA can be performed
CLASS IIB	Preferably septal myectomy, but ASA remains an option. If the patient's gradient is over 30 mmHg a septal myectomy is more effective. However, if the patient prefers an ASA, this procedure can be performed.
CLASS III	No treatment, because of contra-indications: - No septal myectomy when asymptomatic. - No ASA when: the patient requires additional treatment for comorbidities that require open heart surgery (if so, a septal myectomy is performed) or if the patient is younger than 21. The advice is to prevent ASA for patients younger than 40.

Table B.3: Treatment for symptomatic patients.

Appendix C – Challenges of the Septal Myectomy

As described in paragraph 1.6 a septal myectomy is the golden standard in the treatment of HOCM. However, this treatment has several challenges:

- Invasive therapy[59]
- Limited visibility[16,17]
- Inaccurate determination of the resection size[18]
- Embolization of the myocardial tissue[19]
- Damaging of important structures[19]
- aortic valve cusps
- mitral valve
- chordae
- nerves, with a LBBB as a result
- Septum, with a septal defect as a result
- Difficult procedure to perform[17]

C.1 Invasive therapy

The heart is an important organ and is therefore well protected by the body. This has an evolutionary advantage, however it makes cardiac surgery more difficult[59]. To get access to the heart, the rib cage is opened by using a median sternotomy. This approach is considered invasive.

C.2 Limited Visibility

In order to get access to the heart after a median sternotomy, an aortotomy is performed. Retraction of the right coronary cusp provides a passageway to the LV[16,17]. The LV is visualised through the opening in the aorta. This opening is also used as an entranceway for the instruments used during surgery, which limits the visibility.

C.3 Inaccurate determination of the resection size

The size of hypertrophic tissue is determined by using echocardiographic images or by using CMR images. These images are made preoperatively when the heart is beating. However, during surgery the heart is cardioplegic. The heart is therefore relaxed and both the shape of the heart and the hypertrophic tissue changes[18]. This results in a more complex procedure, which may result in either of two outcomes. On the one hand, cutting away too much tissue may induce a septal defect or a LBBB. On the other hand, cutting away too little tissue may not reduce the obstruction, which makes reintervention necessary.

C.4 Embolization of the myocardial tissue

While cutting away the hypertrophic tissue, there is a risk of embolization of myocardial tissue particles. After surgery, this may cause damage throughout the body[19].

C.5 Damaging of important structures

As described in paragraph C.2 an aortotomy provides the passageway to the heart via the aortic valve. The needed instruments are also inserted through this passageway. Therefore, these instruments may cause damage to the aortic valve. Another problem is the limited visibility. Therefore, important structures such as the mitral valve, the papillary muscles and the chordae are poorly visible. During surgery, these structures may be overlooked, resulting in damage of the structures. The inaccurate resection provides the biggest risk of damage. This may cause damage to the conduction system of the heart and may cause a septal defect[20].

C.6 Complex procedure

Due to the high degree of complexity involved in performing a septal myectomy, the training required by a surgeon to perform it is extensive. Therefore, only few experienced thorax surgeons can perform the surgery[17].

Appendix D – Research Questions

The main question of this research is:

How can the treatment of HOCM be improved in order to realise an accurate treatment which minimizes the described challenges of the septal myectomy?

Based on this main question, several sub-questions are formulated:

1. What are the challenges in the treatment of HOCM?
2. What are viable solutions to the challenges of the current treatment of HOCM?
    a. How is an open-heart surgery performed?
    b. How is a minimally invasive heart surgery performed?
    c. What are the differences between the contracted heart and the relaxed heart?
3. Which (combined) solution takes away (most of) the challenges of the septal myectomy?
4. How can this solution be implemented in the current treatment of HOCM?

Answers to these questions are:
Question 1: change in anatomy due to cardioplegia, limited visibility, chance of ventricular septal defect and a chance of partial or complete heart block
Question 2: The Literature Report of Appendix F is dedicated to answering this question.
Question 3: The advice given in the Literature Report of Appendix F answers this question.
Question 4: Paragraph 5.3 answer this question by suggesting a way to implement the (combined) solution into the clinic.

Appendix E – Search Strategy of Literature Study

A literature study is performed with the goal to obtain information about the current treatment techniques involved in curing HOCM. Another goal is to find new techniques that could be used in the future to optimise the treatment of HOCM. The literature study is divided in four challenges:

1. Access routes to the heart
2. Reduction of hypertrophic tissue
3. Preoperative planning
4. Intraoperative demarcation and localisation of the hypertrophic tissue

For each of these challenges, several solutions are given. These solutions are either given in the literature, or they are invented during brainstorms. The solutions are further investigated in which the mechanism of the technique is investigated, as well as the advantages and disadvantages. The scientific articles were found using several digital databases, such as Scopus, Google Scholar, PubMed, and LISA (online library of the University of Twente). The reference lists in the found articles were also used to find interesting articles in the topic. In addition, several experts were interviewed to get a better understanding of the techniques used in the daily practice. These experts are specialists in the fields of MRI imaging, ASA, and cardiac surgery. At last, each of the authors were invited to the cardiothoracic OR in the MST in Twente. It was not possible to witness a septal myectomy. Therefore, an aortic valve replacement and coronary artery bypass grafting surgery were witnessed. During these days in the OR, several surgeons were questioned, as well as other members of the medical staff.

Search terms used in challenge 1:

- Open cardiac surgery
- Minimally invasive Myectomy
- Surgery on beating heart
- Endoscopic cardiac surgery
- Robot-assisted cardiac surgery
- Radiation in cardiac surgery
- Endovascular entryways

Search terms used in challenge 2:

- Ablation methods
- Thermal ablation
- Cryoablation
- Radiofrequency ablation
- Acoustic surgery
- Radiation techniques
- ASA
- Septal Myectomy
- Modern surgery techniques

Search terms used in challenge 3:

- Preoperative cardiac imaging
- Practice surgery
- Visualisation of cardiac anatomy
- 3D printed heart
- 3D cardiac computer models
- Ultrasound of heart
- MRI heart
- CT heart

Search terms used in challenge 4:

- Intraoperative ultrasound
- Use of CT during cardiac surgery
- Intraoperative MRI
- Surgery guidance systems
- Assisted surgery
- Robotic Surgery

The search terms above were the base of the literature study. Based on these terms, other search terms were formed which enabled further investigation of the topics and techniques.

Appendix F – Literature Report

F.1 Challenge 1 - Access routes to the heart

F1.1 The surgical entry ways

The current route for a septal myectomy is straightforward[60,61]. The surgeon makes an incision over the length of the entire sternum and cuts the sternum open. Both sides of the chest are pushed aside, and the pericardium is opened to gain access to the heart. The heart is inspected and, depending on the way the surgeon wants to enter the heart, the apex of the left ventricle or the ascending aorta is opened. Through the apex, the left ventricle is immediately visible. Through the aorta, the aortic valve has to be pushed aside to see the left ventricle (Figure F.1) .

Now access to the left ventricle is gained and the septal myectomy can start[21]. The benefit of this entry way is that the surgeon has plenty of workspace and has immediately gained access to the aortic and mitral valve, which is useful if repair is necessary. Nevertheless, this procedure is the most invasive way to enter the thorax and therefore has a longer recovery period and a higher chance of postoperative complications.

A septal myectomy can also be performed with a minithoracotomy[22]. With the help of a computed tomography (CT)-scan the location of the ascending aorta is determined.

The surgeon checks whether 50% of the ascending aorta is positioned at the lateral side of the right sternal border. He also checks whether the anteroposterior distance from the sternum to the ascending aorta is less than 10cm. These criteria make the myectomy easier to perform, but are, if not fulfilled, not a complete contraindication. In most cases a right parasternal minithoracotomy is performed through an incision in the second intercostal space of 4-5 cm. When the intercostal space is not big enough, the third costal cartilage can be dislocated, and it can be pushed out of the way. A femorofemoral cardiopulmonary bypass is inserted and the heart is stopped. Through a transverse aortotomy the left ventricle is entered and the myectomy can be performed in the normal fashion.

When the aorta meets the specified criteria, a minithoracotomy has the benefit of a less invasive treatment with less recovery time and less postoperative complications compared to a sternotomy, but with the same view inside of the left ventricle[21].
Disadvantages are a small working space and a longer aortic cross clamp time when operating through an apical minithoracotomy.

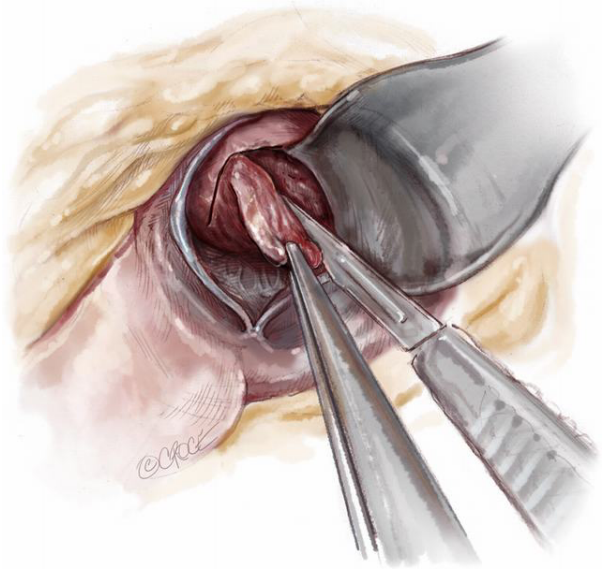


Figure F.1: View of the surgeon into the aorta. In this picture the septum is resected[62].

F.1.2 Endoscopic techniques

Another way of gaining access to the heart is via endoscopic techniques. The robot assisted-approach is described. Different endoscopic approaches, which are interesting but not (yet) for the treatment of HOCM, are described in F.5.4.

F.1.2.1 Robot-assisted

The robot-assisted approach cannot be performed on a beating heart[24,25]. After the patient's right lung is deflated, 3 ports at the third, fifth, and seventh intercostal spaces are inserted. The robot is docked to those ports using a topographic approach. Cardiopulmonary bypass is instituted using the femoral artery and vein cannulation. Now both lungs are deflated, and robotic instruments are used to open and tack the pericardium to the chest wall. The left and right atria are separated. Next, the left atrium is incised, and the left atrial retractor is inserted. The mitral valve can be inspected. The anterior leaflet is opened to identify the septum and aortic valve, whereupon the hypertrophy can be resected.

An advantage of the robot-assisted approach is that it is less invasive than the Morrow procedure[23,24]. The visual sight is good, and the procedure can be performed accurately. However, the intervention is difficult to perform for the surgeon.

F.1.3 Endovascular ways

There is a variety of endovascular access ways to reach the hypertrophic septum. In an antegrade approach, the vena cava superior or inferior is used to access the right atrium. In order to ablate the hypertrophic septum, the left atrium is accessed through the atrium septum by performing a transseptal puncture (TSP)[32]. Then the catheter is positioned onto the septum via the mitral valve. A transseptal puncture can stabilise the catheter, this can also be achieved by rapid pacing of the ventricles[63].

Sometimes the hypertrophic septum is too large for adequate access using the antegrade approach. In that case, a retrograde approach can be used instead to access the left ventricle. A femoral or radial artery is used to access the aorta and to reach the left ventricle through the aortic valve[64]. If the ablation or embolization takes place in the septum, the catheter is inserted through the coronary ostium. The ostium is accessed through the aorta using a transfemoral or trans-radial retrograde approach. The septal branches are connected to the left anterior descending (LAD) artery, which originates from the left main coronary artery[65].

Advantages of percutaneous endovascular interventions are a shorter hospitalisation and recovery time and less postoperative discomfort[26]. However, these procedures need to be performed in experienced hospitals and the ability to perform relies on the coronary and peripheral anatomy of the patients.

F.1.4 Access from the outside

The accessways described in the previous paragraphs all require some percutaneous incision and are therefore invasive accessways. However, there are also accessways which do not require an incision. Possibilities are:

- using a needle;
- using radiation.

F.1.4.1 Needle

There are several ways in which access to the heart is gained by using a needle[29]. However, structures like the ribs and the lungs make the passageway more complicated. In order to make this passageway minimally invasive, these structures must be avoided. In figure F.2 the anatomy of the viscera and bones in the thorax are shown. There is a small opening in the fourth intercostal space on the left side where the apex of the heart can be entered without puncturing the lung. This is a narrow opening and it does not allow much movement of the needle. Preoperative surgical planning might be a solution in order to get the best angle for needle injection.

A disadvantage of this accessway is the risk for major complications, such as ventricular arrhythmias, pneumothorax, hypotension etc[29].

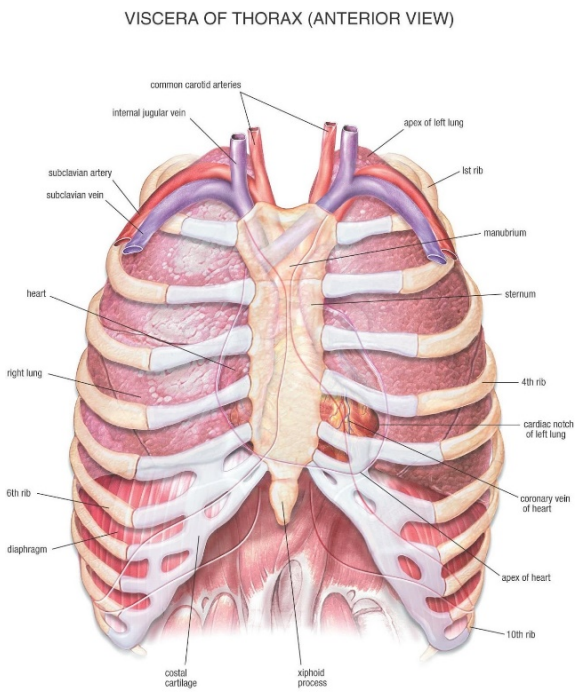


Figure F.2: Small passageway for the needle in the left ICS 4[66].

F.1.4.2 Stereotactic Radiation

Radiation is a broad physical term and it can be used to gain access to the heart without the need of a needle or an incision. The term radiation is defined by 'the emission or transmission of energy in the form of waves or particles through space or through a material medium' and it includes[67]:

- Electromagnetic radiation
- Particle radiation
- Acoustic radiation
- Gravitational radiation

Gravitational radiation cannot be used in medical applications, but the other three types of radiation can be and already are used to interact with tissues. Some examples:

- Electromagnetic radiation is used in radiofrequency ablation[68]
- Particle radiation is used as a therapy for cancer[69]
- Acoustic radiation is mainly known as ultrasound imaging, but it can also be used as therapeutic ultrasound in for example High-Intensity Focused Ultrasound[70].

Electromagnetic waves comprise many kinds of waves: from radio waves with low energy levels to gamma rays with high energy levels. The authors of this report think that in order to interact with the hypertrophic cardiac tissue, a certain resolution is required to avert unwanted damage. Therefore, waves with a short wavelength are needed, but these waves have high energy levels. This causes one big disadvantage: the capability of inducing mutations in DNA[30]. This makes radiation a controversial topic when using it for benign diseases. However, the treatment of benign diseases may require a low to intermediate dose (3-50 Gy) which reduces the risk for Radiation Induced Cancer (RIC)[71]. Besides, modern techniques can deliver the radiation with such accuracy, that the consideration of using it in HOCM must be considered.

Particle radiation is acquired by radioactive decay in which radioisotopes lose subatomic particles. The main categories are, from low penetration depth to high penetration depth: alpha, beta, gamma, and neutron radiation. All the particle radiation types have ionizing capabilities and can, therefore, induce mutations in our DNA. Therefore, this type of radiation has the same disadvantages as electromagnetic radiation[72].

Acoustic radiation, known as sound waves, propagates as a longitudinal wave by creating compression and decompression in a medium. It is a non-ionizing type of radiation according to the International Commission of Non-Ionizing Radiation Protection (ICNIRP). Therefore, it may provide a safer type of radiation to reach the hypertrophic septum. Currently, acoustic waves are used in High Intensity Focused Ultrasound. The use of this technique is described in Appendix F.2.3

F.2 Challenge 2 – Reduction of the Hypertrophic Tissue

F.2.1 Septal Myectomy

To perform a septal myectomy you enter the heart using one of the "surgical entry ways" described in the previous section. With the help of echo, CT and/or CMR imaging the location, size and amount of obstruction caused by the hypertrophic tissue can be determined. The surgeon localises intraoperatively the area where the obstruction is. Unfortunately, hypertrophic tissue changes volume and shape in a cardioplegic heart[18]. The amount of tissue that must be removed is predetermined using the imaging (thickness, length, width). This amount is removed by the surgeon using a number 10 or 11 scalpel or surgical scissors (Figure F.3)[60,61]. In both open chest surgery and the minithoracotomy procedure the hypertrophic tissue is removed in the same way.

An advantage of this procedure is that the excess hypertrophic tissue is immediately removed, so no tissue that is blocking the LVOT remains present. This means that there will be almost no chance of a follow up procedure, since the drop in gradient is immediately achieved and measured. Unfortunately, there is still a chance of intraoperative death (1%), complete heart block (1,5%), permanent pacemaker implant (5-10%), septum defect and coronary dissection[31]. Nevertheless, this method of reducing the septal thickness remains the gold standard in the MST[18].

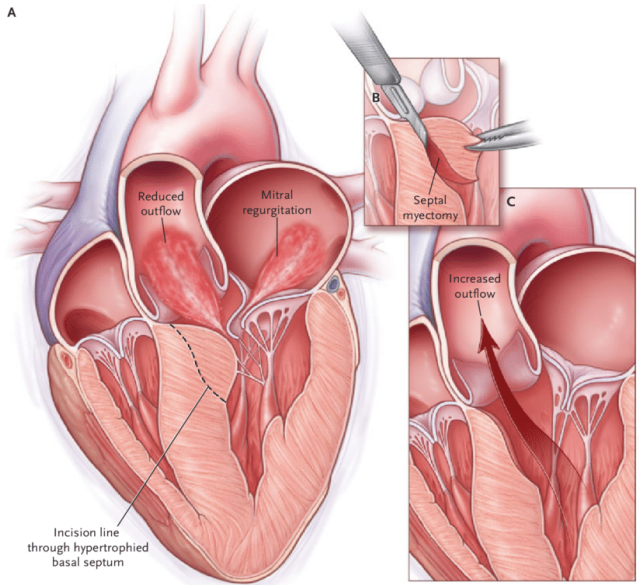


Figure F.3: Septal myectomy procedure[73].

F.2.2 Ablation

F.2.2.1 Alcohol septal ablation

By using a catheter, access is gained to the aorta which leads to the coronary ostium. The catheter is guided through the LAD into the first septal branch. Then a balloon catheter is guided over the guidewire and inflated in the first septal branch (Figure F.4). This occlusion will minimise the escape of alcohol into the LAD[27,33,65]. TTE is used to decide whether the chemical ablation of the first septal branch is sufficient to reduce the LVOTO. An ultrasound contrast agent is used to determine which septal branches provide the hypertrophic area of oxygen. If the right septal branch is found, the alcohol is injected at a rate of one millilitre per minute with a total volume millilitre per ten millilitres septum. After the ablation, there will be a five to ten-minute waiting time to minimise the risk of complications. After the procedure, there is a significant drop in LVOT gradient and the minimally invasive approach results in less discomfort for the patient. However, ASA has a high number of postprocedural temporary AV or right bundle branch blocks and sometimes a pacemaker is needed[26]. Furthermore, the ASA procedure is not suitable for someone with difficult coronary anatomical structures such as coronary collaterals and misplaced septal branches.

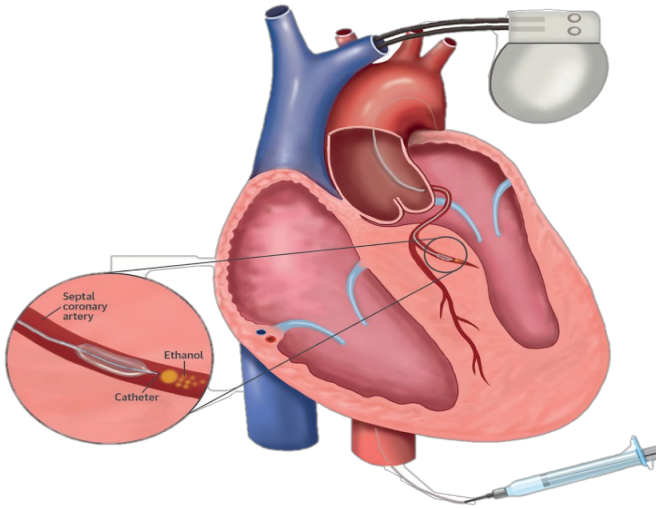


Figure F.4: ASA procedure. This figure shows how the first septal branch is ablated with alcohol[74].

F.2.2.2 Radiofrequency ablation

Radiofrequency ablation is already a common treatment for various arrhythmias. However, it is not the standard ablation technique for HOCM. A couple of exploratory studies are performed, and they show promising short-term effects[28,32,63]. For this treatment, a sheath is inserted in both the femoral vein and femoral artery. The venous sheath is used to obtain antegrade access to the right atrium[32,63]. The arterial sheath is used for invasive real time blood pressure measurement or retrograde access, when necessary. First a Quadripolar diagnostic catheter is inserted to locate the His bundle. Then a 10 polar catheter is inserted in the coronary sinus, as a reference for the mapping catheter. Subsequently, the 12 polar mapping catheter is inserted through the tricuspid valve into the right ventricle after which it is guided through the atrial septum and the mitral valve in the left ventricle. Once both ventricles are mapped, the ablation quantity is determined. This is done by using concentric circles that show the ablation time. Concentric circles are used in order to create a clear border between ischemic tissue and the hypertrophic myocardium and in order to ablate the right amount of tissue. The tissue is ablated using an alternating electrical current which induces thermal damage to the cells[75].

Radiofrequency ablation shares most advantages with ASA, such as shorter hospital stays and less discomfort [28,32,63]. Other advantages are no dependency on coronary anatomy and more precise ablation. This technique comes with several disadvantages: risks are arrhythmias, such as left bundle branch block and total heart block. Furthermore, a retroperitoneal haemorrhage is a risk in all catheter-based treatments.

F.2.2.3 Embolization of septal coronary artery

A newer approach for reducing the LVOT gradient in HOCM patients is the use of subcutaneous fat or a coil to obstruct the first and/or second septal coronary artery[34,76–78]. Using the coronary entry ways, a catheter with a balloon is placed in the designated area. An ultrasound contrast fluid is injected to image the septal tissue supplied with blood from the first septal coronary artery. The first septal coronary artery is occluded with subcutaneous fat or two to three coils. This fat or these coils will stop the blood from reaching the enlarged part of the septum, thus causing it to infarct. This infarction results in a significant drop in LVOT gradient immediately after stopping the blood flow through the septal coronary artery, like alcohol septal ablation.

Only a few case studies and some bigger reports have been published and all these reports seem very promising. In one study[31] an average gradient drop of 60 mmHg is achieved over 19 patients. Results of all these reports seem to encounter the same complications as those seen in alcohol septal ablation, but less severe and less frequent[34,76–81].
Benefits of this approach are expected to be less complications for patients with a septal thickness of 15-20 mm compared to alcohol septal ablation[34]. A downside of this technique is that it is quite new and there are few studies available confirming its superiority over alcohol septal ablation.

After speaking to an interventional cardiologist it became clear that this method will not be usable, because the septum is not only perforated by the first septal branch of the coronary arteries[27]. There is a chance hypertrophic part of the septum is supplied with blood by more coronary arteries and therefore, the obstruction of just the first septal branch will not be sufficient.

F.2.3 High intensity focused ultrasound (HIFU)

HIFU is an acoustic modality using ultrasound energy focused to operate on an internally targeted tissue without damaging overlying and/or underlying tissues as described in Subsection F.1.4.2[35].

The HIFU energy delivery to the heart is controlled by an algorithm that recognises a beating cycle. This algorithm controls the computer aided HIFU energy delivery to the atrial septum, based on predictions of the right timing. A 2D-US tomographic image, including the atrial septum, shows the motion of the beating heart. The HIFU delivery timing is determined by using this image[35]. In a study, focal myocardial lesions were created with 200-millisecond HIFU pulses gated tot the electrocardiogram. The lesions ranged in length from 2 to 6 mm, depending on the dose used. The focal lesions in the mid myocardial wall spared both endocardial and epicardial surfaces[82].

F.2.3.1 HIFU in combination with MRI

MRI can provide image guidance for HIFU targeting and performs real-time monitoring of myocardial temperature during ablation. An MRI-guided HIFU ablation system can be used on a 3T MRI scanner. MRI scout imaging can be performed to identify and guide the myocardial treatment areas to the septum. During lesion formation MR thermometry can be performed to verify correct ablation location and achievement of thermal ablation threshold (>55 C°). T2-weighted imaging can be used to image lesions post-ablation. [Bron 3 Swaminathan]

The advantages of HIFU are that the technique is not invasive and precise lesions can be made. The disadvantages are that the technique is only tested on animals and the side effects are still unclear.

F.2.4 Radiation Therapy

RT is mainly known as a therapy against cancer, but it can also be used in benign diseases as described in several researches[71,83,84].It is for example used in several hyperproliferative and inflammatory benign diseases. Nowadays it is not used or researched as a therapy for HOCM, but it could be a future treatment. The two main categories of RT are External Beam Radiation Therapy (EBRT) and Brachytherapy (BT). These two categories will be explained in this paragraph. Afterwards, the consequences of the toxic radiation will be discussed.

F.2.4.1 External Beam Radiation Therapy

Modern radiation techniques can deliver the radiation with such accuracy, that the consideration of using it in HOCM must be considered. These modern techniques are for example: Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT) and Stereotactic Ablative Radiation Therapy (SABR), also known as Stereotactic Body Radiation Therapy (SBRT).

In IMRT the radiation delivery is divided into many smaller radiation beamlets. The intensity of these beamlets vary in order to deliver a high dose to the tumour and a smaller dose to the surrounding tissues. This yields a high dose gradient which makes it useful in the treatment of for example head and neck tumours. Advantages of this technique are the high accuracy and the low dose delivery to healthy tissue[38]. A disadvantage is that, despite the lower dose delivered to healthy tissue, an overall larger volume receives a dose of radiation. Another disadvantage is the excessive cost of this technique.

IGRT uses imaging techniques to improve the accuracy and precision of the RT. Although all radiotherapy uses imaging throughout the treatment, IGRT uses it during the radiation delivery. A wide range of imaging techniques can be used: from radio-opaque seeds to the use of CT[38]. By using these imaging techniques, movement of organs can be compensated, and a higher accuracy can be achieved. Therefore, it is used for example in RT for lung cancer, but it is also used in regions which require a high accuracy such as the neck and head region[85]. IGRT is often combined with IMRT, because the high dose gradient in IMRT needs to be delivered specifically to the target.

SBRT or SABR is a technique which uses small high dose beams to deliver highly targeted radiation. The targeting is also improved in SBRT using imaging during the dose delivery. Metal markers are often needed to track the tumour during the treatment, but newer techniques can also track the tumours without the need of metal markers[38]. Advantages of SBRT are the accurate and high dose delivery and the shorter treatment time. A disadvantage is the dependency well-defined and small tumours which can be seen accurately in the imaging.

F.2.4.2 Brachytherapy

BT is another radiotherapy modality and it differs from EBRT in the fact that in BT the radioactive source is placed inside or next to the region of interest. The advantage of BT lies in this placement: the tumour, or hypertrophic tissue in this case, receives a high dose, whereas the surrounding tissue receives a lower dose due to the rapid fall-off of radiation intensity[86,87]. Although BT was originally a cancer treatment, nowadays it is also used in several non-cancer applications. It is for example used intravascular to prevent restenosis in stents and it is used in several hyperplastic diseases[88–90]. BT offers a diverse range of therapies and can therefore be classified into several different categories[39]: from the source being used to the technique used to load the sources. In the next paragraphs BT will be divided into two categories: permanent and temporary implantation.

Permanent implantation often makes use of radioactive seeds. These seeds consist of a non-radioactive shell surrounding the radioactive source. This is a common treatment for prostate, head and neck cancers[39]. Radioactive sources with low energy or short half-lives are used in order to minimise dose delivery to the people surrounding the patient. Advantages of permanent implantation are the short hospitalisation and the minimally invasive implantation.

In temporary implantation, the sources are only implanted for a limited amount of time. This can be either minutes as in high dose rate (HDR) BT, or days as in pulsed dose rate (PDR) or low dose rate (LDR) BT[39]. The radioactive sources can be implanted with the use of an afterloading system. There are many different afterloading systems, all with their own advantages and disadvantages. An advantage of the use of temporary implantation is the high dose delivery to a specific region of interest. The disadvantages are the dose delivery to hospital staff as well as the longer hospitalisation. The patient has to stay in the hospital during the entire treatment.

F.2.4.3 Cardiotoxicity

The delivery of radiation to the cardiac area entails some risks. As described above in paragraph 2.4.1, radiation with an intensity of 3-50 Gy might suffice in the treatment of benign diseases. Scientists used to think that doses below 30 Gy did not affect the heart. However, in the last years research showed that even lower doses might cause damage to the heart[37]. These risks are covered in the term cardiotoxicity or RIHD. Cardiotoxicity comprises complications such as coronary heart disease, pericarditis, myocardial fibrosis, valvular heart disease and arrhythmias. The exact risk assessment cannot be given, because there are no records of using RT in the treatment of HOCM.

The use of the most modern radiation techniques is advised in order to reduce the risk of cardiotoxicity. With these modern techniques, the radiation can be targeted with high accuracy as described in the paragraphs before. Next to the use of modern techniques, more research must be done to assess the risks. A standardised risk assessment like QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) can be used to give an estimation of the risks involved.

F.3 Challenge 3 - Preoperative Planning

F.3.1 Magnetic Resonance Imaging

There are several MRI techniques that are used to get a visualisation of the heart and its structures. Two categories of these techniques are cardiac magnetic resonance imaging (CMR) and diffuse tensor imaging (DTI). These techniques are described.

F.3.1.1 Cardiac Magnetic Resonance Imaging (CMR)

CMR, also cardiac MRI, is an imaging technique used to get a non-invasive visualisation of the anatomical structures and the function of the heart. It is increasingly used in the diagnosis of HOCM[91], however, ultrasound imaging is preferred in the MST in Twente[40] because of the easy access and sufficient visualisation. If CMR imaging is used, it is used to assess the severity of the hypertrophic tissue and the presence of any myocardial fibrosis using Late Gadolinium Enhancement (LGE)[40]. Implementation of techniques such 4D-flow MRI may increase the use of CMR in the future.

4D-flow MRI provides information about the complex blood flow[92] (figure F.5). When used to assess the blood flow in the heart, it can provide more information about the influence of the hypertrophic tissue in the blood flow pattern. It is possible to use the 4D-flow MRI in the future to model the change in flow pattern after virtual removal of the hypertrophic tissue. If this is possible, it might become a great tool to assess the influence of surgery beforehand. Currently, researchers are investigating the use of computational fluid dynamics (CFD) to model the blood flow in the heart. This might also become an interesting tool in the future[93].

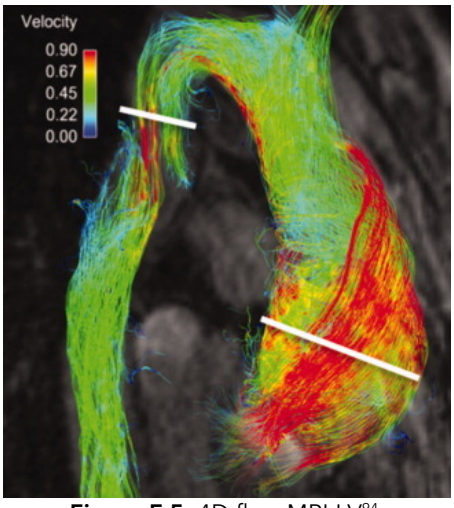


Figure F.5: 4D flow MRI LV[94].

F.3.1.2 Diffuse Tensor Imaging

In DTI specific MRI sequences are used to generate data about the diffusion of water molecules. This technique became important in the tractography of white matter in the brain. However, it can also be used to get a visualisation of the cardiac conduction system[43,44] (figure F.6). DTI is currently not used in the diagnostic process of HOCM, it requires more research in order to become an integrated technique. In the future however, it might become the leading technique for imaging of the microstructure of the heart. By imaging this microstructure, it can provide information about the myocyte disarray and the arrhythmia. Furthermore, it might supply more information to the surgeon about the risk of cutting through nerve tissue during the surgery. However, more research must be done to investigate the possibilities of the use of DTI in the diagnostic process of HOCM.

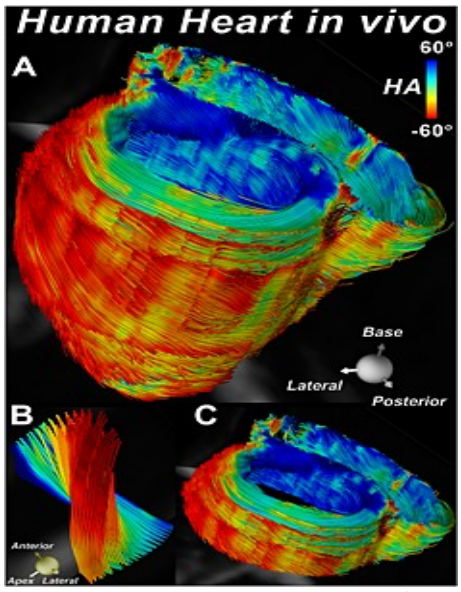


Figure F.6: DTI MRI of the heart. [95]

F.3.2 Ultrasound

Both transthoracic echocardiography and transoesophageal echocardiography are used to visualise the anatomical structures of the heart and the hypertrophy. These techniques are the current workup and described in the next paragraphs.

F.3.2.1 Transthoracic Echocardiogram (TTE)

During a transthoracic echocardiogram a probe is placed on the chest or abdomen to get a visualisation of the heart[45]. The images obtained are either still or moving. The structures of the heart that are visible on TEE include all four chambers, all four valves, the aorta, the pericardium, ascites, pleural effusions, and the inferior vena cava. A transthoracic echocardiogram can be used to diagnose hypertrophy of the heart, a heart attack, infiltration of the heart, weakness of the heart and cardiac tumours. With tissue doppler diastolic function, fluid status and ventricular desynchrony can be measured.

A disadvantage is that the views of structures at the back of the heart are limited[45]. Moreover, TTE is a surface modality, the structures closest to the skin are better visualised than deeper structures. And, like all echocardiography, TTE is limited to function and structure. Considering precise preoperative planning for reduction of the hypertrophy, TTE does not show the hypertrophy well enough.

F.3.2.2 Transoesophageal echocardiography (TEE)

During transoesophageal echography (TEE) a flexible tube with a transducer tip is guided through the patient's throat into the oesophagus. This allows for clearer images of the heart, since the ultrasound beam only has to travel a few millimetres. The aorta, pulmonary artery, valves of the heart, both atria, atrial septum, left atrial appendage and arteries can be visualized and evaluated better with TEE than TTE[47]. 3D-echocardiography clearly shows SAM and the deformed geometry of the LV outflow tract. Both 2D, 3D and doppler images can be obtained from transoesophageal echocardiography. Transoesophageal pulsed doppler echocardiography allows an estimation of the cardiac output and flow velocity profiles of the arteries, such as the left descending coronary artery[46].

During surgery TEE can be used to detect segmental wall-motion abnormalities, myocardial ischemia, infarction, hypovolemia, and hypervolemia. Intraoperative colour doppler TEE allows immediate assessment of the operative results. In patients with hypertrophic obstructive myectomy TEE determines the extent of ventricular myectomy[48].

Disadvantages of TEE are that it takes longer than a TTE. It may be uncomfortable for the patient, who may require sedation or general anaesthesia and a TEE needs a team of medical personnel[49].

F.3.3 3D printed heart

A 3D printed model of the patient's heart may help the surgeon in the visualisation and determination of the size of the hypertrophic tissue. A 3D printed heart can be obtained by the segmentation of CT or CMR imaging. The process from imaging to a 3D printed heart takes about 2 hours[50].

The hypertrophic region can be mechanically cut away to visualise the exact volume that has to be resected during the myectomy[50]. The 3D print can also be used intraoperatively to lay the resected material into the mould, to determine if the right amount of tissue has been removed. (figure F.6) A 3D model was used in two case studies, to perform a septal myectomy. These studies showed better results compared to a myectomy performed without 3D printed models. At this moment, the clinic still uses the 3D printing technology as an addition to the preoperative planning. Since 2017 there are 75 HCM patients who have undergone a septal myectomy with this form of preoperative planning of which 65 HOCM patients. Programs have been started with surgeons from Germany and the United Kingdom to teach this way of myectomy[96].

In another research the surgeons were trained to perform a myectomy by using the 3D model. The 3D models were produced by 3D printing a porous copy of the myocardium and aorta. The density of the real heart was simulated by using a combination of silicone and 2 hydrogels. The surgeon can practice on the flexible 3D printed heart and use his experience to resect an identical piece of tissue in the patient's heart[57].

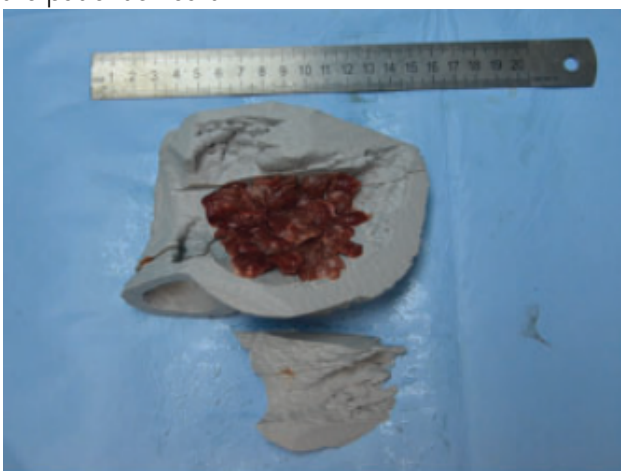


Figure F.6: 3D printed LV septum. At the bottom, the preoperative cut out of the 3D model is shown. Inside the top part of the 3D model the intraoperative cutout of the hypertrophy is placed to see whether the right amount of tissue is resected[50].

All in all, printing a 3D model of the patient's heart could be a useful addition to preoperative planning. Even though it is hard to truly simulate the heart tissue due to its heterogeneous structure and the disability of printing soft tissue.

F.3.4 Augmented Reality (AR)

Creating an augmented reality (AR) heart to use in the operating room (OR) is another way to use 3D models as anatomical support in the operating room [Hansen C] . There are three possibilities: project a 3D model, acquired from preoperative MRI-data, onto the heart of the patient intraoperatively. Hover a 3D model of the heart intraoperatively above the patient. Or use AR as a training modality preoperative[52].

AR as a training modality can be useful when a 3D model is already available, but there is no option to make a tangible model. The 3D model can be coloured to distinguish the different tissues. The surgeon can scroll through the model and is able to visualise the inside of the LV. The other two options can be used as an additional point of view, which can be useful for the surgeon, because of the low vision through the aorta.

However, challenges need to be overcome. One of these challenges is the placement of the AR heart on or above the patient. In order to assure good visibility of the model and positive contribution of the AR, the surgeon's and patient's position needs to be constantly monitored[97]. Only that way the heart can be depicted at the right angle and cannot hover away to a corner of the OR. Direct feedback of the resection plane is possible, but then again there needs to be constant monitoring of the scalpel's placement. Another challenge of this technique is the transition from a beating heart in the preoperative images of the heart to an inactive heart during surgery. This challenge remains a disadvantage as this transition still cannot be modelled. In the ideal situation images can be obtained during surgery and remodeled into an AR image.

F.4 Challenge 4 - Intraoperative demarcation and localisation

F.4.1 Laser guided surgery

To maximise the precision of an incision made by the surgeon, laser guidance can be used. This technique uses preoperative images to determine where an incision must be made and projects this incision line intraoperative on the patient. Currently this technique is developed to guide a needle into tissue, by determining the location and angle to reach the target area, see figure F.7[98]. During septal myectomy it is hard to determine on which angle the scalpel should be pushed into the septum, to prevent a heart block or septum defect and resect the LVOTO. Laser guided techniques could help the surgeon determining the right angle[23].

The problem that arises is that the preoperative imaging does not represent the intraoperative anatomy of the patient's heart[18]. Therefore, Laser guided techniques would only work when intraoperative imaging could be made of the cardioplegic heart. Thereafter, this imaging should be translated to a laser guidance within an acceptable amount of time. If it is possible to make an intraoperative CT-scan that is automatically translated to a laser guide within 5 minutes of time laser guidance could be a great new way to help the surgeon. During these 5 minutes the heart does not have to be restarted. The surgeon can use this time to study the imaging and compare the anatomy of the heart before and after cardioplegia.

F.4.2 3D tracking system

Another method for the intraoperative demarcation and localisation is using a 3D tracking system. The 3D tracking system will provide the surgeon with an action plan for the placement of the instruments. Optical markers will be placed on or inside the instruments, see figure F.8. An optical tracking system follows the markers by using a camera[99]. This is shown on the screen in the operating room. The instructions for the surgeon will also be shown on this screen as seen in figure F.9 [53]. The advantage of this method is that it provides the surgeon with a plan of action and real time feedback about the placement of the instruments. The disadvantage is that tracking is difficult within the complex surgical area of the heart. The technique is applicable in liver surgery but needs much more improvement before it is also applicable in heart surgery.

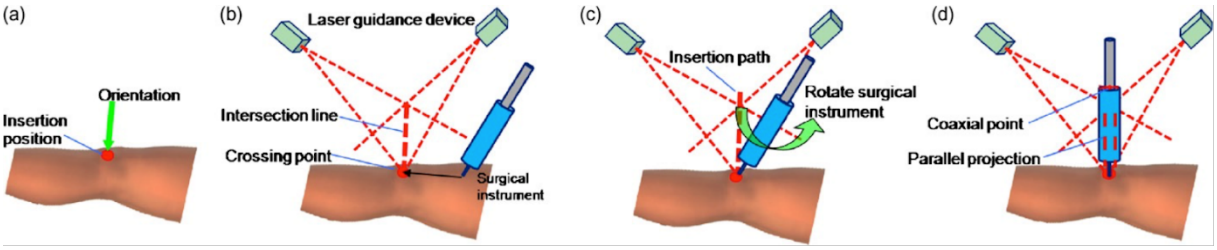


Figure F.7[98]: Procedure of surgical instrument alignment by using a laser guidance system: (a) target in surgical area; (b) move the tip of surgical instrument to the insertion point; (c) rotate surgical instrument and adjust its orientation; (d) align surgical instrument to the target orientation by using coaxial point or parallel projection lines.

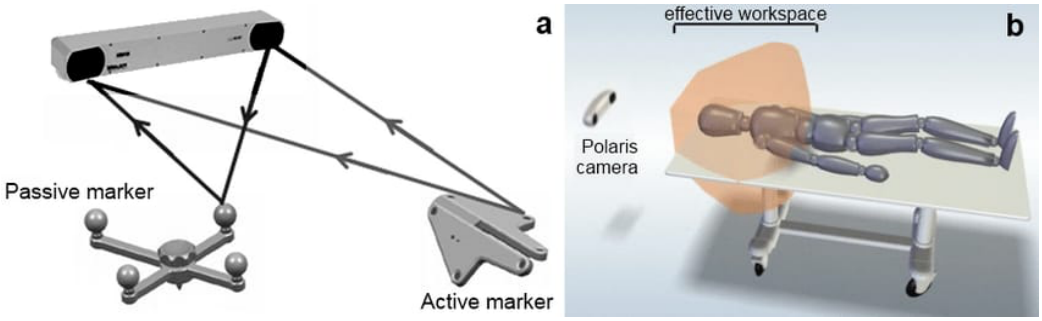


Figure F.8: 3D tracking system using optical markers. (a) The NDI Polaris intra-operative navigation system can track two or more rigid bodies (sets of markers) at a time, providing the position and orientation of the two frames relative to each other. (b) Effective workspace of the Polaris Vicra camera. (Courtesy of NDI.) Theory and method to enhance computer-integrated surgical systems[101].

Figure F.9[53]**:** Placement of the navigation system in the operating room.

F.4.3 Cutting mould & Aortaplug

F.4.3.1 Cutting Mould

At last the method that already has been researched was looked at. This method relies on a 3D printed mould with a hypertrophic recess. The hypertrophic recess is a cavity the exact same volume and shape as the hypertrophy of the patient's heart, see figure F.10[54]. The mould will be inserted through the aorta into the left ventricle. Then, the cavity will be shoved over the hypertrophy. When the hypertrophy is secured in the mould, a semi-circular knife will cut into the hypertrophic septum. The cut hypertrophy is secured inside the mould and can be removed out of the ventricle safely.

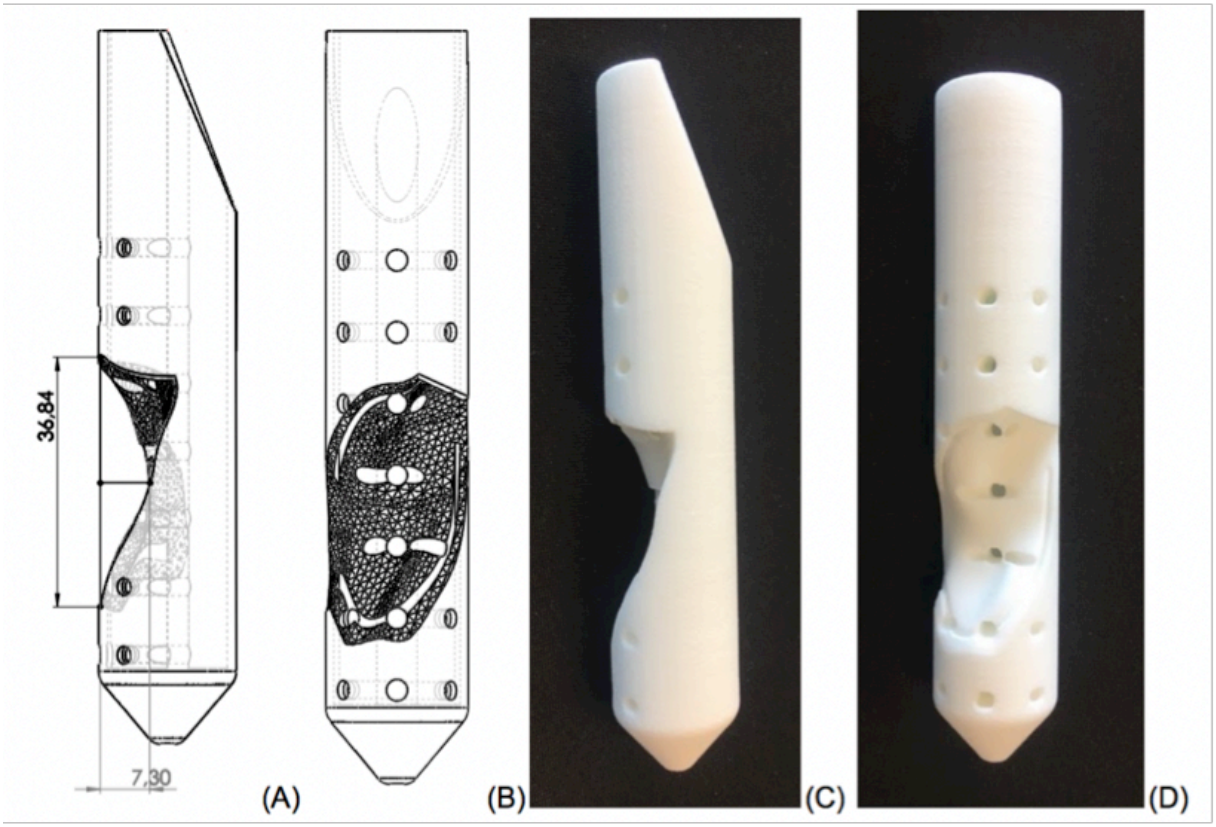


Figure F.10: The final version of the 3D printed cutting mould, made by Technical Medical bachelor students during their bachelor's thesis. *(A), top view (B) and printed cutting mould; right view (C), top view (D)* [54]

One of the advantages of this surgical technique is the uniformity. The technique can be standardised, so the resection does not rely on the surgical skills and complications can be reduced to a minimum. Furthermore, this technique might reduce the chance on embolization due to residual pieces of the septum in the ventricle. On the other hand, there are some challenges that need to be overcome. For example, it is hard to get the correct placement of the septum in the mould. During surgery, the heart is cardioplegic and the muscle tension is absent, which will cause a change in the anatomy of the septum and might cause a different fit into the hypertrophic recess. Another challenge is the intraoperative imaging, which can be used to check if the mould is placed right. It is expected that the mould will scatter most of the US signal. Therefore, it is important to make sure the probe is placed at the right position to get optimal imaging.

F.4.3.2 Aorta plug

In addition to the cutting mould an aorta plug can be designed. The goal of an aortaplug is to enable per-operative imaging with TEE. The aorta plug will provide a way to fill the heart with a fluid and raise intraventricular pressure. After inserting the 3D cutting mould the aorta plug is positioned as a ring along the cutting mould just above the height of the aortic valve. Additionally, physiological saline is inserted into the left ventricle via the 3D cutting mould. Inserting the fluid has two advantages: the placement of the 3D cutting mould on the hypertrophy can be assessed and the pressure could raise, which could lead to a better representation of the active heart in its inactive state. The aorta plug prevents the fluid from leaking alongside the 3D-cutting mould. When the 3D-cutting mould is indeed in the right position, the hypertrophy can be resected.

F.5 Searches without potentially interesting results

When searching for the best way to treat a disease, there will always be some disappointments, because not every idea will be supported by literature. Clinical technician students learn a lot about recent technologies, and they will use their creativity when implementing these techniques into the clinical problems they face. In this literature study there were also a couple of creative ideas that deserved to be looked into. In this chapter the ideas that could not be validated by literature and thus showed less potential will be discussed.

F.5.1 Cryo- and thermal ablation

Cryoablation and thermoablation are two ablation methods that respectively freeze or heat tissue to damage it. In the heart, cryoablation is already used for the treatment of cardiac arrhythmias[102]. This procedure is performed through the coronary arteries. There was no evidence in the literature that a transthoracic cryoablation could be performed.

The area that is frozen or heated by the needle will affect all the tissue in a spherical radius. Therefore, the needle must be placed in the middle of the hypertrophic tissue to prevent damaging the electrical system of the heart. Because this is not possible through the septal coronary arteries that supply the hypertrophic septum area, cryo- and/or thermoablation are no viable options to treat HOCM.

F.5.2 Nanoparticles

Nanoparticles (NP) can be used as contrast agents to differentiate ischemic tissue from healthy tissue, map angiogenesis, help identifying extracellular matrix remodelling and detect inflammation[103]. Future perspectives using NP's as contrast agent (CA) include making the translation from new NP synthesis to clinical trials and testing for diagnostic and therapeutic purposes more frequent. Therefore, NP's could help determine how severe the HCM has affected the heart's muscle tissue. This in turn, can help in planning the surgery.

NP's are also used for therapeutic purposes like stimulating angiogenesis to help cure a myocardial infarction[104] or help destroying tumour tissue[105]. Unfortunately, there is not yet any published literature about using NP's to cure patients with HOCM. Currently there can only be speculated about the therapeutic capabilities of NP's. NP's which induce cytotoxicity to myocardial tissue are suitable to destroy the thickened part of the septum and thus help reducing the LVOT gradient [106,107]. Nevertheless, this will give comparable results as ASA and therefore, will not add any value to this treatment.

For nanoparticles, the diagnostic domain of HOCM remains a field of opportunities, but the therapeutic domain probably will not benefit from this kind of research.

F.5.3 Bubbles

Micro bubbles have several purposes in the medical field for example in monitoring, diagnostic and therapeutic applications. Together with ultrasound, bubbles can cause a cavitation. The cavitation produces high pressures and temperatures, microbubble expansion and collapse. The collapse can lead to cellular damage or haemorrhage in biological tissues[108]. Resecting the hypertrophic tissue in patients with HOCM by bubble explosions still is a non-realistic idea. The damage created by bubbles in biological tissue is small. The therapy is at most enough to explode small and solid structures, and is for example used to explode thrombosis, kidney stones and the vascularisation of tumours[108–110]. Aside from creating tissue damage, bubbles can also be used to deliver medicine at specific locations in the body. This method can be used to deliver medicine to the heart, however HOCM does not have any specific tissue receptors, which results in non-specific drug delivery[108]. Another idea is filling bubbles with alcohol to disrupt the hypertrophic tissue, this is not yet possible and bubble explosion with alcohol will cause problems to the surrounding tissue. Bubbles can be used as a contrast dye to perceive the extra myocardial blood flow during ultrasound[111]. This technique can be used to evaluate the effect of the myectomy or alcohol ablation on the blood flow of the heart. All in all, bubbles are a promising technique for many different applications in the medical field, nevertheless, they will not be of any use in the development of an improved and reliable treatment for patients with HOCM.

F.5.4 Percutaneous and transapical endoscopic approach

Endoscopic techniques can be used to visualize the inside of the heart and might be able to perform small procedures[112–114]. In a study a percutaneous endoscopic approach was used for transapical aortic valve implantation in pigs, this required one camera port and two endoscopic ports. The study described that the results were promising, however the differences in pigs and humans' anatomy should be kept in mind[112]. In another study intracardiac structures were visualized by a transapical endoscopic approach. The transapical access for the cardioscope can be performed by way of a median sternotomy or a minithoracotomy. The cardioscopy will provide video images and a catheter can be used to perform small actions[114]. Both the studies for percutaneous and transapical approach show interesting results considering less invasive heart surgery with small interventions, however it is not possible to use these techniques for more complicated interventions such as resecting the hypertrophic tissue of the heart septum.

Appendix G – Material Requirements of the Cutting Mould

Material requirements cutting mould

Requirement	Remarks
Hard / stiff	The mould should not deform while sucking in the hypertrophic tissue using the suction system.
Mechanically Strong	The embedded structures, such as a sucking system and an ultrasound probe will weaken the structural stability. Therefore, the material has to be mechanically strong to withstand these structural instabilities.
Sterilizable	During surgery, the mould must be sterile. Therefore, the material must be able to be sterilised before surgery without being damaged.
Ultrasound-compatible	De embedded ultrasound-probe must visualize both the hypertrophic tissue and the cutting mould itself. The printed material must be visual on the ultrasound and it must not attenuate the signal too much (prevent acoustic shadowing).
Affordable	Preferably the material is as inexpensive as possible, but this is not a hard requirement.
Biocompatible	The material can perform with an appropriate host response during surgery. The material will only be in touch with the patient for a brief time and therefore any material will quickly fulfil this requirement. The material should not induce any hypersensitivity reaction.
3D printable	The cutting mould will be designed in SolidWorks® and afterwards it will be 3D printed. Therefore, the used material must be compatible with the 3D printers that were at the disposal of the UTwente or the MST.
Water-resistant	To make use of the material in a water/fluid filled heart, the material should be water-resistant.

Table G.1: Material requirements specifically composed for the cutting mould.

Appendix H – Test protocol of Experiment

H.1 Test protocol - placement cutting mould & resection hypertrophic tissue

Background

For the resection of the hypertrophic tissue to be made, it is of significant importance that the 3D cutting mould is placed precisely over the hypertrophy. During this research there is a need to investigate if the 3D cutting mould can be placed precisely over the hypertrophic tissue and how the placement and the imaging of the placement can be improved. Furthermore, there is a need to investigate whether the 3D cutting mould cuts the hypertrophic tissue precisely.

Goal

To test and improve the accuracy of the placement of the cutting mould and to test the resection the cutting mould makes of the hypertrophic tissue.

Questions of this research are:

1. Does the suction system of the cutting mould work?
2. Does filling the heart with a fluid improve the ultrasound imaging?
3. To what extent is the cutting mould able to cut away the hypertrophic tissue accurately?
    - How accurate is the placement of the cutting mould? (Using the ballistic mould)
    - How hard / easy is the cutting? (using the pig heart?)

Required materials

- Pig hearts (2x)
- Ballistic heart mould
- Ballistic ventricle mould
- Cutting mould
- Rubber gloves
- Ultrasound system
- Large container
- USB stick
- Syringe (20cc)
- Balloon / donut balloon
- Ty-Rap / rubber band / rope /
- Glass / plastic rod
- Cling film
- Tape

Method

The method is separated into the three questions of this research. It is advised to put the pig heart in warm water before the experiment. This will make the tissue more flexible.

Does the suction system of the cutting mould work?

1. Place the pig's heart in the large container without water.
2. Place the cutting mould on the pig's heart, place the hypertrophic recess at the heart.
3. Place the syringe at the suction hole on the cutting mould.
4. Use the suction system of the cutting mould by using a syringe to suck the pig's heart into the hypertrophic recess. Suck step by step and test if the pig's heart is fixed inside the cutting mould.

Does filling the heart with a fluid improve the ultrasound imaging?

1. Place the pig's heart in the large container without water
2. Wrap the cling film around the ultrasound probe and use tape to secure the upper end from leakage. Use the 6C2 probe which delivers the best view.
3. Push the cutting mould through the aorta. When using the pig heart, the aorta is could be by the cutting mould. If not, use a balloon to fully seal the aorta.
4. Use the ultrasound system to get a visual of the different anatomical structures in the heart. Focus on the LV and make an image in which both the interventricular septum and the cutting mould are visible. Use the ultrasound positions shown in the Appendix H.2. Save these images on the USB stick.
5. Next, use the syringe to inject fluid through the fluid channel within the cutting mould. The LV should be filled entirely with water, which can be checked by using the ultrasound.
6. Again, use the ultrasound system to get a visual of the different anatomical structures in the heart. Focus on the LV and make an image in which both the interventricular septum and the cutting mould are visible. Use the ultrasound positions shown in the Appendix H.2. Save these images on the USB stick.

To what extent is the cutting mould able to cut away the hypertrophic tissue accurately?

- *How accurate is the placement of the cutting mould? (Using ballistic mould)*
  1. Place the ballistic gel model at the workplace.
  2. Insert the cutting mould into the left ventricle of the ballistic gel model via the aorta, covering the hypertrophic tissue.
  3. Asses the placement by looking through the gel.
  4. Cut the hypertrophic tissue with the cutting mould.
  5. Take the cutting mould out of the ballistic gel mould and asses if the right amount of tissue is resected. Check the cutout in the gel heart.

- *How hard / easy is the cutting? (using pig heart?)*
  1. Place the pig's heart in the large container without water.
  2. Place the self-made razor blades over the cutting mould.
  3. Push the cutting mould through the aorta. Make sure the hypertrophic cut out is placed at the same height as the hypertrophic bulge in the human heart. (This is just below the aortic valve)
  4. Push the razor blades over the cutting mould and over the hypertrophic cutout.
  5. Pull the cutting mould back.
  6. Check the cutout in the heart using the ultrasound system. Use the ultrasound positions shown in the **Appendix G.2**. Also check the tissue that is in the cutting mould.
  7. If this is the last experiment and the heart is not needed anymore it is recommended to cut the heart open. This will make it easier to assess the cutout made by the cutting mould.

After the experiment, it is recommended to cut the heart open. This provides a better understanding of the anatomy of the heart.

Hypothesis

- The suction system of the cutting mould will work and suck the heart tissue into the cutting mould.
- Filling the heart with a fluid will improve the ultrasound imaging.
- The cutting mould cuts the hypertrophic tissue precisely when placed accurate on the hypertrophic tissue.
- Cutting the pig heart will be hard because the pig heart does not have hypertrophic tissue. Besides, it is still stiff because it was frozen.

H.2 Ultrasound positions

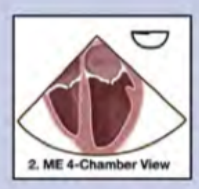
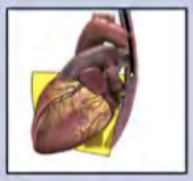
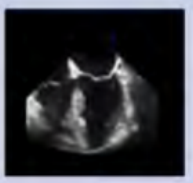
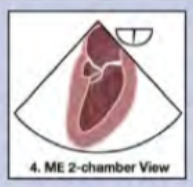
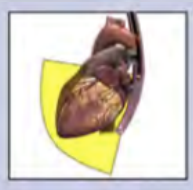
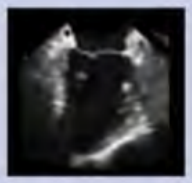
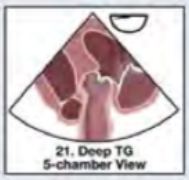
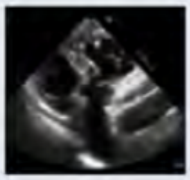
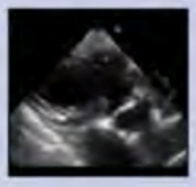
			**Transducer Angle:** ~ 0 - 10^0 **Level:** Mid-esophageal **Maneuver** (from prior image): Advance ± Retroflex	Left atrium/Right atrium IAS Left ventricle/Right ventricle/IVS Mitral valve (A_3A_2-P_2P_1) Tricuspid valve
			**Transducer Angle:** ~ 80 - 100^0 **Level:** Mid-esophageal **Maneuver** (from prior image): NA	Left atrium Coronary sinus Left atrial appendage Left ventricle Mitral valve (P_3-$A_3A_2A_1$)
			**Transducer Angle:** ~ 0 - 20^0 **Level:** Transgastric **Maneuver** (from prior image): Left-flex, Advance, Anteflex	Left ventricle Left ventricular outflow tract Right ventricle Aortic valve Aortic root Mitral Valve
			**Transducer Angle:** ~ 120 - 140^0 **Level:** Transgastric **Maneuver** (from prior image): CCW	Left ventricle Left ventricular outflow tract Right ventricle Aortic valve Aortic root Mitral valve

Table H.1: selection of TEE probe selections that are useful for this experiment [115] .

Appendix I – Lab Report of Experiment

I.1 Background

It is of significant importance that the 3D cutting mould is placed precisely over the hypertrophy, for the resection of the hypertrophic tissue to be made. During this research it was investigated how the placement of the 3D cutting mould over the hypertrophic tissue, how this placement could be improved and how the imaging could be improved. Furthermore, it was investigated if the 3D cutting mould cuts the hypertrophic tissue precisely and if the suction system in the cutting mould worked.

I.2 Goal

To test and improve the accuracy of the placement of the cutting mould and to test the resection the cutting mould makes of the hypertrophic tissue.

I.3 Method

'Test protocol experiment' was used. At the start of the experiment the pig's heart were still too cold and stiff, the pig's hearts were placed into warm water to get warmer and more flexible. Therefore, it was decided to start with the experiments on the ballistic moulds. The ballistic moulds were prepared by cutting them open and taking the 3D printed LV's out. This procedure created two halves, which were put together.

Ballistic mould

On top of the protocol the imaging of the ballistic moulds was tested. One half of the ballistic mould was placed in water and the 6C2 ultrasound probe was used. The cutting mould was placed inside the ballistic mould on top of the hypertrophy. The one halve of the ballistic mould was taken out of the water and the two halves of the ballistic moulds were put together, creating an entire mould of the whole ventricle, this was placed into the water. The cutting mould with the razor blade was placed into the ballistic mould. A movie was made with the improved oval cutting mould, during this movie the hypertrophic ballistic part was resected with the cutting mould. This process was repeated on the other ballistic cutting mould. The volume of both resections was measured.

Pig's heart - Filling the heart with water

To test if filling the heart with a fluid improve ultrasound imaging, the images with and without a filled heart were compared. First part of the long aorta was cut, 2 cm above the aortic valve. Next the cutting mould was pushed through the aorta. A transversal ultrasound image from the front side of the heart was made. A transversal and horizontal image from the hindsight of the heart was made.

During the next step, the heart was filled with water via the holes in the cutting mould. First the ultrasound probe was placed at the hindsight of the heart showing the length of the cutting mould. A movie was made while the heart was filled with 20 mL water via the cutting mould. The water was taken out of the heart. Next the ultrasound probe was placed transversal on the heart and the heart was filled with 20 mL water again.

It was tried to fill the heart with water again by pulling the cutting mould out and push water inside the heart. Next the cutting mould was pushed through the aorta into the LV. A syringe was used to press more water into the heart, water dripped out.

To prevent the water from leaking out a tie wrap was put around the aorta and the cutting mould. Again, the syringe was placed on the hole on top of the cutting mould and water was pushed inside the LV. Still water leaked out of the mould.

Pig's heart - Cutting with the cutting mould

The cutting mould was placed on the outside of the right ventricle. The razor blade was pushed over the cutting mould.

The cutting mould was pushed via the aorta into the LV. The upper end of the razor blade was positioned at the end of the aortic valve, the razor blade was pushed over the cutting mould to resect the tissue. Both the razor blade and the resected tissue were lost inside the LV. The LV was cut open to search for the razor blade and inspect the resected tissue.

Suction System

The syringe was placed at the hole on top of the cutting mould. The cutting mould was placed on the outside of the LV, the cutting mould was pressed onto the LV. The handle of the syringe was pulled back. The cutting mould sucked onto the tissue but required pressure on top of the cutting mould too, by our experimenter.

The experiment was repeated. The syringe was placed at the hole on top of the cutting mould. The cutting mould was placed on the outside of the LV, this time the cutting mould was not pressed onto the LV. The handle of the syringe was pulled back. The cutting mould sucked onto the tissue and the razor blade was pushed over the tissue.

I.4 Results

Ballistic mould

The imaging on the ballistic mould was clear and the hypertrophy was visible. Figure I.4 shows a clear image of the ballistic mould with the hypertrophy. Figure I.5 shows the ultrasound image of the cutting mould inside the ballistic, this picture also proofs that the cutting mould is visible on ultrasound. Figure I.6 shows hypertrophy in the ballistic mould, figure I.7 shows the aorta in the ballistic mould and figure I.8 shows the LV in the ballistic mould. Figure I.9 shows the transversal ballistic mould with the cutting mould. Figure I.10 shows the lateral view of the ballistic mould with the cutting mould and figure I.11 without the cutting mould (Figure I.1). Figure I.12 shows the cutting mould with the razorblade inside the ballistic mould, no major artefacts were created by the mould. The suction canals are visible on this image. Video 1 (Appendix M) is a movie of the cross section of the LV without cutting mould. Video 2 (Appendix M) is a movie of the cross section of the LV with the cutting mould. Video 3 (Appendix M) is a movie of the cutting mould inside the ballistic mould, the movie shows the resection of the hypertrophic ballistic tissue. Figure I.3 shows the ballistic mould with the resected tissue, the resected tissue lays on top of the cutting mould and fits the recess in the cutting mould. The volume of the resection was measured, for both resections about 3cm^3 was resected.

Pig's heart - Filling the heart with water

Figure I.16 shows a transversal ultrasound image of the cutting mould inside the heart with a measurement of the cutting mould. Figure I.17 shows the length of the cutting mould inside the heart. Figure I.18 shows the hypertrophic recess of the cutting mould inside the heart. Video 4 (Appendix M) shows the movie of the heart being filled with 20mL water via the cutting mould. Video 5 (Appendix M) shows the heart being filled with 20mL water when the ultrasound probe was placed transversal on the heart.

Video 6 (Appendix M) and figure 16 show the heart filled with water without a cutting mould. Video 7 (Appendix M) shows the movie of the filled heart with the cutting mould. Video 8 (Appendix M) shows the water getting into the LV. Video 9 (Appendix M) shows how the LV is successfully filled with water.

Cutting with the cutting mould

The volume of the resected tissue was measured: a bit over 2cm^3 was resected.

The LV was cut open to look at the damage made by the cutting mould and search for the lost blade: the aortic valve was damaged.

Suction System

The suction patterns were visible on the heart after taking the cutting mould off. Some tissue (about 2cm^3) was resected but the required amount was not at all obtained.

I.5 Discussion

This experiment tested if the cutting mould can be placed accurately on the hypertrophy, resects the hypertrophy accurately and if the suction system works. Tests were performed on both a ballistic mould and pig's hearts. The ballistic mould is slightly softer than human tissue. However, due to its ability to harden and low viscosity the ballistic gel was very usable during our experiments. The pig's heart represents human tissue, however the pig's hearts that were used had been frozen and were a bit stiff. Cutting on the ballistic mould went smoothly without any problems, cutting on the pig's heart did not go as smoothly. It cannot be concluded if cutting on human tissue will be easy or hard, since the ballistic mould is softer and the pig's heart is stiffer. Furthermore, the blade was blunt and not as sharp as a scalpel. The experiment should be repeated with a fresh pig's heart and a blade as sharp as a scalpel.

The suction system should be improved, during the experiment the cutting mould did stuck on the pig's heart tissue but was not secured entirely, resulting in an incomplete resection. The authors suggest increasing the number of suction holes in the hypertrophic recess, the suction holes should also be implemented in the sides of the hypertrophic recess. Furthermore, a suggestion is made to investigate the possibility of using an octopus tissue stabilizer.

During this experiment it was investigated if filling the heart with a fluid improves the ultrasound imaging. Filling the heart with a fluid via the cutting mould was a challenge. A 20mL syringe was used. The water kept leaking out along the sides of the cutting mould, a plug is necessary to prevent the fluid from leaking out when filling the heart with water. When this conclusion was made, the authors tried to prevent the water from leaking by wrapping a tie wrap around the aorta and cutting mould, so the water stays inside the heart. After 20mL water the heart was full, as the water started to get out of the heart. It is visible that the heart grows but no major differences considering the visibility of the cutting mould on the ultrasound image were seen. When the ultrasound probe was placed transversal on the heart and the heart was filled with 20mL water the same conclusion was made: no major differences considering the visibility of the cutting mould, but the heart did grow. The question whether the heart was really filled with water or if all the water dripped out via a hole somewhere remains. It cannot be concluded if filling the heart with water leads to better imaging, since it is not clear if the heart was really filled with water or if all the water dripped out. It should also be kept in mind that the authors, as technical medical students, are no ultrasound experts. This experiment should be repeated with a 3D cutting mould with a plug/ sealing system, a fresh pig's heart without any holes and an experimenter with better ultrasound skills.

I.6 Conclusions

1. Does the suction system of the cutting mould work?

The suction system of the cutting mould works to some extent. When using the suction system $2cm^2$ tissue can be resected, the required amount is $3cm^2$. It is necessary to improve the suction system.

2. Does filling the heart with a fluid improve the ultrasound imaging?

Filling the heart with water seems to slightly improve the ultrasound imaging but no major differences were seen. When filling the heart with water it is necessary to use an aorta-plug to prevent the water from leaking alongside the cutting mould.

3. To what extent is the cutting mould able to cut away the hypertrophic tissue accurately?

a. How accurate is the placement of the cutting mould? (Using the ballistic mould)

When using the ballistic mould the cutting mould is placed accurately and cuts away the hypertrophic tissue accurately. The cut out fits the hypertrophic recess in the cutting mould. (the $3cm^3$ was resected)

b. How hard / easy is the cutting? (using the pig's heart?)

Using the pig's heart, the cutting is harder. The cut out did not fit the hypertrophic recess in the cutting mould. ($2cm^3$ was resected). When using the cutting mould inside the heart a built-in cutting system where the blade cannot be lost after resecting the tissue is necessary. Furthermore, a suction system is necessary to hold on to the septal tissue, so enough tissue will be resected. We expect that the aortic valve will be protected by a build in recess in the next cutting mould and the built-in cutting system.

Figure I.1: placement of the probe for figure 7 & 8.

Figure I.2: placement of probe for figure 7 and 8.

Figure I.3: ballistic mould with the resected hypertrophy. Cutting mould with the resection and the razor blade.

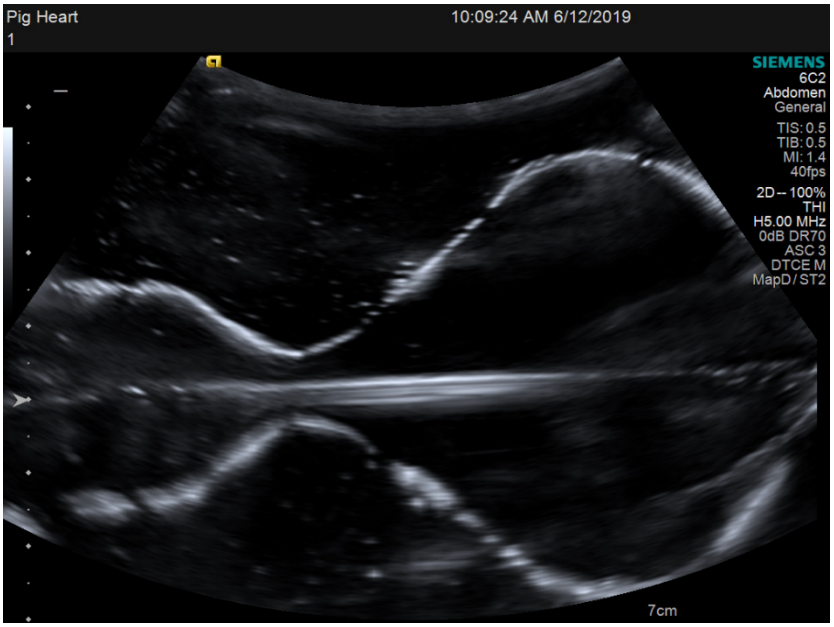


Figure I.4: Ultrasound imaging of the ballistic mould from figure U3.

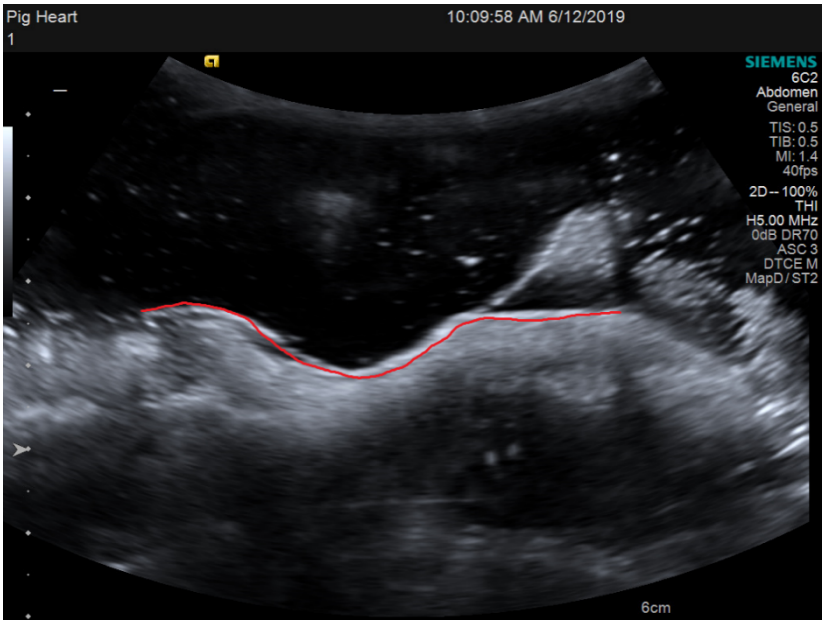


Figure I.5: Ultrasound imaging of the ballistic mould from figure U3 with inserted cutting mould. The cutting mould has been marked in red.

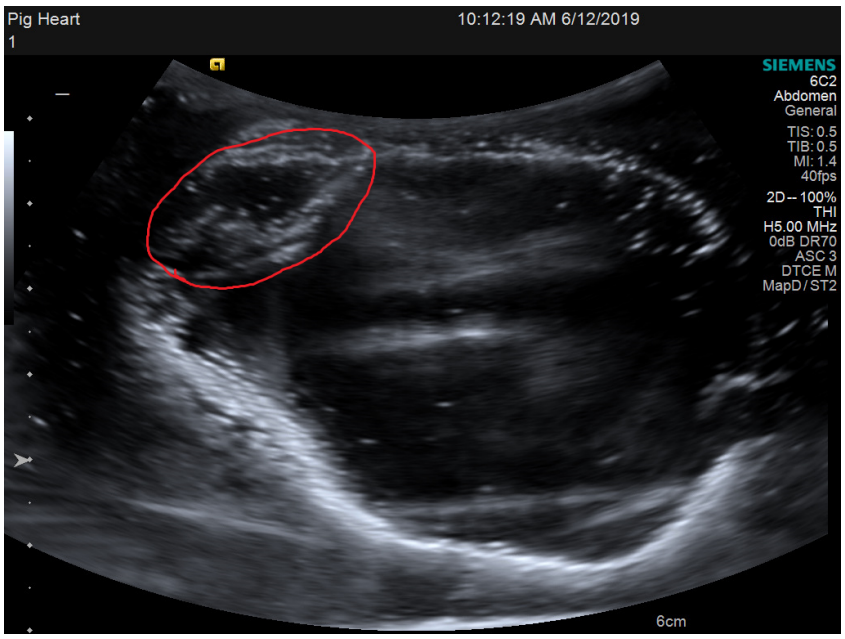


Figure I.6: a view of the hypertrophic section of the heart in the ballistic mould.

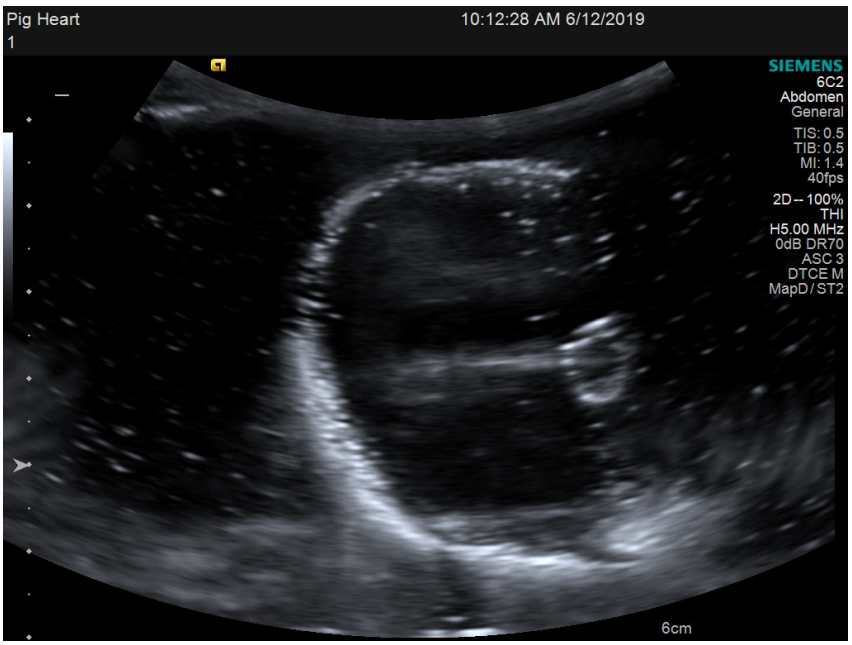


Figure I.7: The aortic section of the ballistic mould just above the hypertrophic section

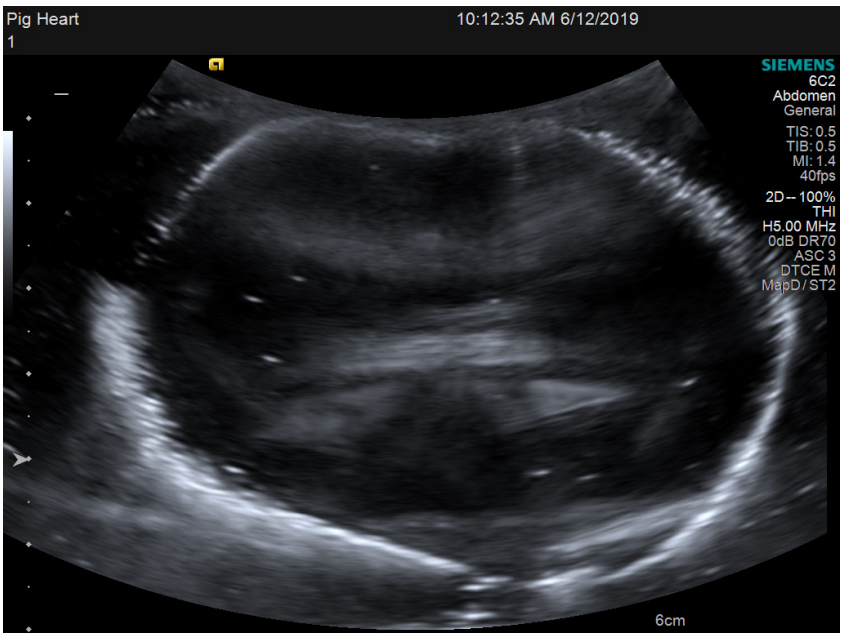


Figure I.8: The myocardial section of the ballistic mould just below the hypertrophic section.

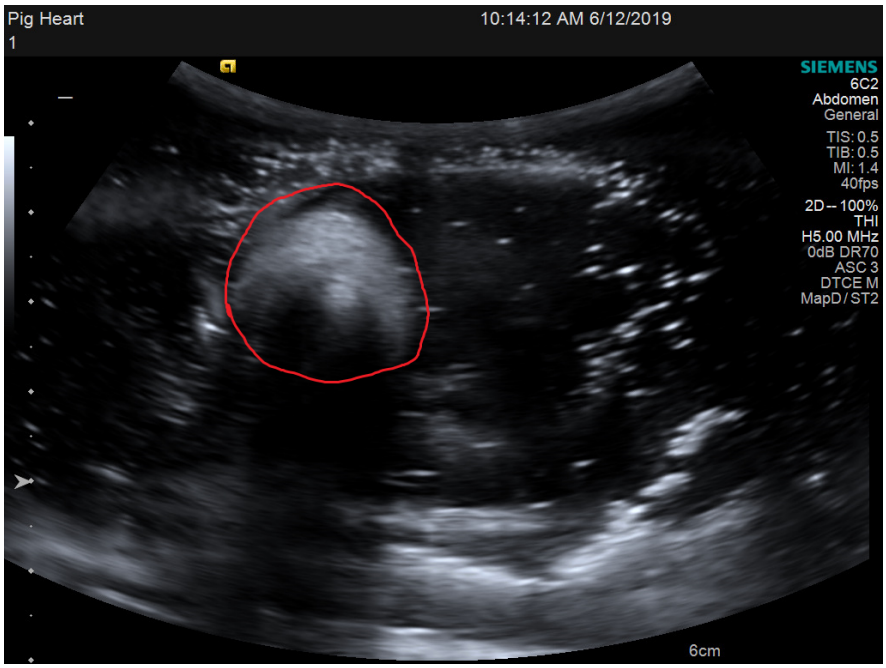


Figure I.9: The cutting mould placed over the hypertrophic portion of the ballistic mould. The cutting mould is marked in red.

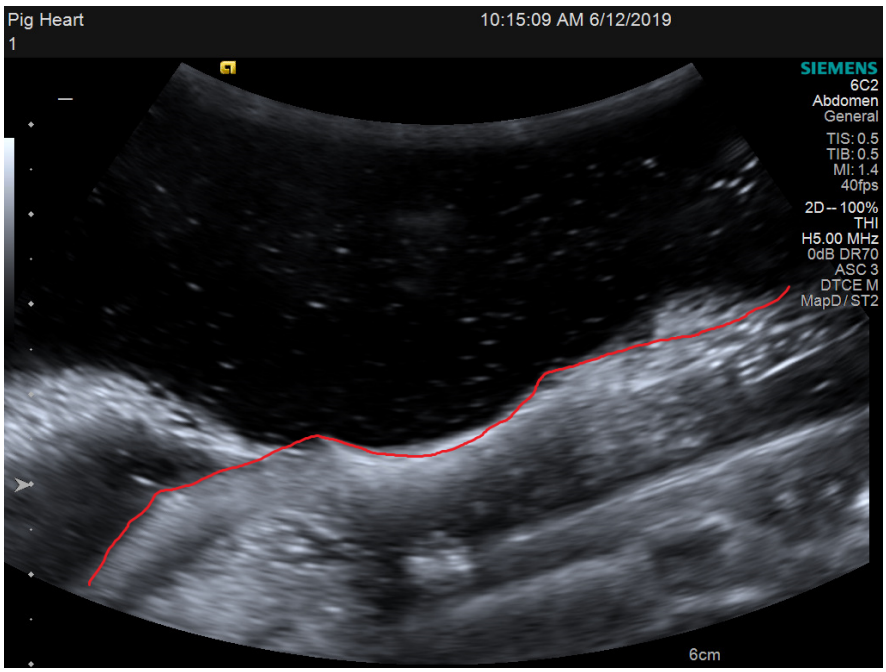


Figure I.10: Cutting mould in the ballistic mould from a lateral view

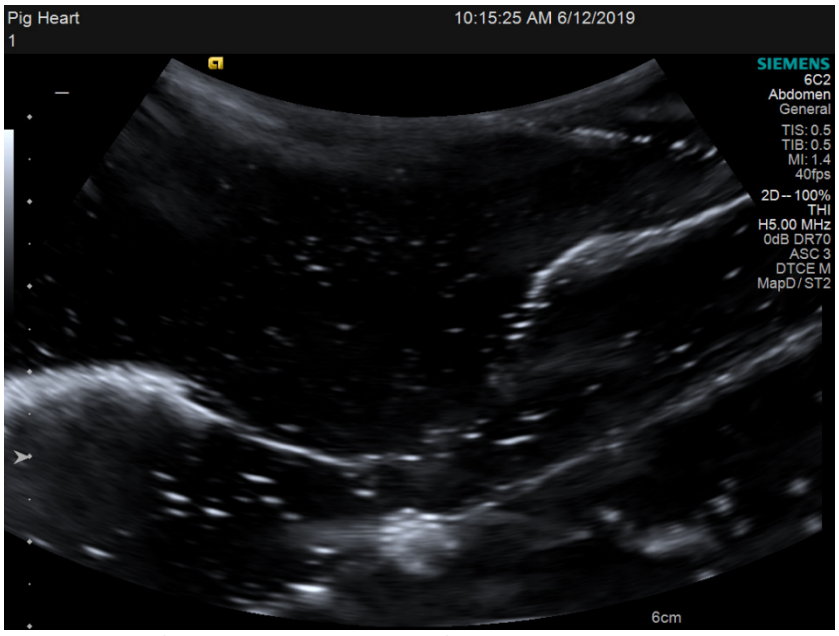


Figure I.11: Lateral view of hypertrophic section of the ballistic mould without the cutting mould.

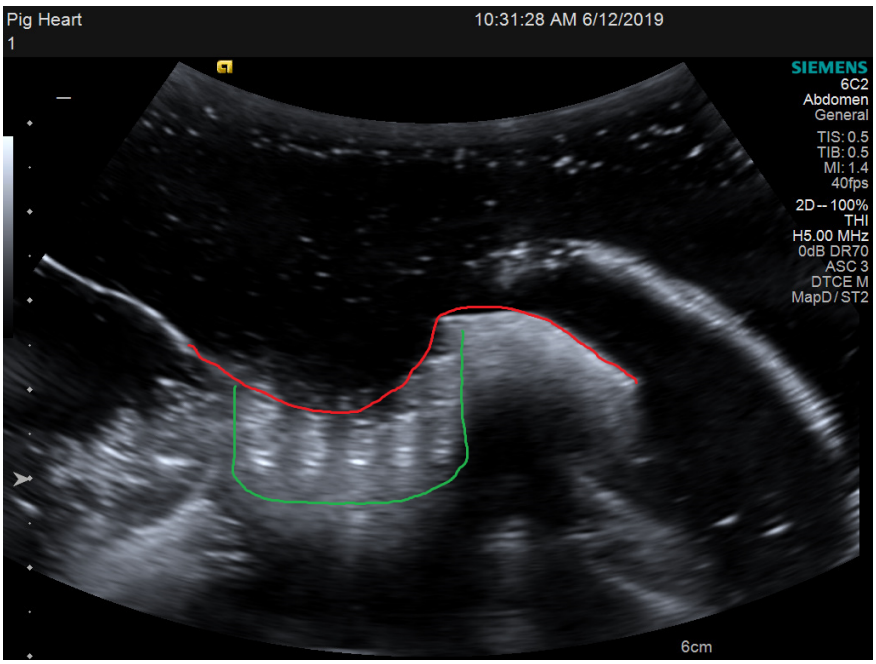


Figure I.12: Cutting mould in the ballistic mould, marked in red. In the green square the suction canals are visible.

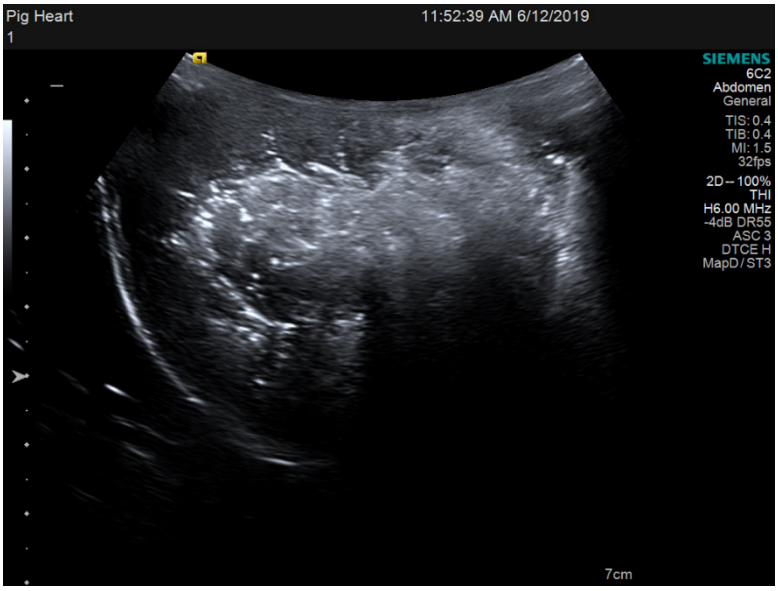


Figure I.13: Ultrasound imaging of the LV of a pig's heart.

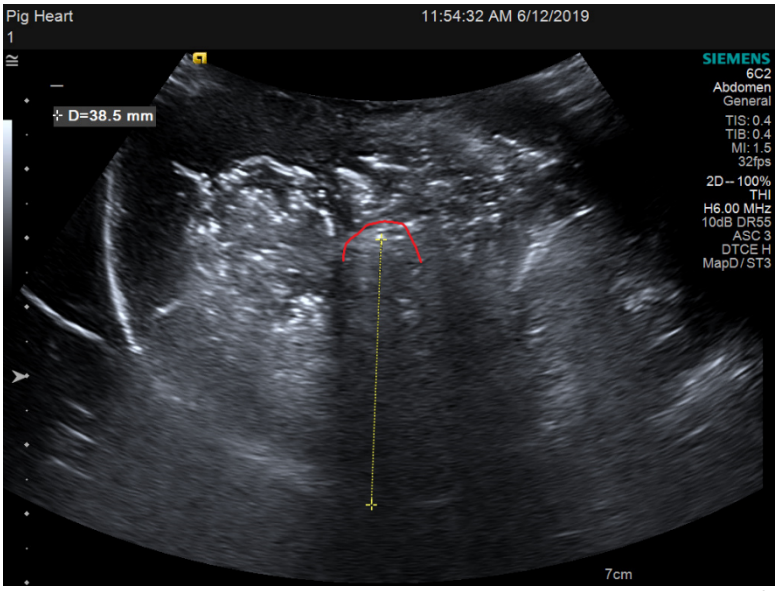


Figure I.14: A tube inserted via the aorta into the LV. Tube marked in red and distance from tube to the anterior side of the heart was measured. (Probe was placed posteriorly on the heart)

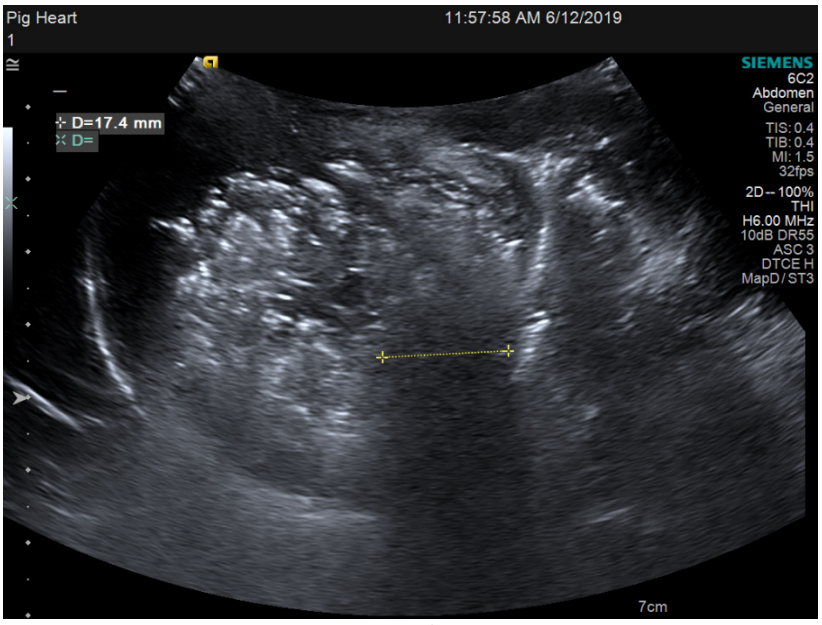


Figure I.15: Measurement of the pig's heart's septum.

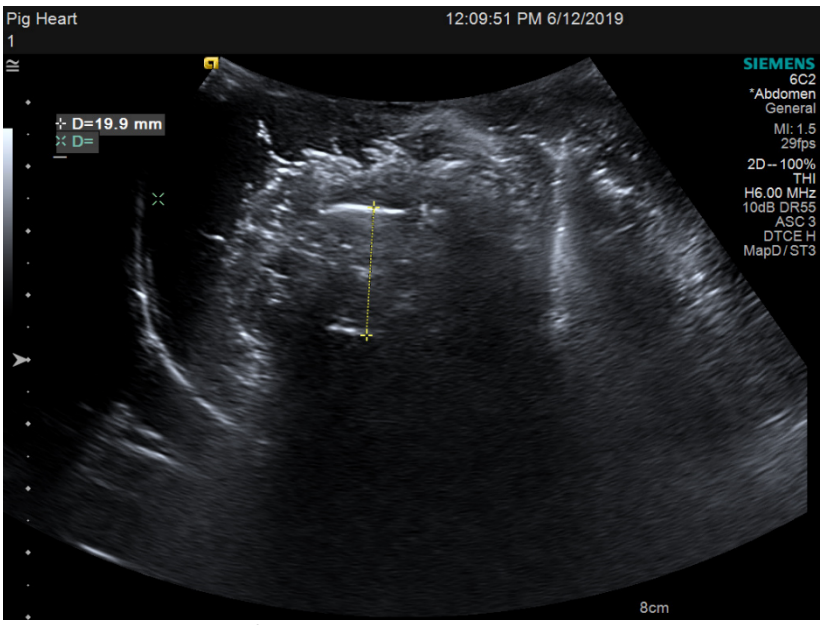


Figure I.16: Measurement of the cutting mould inside the pig's heart: short axis plane.

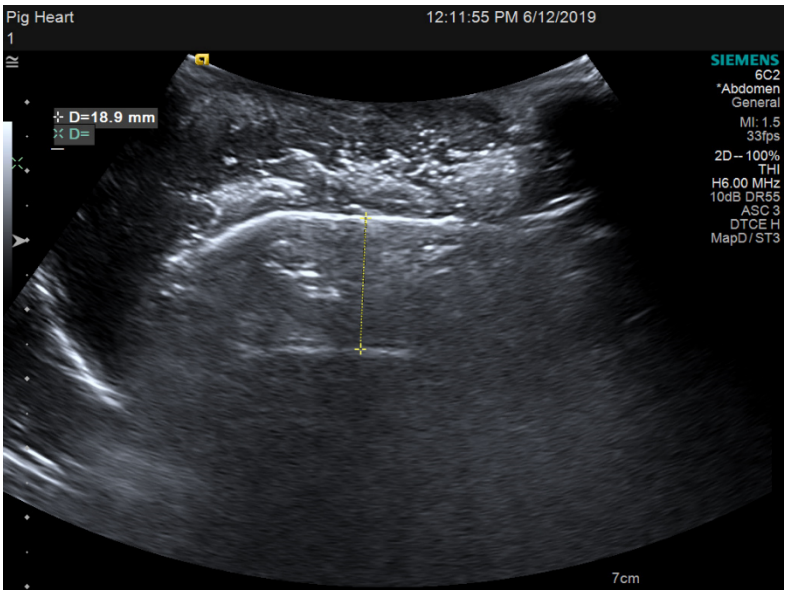


Figure I.17: measurement of the cutting mould in the pig's heart: Long axis plane

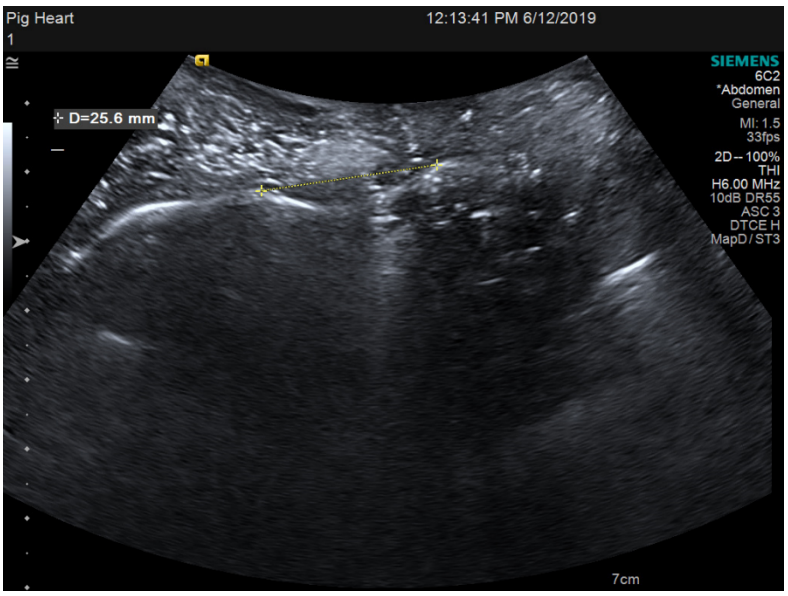


Figure I.18: Image of the hypertrophic recess in a long axis plane.

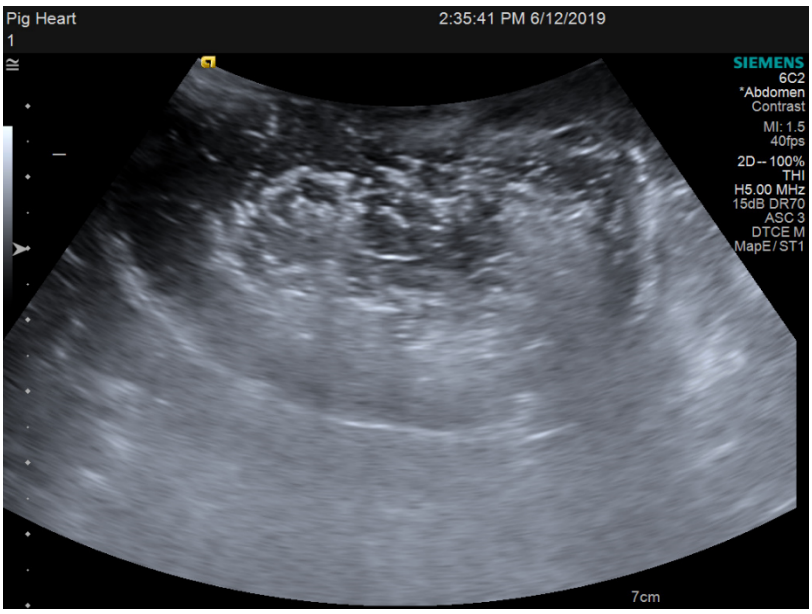


Figure I.19: heart filled with water, short axis plane.

Appendix J – Material Requirements of 3D printed Heart

Material requirements 3D heart

Requirement	Remarks
Comparable to heart tissue (flexible)	Given the many different structures and cells in the heart, it will be hard to exactly fulfill this requirement. However, a flexible material with elastomeric properties will suffice.
Elastic	The material should be deformable without plastic deformation.
Possibility to cut	The 3D heart will be used as a training model for surgeons. In order to practice the surgery with this 3D heart, it must be possible to cut the material with a scalpel in the same way surgeons do during surgery.
Affordable	Preferably the material is as inexpensive as possible, because possibly multiple 3D hearts have to be used while practicing.
Multiple colors	While practicing it would be convenient to get visual feedback on whether the incision made is neither too deep, nor too superficial.
Either 3D printable or pourable into a mould	There are multiple ways to get a realistic 3D heart model. Two possible ways are able to use are either 3D printing or using a mould. Therefore, the materials used have to be compatible with either of these two ways. When 3D printing is used, it has to be compatible with the printers that are at the disposal of the UTwente or the MST.

Table J.1: Material requirements specifically composed for the 3D heart.

Appendix K – Possible Flexible Materials for a 3D printed Heart

Selection of flexible 3D printable materials

Name	Features
NinjaFlex[116]	Material: Customized thermoplastic polyurethane (TPU) Shore Hardness: 85A (hard) Melting point: 216 °C Elongation at Yield: 65% Elongation at Break: 660% Different Colours Chemically inert to water
Cheetah[117]	Material: Customized polyurethane Shore Hardness: 95A Melting point: 220 °C Elongation at Yield: 55% Elongation at Break: 580% Different Colours Chemically inert to water
Flexible Resin[118]	Material: flexible resin Shore Hardness: 70-75 A Elongation at Failure: 60% Vicat softening point: 231 °C Processing: Stereolithography (SLA-SMS)
TPU[119]	Material: TPU Semi-flexible and chemically resistant. Shore Hardness: 95A Melting point: 220 °C Elongation at Yield: 55% Elongation at Break: 580% Processing: Fused Deposition Modeling (FDM)

Table K.1: A selection of flexible materials that can be used to 3D print the heart.

Appendix L - SolidWorks roadmap of the design of the casting moulds, the LV volume imprint, and the cutting mould

Casting moulds

First the STL file of the LV myocardium is loaded, as a solid body, into SolidWorks. The STL is edited in order to remove the recess of the mitral valve. This is done by placing an oval volume on the mitral valve recess, using sketch mode and extrude boss/base. A plane is created parallel to the front plane, the xy-plane. The plane is placed at the widest part of the LV myocardium, so the ballistic gel can easily be separated from the mould. In the plane a rectangle, enclosing the entire solid body, is drawn using sketch mode. The feature extruded boss/base is used to create volume around the LV myocardium to make the option 'up to next' possible. Thereafter, a second plane is constructed parallel to the front plane, this time it is situated below the LV myocardium solid body. In this plane a rectangle is also sketched, but smaller than the rectangle in the plane intersecting the myocardial volume. Thereafter, the rectangle below the volume is converted to a solid body using the feature extruded boss/base. The option 'up to next' is used and the results are not merged, to keep the mould and the volume separable. The other half of the mould is created the same way, only planes and rectangles are mirrored with respect to the ones explained.

First a sketch is made using 'centre point straight slot' with a radius of 8mm and a straight of 6mm in the top plane, the xz-plane. Now a volume can be created by using the 'extruded boss/base' feature and the sketch was extended by 100mm in the negative y-direction. In the positive y-direction the sketch was extended 10mm with a draft of 35 degrees in order to create a pointed shape. The sharp edges between the two extruded boss/base volumes and the edge at the end of the draft were rounded using the feature 'fillet' with a radius of respectively 8mm and 1mm.

Cutting mould and LV volume imprint

Once the body of the mould is created the interior can be constructed. First the main duct of the suction system was made by sketching a circle in the top plane. This circle has a radius of 2mm in order to fit a normal clinical syringe and make a proof of concept test of the fluid delivery system possible. The duct is 90mm long and is made using the feature 'extruded cut'. The straight centre ducts were constructed using the same method as the main duct but only the front plane, the xy-plane, was used, the radius is 1mm and the extruded cut was 12mm deep. Six centre straight ducts were constructed, beginning at 10mm above the origin reaching up to 35mm. Each centre of the ducts was separated by 5mm. The side ducts were placed at both sides of the centre ducts. These side ducts were made using the feature 'Hole Wizard', with an DME-size of 7/64 size(2.78mm). The centres of the centre straight duct and side ducts had 6mm of space between them. At last a fluid channel was created by sketching a circle with a radius of 2mm in the top plane and using extruded cut, cutting a hole over the entire length of the mould.

This is how the last version of the mould was constructed. In order to make it usable as a cutting mould for HOCM, the 3D-model of the LV volume of the HOCM patient was used. The LV volume was obtained through the MST, which gave us sliced MRI-data in an STL format. The STL file was inserted in SolidWorks as a solid body. A plane was created parallel to the top plane and intersecting the LV volume, cutting the aorta in half. The hypertrophic region was located beneath this plane. In this plane a rectangle was drawn using sketch mode. The dimensions of this rectangle were 130x110mm, because the rectangle must cover the entire LV volume. Of this sketch a volume was created towards the top plane using the feature 'extruded boss/base.' Thereafter, a second plane was created parallel to the top plane and below the LV volume. In sketch mode a rectangle, with the dimensions of 125x100mm, was drawn, enclosing the LV volume.

A volume was also made of this sketch using the feature extruded boss/base, within this feature the option 'up to next' was used. 'Up to next' ensures that the volume creation will stop when it reaches another solid body, the results were not merged in order to obtain the negative of the LV volume.

In order to use the mould as a HOCM cutting mould the hypertrophy needs to be imprinted. The MRI data of the patient is used to measure the dimensions of the tissue that must be resected. Using RadiAnt viewer 4.2.1, the length of hypertrophy and the angle between the septum and aorta were measured. The mould was placed on the LV volume negative according to these dimensions. When the mould was placed correctly the part was edited. The function 'cavity', found under mould tools, was used to imprint the hypertrophy in the cutting mould.

Subsequently, a plane was created parallel to and intersecting with the fibrous ring of the aortic valve. A split line was sketched at the intersection of the mould and this plane. The split line was used to create a CompCurve, then a plane perpendicular to the curve was created in which a circle was sketched. With the feature 'swept cut', the CompCurve and the circle, perpendicular to the CompCurve, were used to form a reference ring to assure good intraoperative placement of the mould.

Appendix M – List with links to videos

Video 1: https://drive.google.com/open?id=1yqesulJ95lmioMpbZlPZ_vOUu8Je2C9V

Video 2: https://drive.google.com/open?id=1_xSanSoVnLHr3gggE860cUckeAR_0nXc

Video 3: https://drive.google.com/open?id=1qFj8J7HCe8GbTltlNfOGmHvLjEHJ8G4z

Video 4: https://drive.google.com/open?id=1_mgab-VZM9BmsCZKFOXa2dC3srzweflT

Video 5: https://drive.google.com/open?id=1xZuKIwPV9V7UrT__JtjOZOA-48GyEJCq

Video 6: https://drive.google.com/open?id=1vbk13W9Erz6D8cxjt7-ee8T2dsmKTr5c

Video 7: https://drive.google.com/open?id=1rgRSNehBS5n1yOwcfLzOcb2IiBh-YGkW

Video 8: https://drive.google.com/open?id=1ktNz0YKN64lQJtao0I78V4_49owzFmFa

Video 9: https://drive.google.com/open?id=1RJt1qnDbKfP7ENI6iRBWw4O0gTl_4O6B

Video 10: https://drive.google.com/open?id=1XF6mrV5_C3u-XBHOBgMhueXq7zGkMysS

Video 11: https://drive.google.com/open?id=1gkVG3-KT8xTHC31uclxzBAGsAL1Ejc3o