



## MASTER THESIS

# **Three Dimensional Transesophageal Echocardiography as a Predictive Tool to Assess the Outcome of Mitral Valve Plasty.**

R. Bruggink, BSc

## **TECHNICAL MEDICINE Medical Imaging and Interventions**

### **Examination Committee:**

Prof. C.H. Slump, PhD – Chairman / Technical supervisor

Prof. G.J. Grandjean, MD, PhD – Medical supervisor

M. Groenier, PhD – Process supervisor

Prof. C.H. Venner, PhD – External member

R. Hagmeijer, PhD – External member



UNIVERSITY OF TWENTE.



# Preface

With this master thesis, I, Robin Bruggink would like to present my research at the department of Cardio-thoracic surgery at the Thorax Centrum Twente located in the Medisch Spectrum Twente hospital. This thesis is produced, with care, as completion of the Master course '*Medical Imaging and Interventions*' in Technical Medicine at the University of Twente located in Enschede.

Before I present my research, I would like to address the persons who have helped and inspired me to produce this Master thesis. At first I would like to thank my direct medical supervisor professor Jan Grandjean, for granting me this inspiring and challenging research. His expertise and vision helped a lot in producing the model. Furthermore, he helped me with clinical working and thinking.

I would thank the anaesthesiologists, and especially Rob Lindeman, for the acquisition of these datasets, and their expertise to learn me to understanding TEE ultrasound

Furthermore I thank my technical supervisor professor Kees Slump and my process supervisor Marleen Groenier for their help during this and previous internships, which shaped me towards a practitioner in Technical Medicine.

For the daily supervision, Frank Halfwerk was present to help me when needed, and therefore I am grateful and thankful.

I would like to thank the nurse-practitioners of the department of cardio-thoracic surgery for creating an environment in which I could increase my medical and professional skills. Furthermore their social aura made this graduation internship a fun and learning happening.

A special thanks goes out for my parents, for supporting and being there for me during my life.

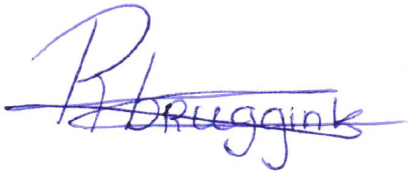
Last but not least I thank my fellow colleague students and especially Timon Fabius, Frank Baan, Arico Verhulst and Gert-Jan Snel for the discussions, ideas and fun interludes.

I hope that you will enjoy reading this thesis and get inspired by the current developments in cardio-thoracic surgery.

**Signed by:**

R. Bruggink, BSc

*29th of October, 2015*

A handwritten signature in blue ink, appearing to read 'R. Bruggink', with a large, stylized 'R' at the beginning and a horizontal line crossing through the middle of the name.

# Abstract

**Aim:** Mitral valve plasty has shown its advantages in comparison with mitral valve replacement. However, a lot of patients get a replacement while repair is preferred, which can be explained by the high complexity of the surgery. The aim of this study was to create a model to predict the annuloplasty ring size and leaflet resection based on 3D-TEE images. This gives the surgeon more scientific rationale for the choices made during surgery which makes the procedure more evidenced based, instead of experienced based.

**Method and Materials:** Retrospective per-operative 3D-TEE data was collected from patients who underwent mitral valve plasty. The annulus circumference, leaflet lengths, leaflet area and intercommissural distance were determined with use of the Mitral Valve Navigator<sup>1</sup> and in house made software created with Matlab<sup>2</sup>. With SPSS<sup>3</sup> these parameters were compared with the implemented ring for creating univariate prediction models. Initial validation was performed to test the performance of the model.

**Results:** 28 patients were included into this study. The intercommissural distance, leaflet area and circumference are significant predictors for the implanted ring size ( $p < 0.01$ ,  $r^2$ : 0.76, 0.74 and 0.74). No multivariate model could be created due to multicollinearity. Initial validation was performed with 11 patients, in which the model had a  $r^2$  of 0.85, which is promising. However, more patients have to be included into the validation to assess its predictive value.

**Conclusion:** In this study a new, promising, tool is created to standardize the current annuloplasty sizing technique. However, adaptations in the measurement software have to be made to increase the intra-/inter-observer variability. A model to predict the increase of the effective leaflet lengths during annuloplasty is introduced, but yet not validated.

---

<sup>1</sup>Philips Electronics, The Netherlands, Version 10.2

<sup>2</sup>Matworks Inc, Massachusetts, Version 2015b

<sup>3</sup>IBM, USA, Version 23



# Contents

|          |                                                                                                                                                    |           |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>1</b> | <b>General Introduction</b>                                                                                                                        | <b>1</b>  |
| <b>2</b> | <b>Three Dimensional Transesophageal Echocardiography as a Predictive Tool to determine the Annuloplasty Ring Size during Mitral Valve Plasty.</b> | <b>5</b>  |
| 2.1      | Introduction . . . . .                                                                                                                             | 5         |
| 2.2      | Methods and Materials . . . . .                                                                                                                    | 5         |
| 2.3      | Results . . . . .                                                                                                                                  | 10        |
| 2.4      | Discussion . . . . .                                                                                                                               | 14        |
| 2.5      | Conclusion . . . . .                                                                                                                               | 16        |
|          | Conclusion . . . . .                                                                                                                               | 16        |
| <b>3</b> | <b>The use of Pre-operative Two Dimensional Echocardiography to Identify patients at Risk for Systolic Anterior Motion.</b>                        | <b>19</b> |
| 3.1      | Introduction . . . . .                                                                                                                             | 19        |
| 3.2      | Methods and Materials . . . . .                                                                                                                    | 20        |
| 3.3      | Results . . . . .                                                                                                                                  | 22        |
| 3.4      | Discussion . . . . .                                                                                                                               | 23        |
| 3.5      | Conclusion . . . . .                                                                                                                               | 24        |
| 3.6      | Disclosures . . . . .                                                                                                                              | 24        |
| <b>4</b> | <b>General discussion and future perspectives</b>                                                                                                  | <b>25</b> |
| 4.1      | Introduction . . . . .                                                                                                                             | 25        |
| 4.2      | Back to the aim of this study . . . . .                                                                                                            | 25        |
| 4.3      | Future perspectives . . . . .                                                                                                                      | 26        |
|          | 4.3.1 3D visualization . . . . .                                                                                                                   | 26        |
|          | 4.3.2 Augmented reality . . . . .                                                                                                                  | 26        |
| <b>5</b> | <b>Appendix</b>                                                                                                                                    | <b>29</b> |
| 5.1      | Anatomy . . . . .                                                                                                                                  | 29        |
| 5.2      | Pathofysiology . . . . .                                                                                                                           | 32        |
|          | 5.2.1 Mitral Valve Regurgitation . . . . .                                                                                                         | 32        |

|       |                                                                   |    |
|-------|-------------------------------------------------------------------|----|
| 5.2.2 | Systolic Anterior Motion . . . . .                                | 34 |
| 5.2.3 | Mitral Stenosis . . . . .                                         | 35 |
| 5.3   | Ultrasound . . . . .                                              | 37 |
| 5.4   | Mitral Valve Plasty . . . . .                                     | 39 |
| 5.5   | Mitral Valve Navigator . . . . .                                  | 41 |
| 5.6   | Prediction Tool . . . . .                                         | 45 |
| 5.7   | MVP/MVR ratio's in the Medisch Spectrum Twente hospital . . . . . | 47 |
| 5.8   | Additional model graphs . . . . .                                 | 49 |
| 5.9   | 4D volume measuring tool . . . . .                                | 50 |

**Table 1:** Table of abbreviations

| Acronym     | Definition                                                          |
|-------------|---------------------------------------------------------------------|
| ∠AoA        | Angle of attack                                                     |
| ∠Ao-Mi      | Aortomitral angle                                                   |
| AMPL        | The antero-medial to postero-lateral distance of the mitral annulus |
| AML         | Anterior mitral leaflet                                             |
| ALPL        | Anterior posterior leaflet ratio                                    |
| AP          | The anterior to posterior distance of the mitral annulus            |
| C-C         | Commissure to commissure distance                                   |
| C-Sept      | Coaptation to septum distance                                       |
| HCM         | Hypertrophic cardiomyopathy                                         |
| HOCM        | Hypertrophic obstructive cardiomyopathy                             |
| LVOT        | Left ventricular outflow tract                                      |
| LVOTO       | Left ventricular outflow tract obstruction                          |
| IVS         | Intra-ventricular septum                                            |
| PML         | Posterior mitral leaflet                                            |
| MR          | Mitral valve regurgitation                                          |
| MVN         | Mitral valve navigator (software from Philips)                      |
| MVP         | Mitral valve plasty (repair)                                        |
| MVR         | Mitral valve replacement                                            |
| SAM         | Systolic anterior motion                                            |
| S-Thickness | The thickness of the septum                                         |
| TEE         | Transesophageal echocardiography                                    |
| TTE         | Transthoracic echocardiography                                      |



# Chapter 1

## General Introduction

The main function of the mitral valve is preventing blood-flow from the left ventricle (LV) back in to the left atrium (LA) during systole. In diastole, blood pressure builds up into the LA which opens the mitral valve, allowing blood to flow into the LV. Subsequently during systole, as the LV contracts, the pressure in the LV gets higher than the LA which closes the mitral valve. To contain optimal functionality, the mitral valve has an eminently complex structure which is still not fully understood. [1–3] When this structure is deformed, e.g. due to calcification, blood can flow back into the LA, causing an increased LA pressure and lower LV output into the main circulation. [4,5] This back-flow is called mitral valve regurgitation (MR) and can have serious consequences which eventually induce heart failure if not treated properly. [6] MR is one of the most common valvular heart disease and it affects around 2.5% of the population in industrialized countries. The prevalence is correlated with age, increasing from <2% for the population below the age of 65 years to 13.2% above the age of 75 years. [7] This can be explained as MR can be induced due to age dependent degenerative diseases. [7]

Patients suffering from MR are associated with a higher mortality rate when compared to the general population. This rate increases with the severity of the disease and therefore it is important that MR is monitored. MR treatment differs between patients depending on several factors like: its acuteness, severity, anatomy and physiology. The therapy with the most proven efficacy to treat MR is surgery. [8–15] Two options existing in surgery are mitral valve plasty (MVP), in which the valve is repaired and thereby preserved, or a total mitral valve replacement (MVR). Clinical studies have shown that MVP has more advantages over replacement. These advantages include a lower operative mortality improved ventricular function, lower rates of thrombo-embolism and endocarditis and a better long-term survival. Furthermore the majority of patients which underwent MVP do not have to use anticoagulation. [5, 16–18]

Despite the better outcome, MVP is still a risky procedure as new defects can oc-

cur during surgery. [19, 20] For optimal repair, the surgeon must have acquired a good understanding of the physical processes of the heart under physiological circumstances. During MVP surgery, cardiopulmonary bypassing is used to temporarily take over the function of the heart. During this procedure no blood is present in the heart, deforming its geometric properties. This makes it challenging for the surgeon to evaluate the problems in the heart per-operatively. Furthermore, measurements to determine the e.g. ring size in annuloplasty are less precise, which is not beneficial for an optimal repair. When a surgeon does not possess this knowledge, errors can be easily made. A possible complication is the onset of systolic anterior motion (SAM). This is a phenomenon in which the anterior leaflet of the mitral valve (AML) moves into the left ventricular outflow tract (LVOT), causing LVOT obstruction. This obstruction leads to an increased outflow resistance, decreasing the stroke volume of the heart. [21] Additionally, SAM can induce a new MR. Previous studies show a higher risk of SAM in patients suffering from hypertrophic obstructive cardiomyopathy (HOCM). [22]

The MVP procedure is patient specific as the dimensions and the kind of valvular damage differs between each patient. This makes it important to use pre- and per-operative imaging modalities for inspection. [23] In most cases a ring is placed inside the mitral valves annulus to restore coaptation between the leaflets and to stabilize the annulus after surgery. As implementation of a ring alters the position and the length of the coaptation plane, often posterior resection is performed to prevent SAM. A more detailed explanation of MVP can be found in Appendix 5.4. Despite the fact that valve repair is preferred, this only happened in 43% of the cases in the USA [24] and 47% in Europe [25]. The low repair rates can be explained by the high complexity and low scientific basis for this type of surgery and is therefore 'experienced based', meaning its actual based on the experience of the surgeon and not scientific evidence. [26] To shift towards the 'evidenced based' surgery, research is needed to standardize this process. 3D transesophageal echocardiography (3D-TEE) can aid in this process as it gives a 3D moving image of the mitral valve in physiological circumstances. [23, 27] TEE does not alter the geometrics of the heart, creating physiological correct datasets.

The goal of this study is to create a standardized, per-operative diagnostic method based on 3D-TEE to help the surgeon to determine which techniques or tools to use during surgery. Based on an internal study, which is presented in appendix 5.7, the repair rate in the 'Medisch Spectrum Twente' hospital in Enschede is around 75 percent. This ratio is almost double compared to the rest of Europe. [28] This makes the Medisch Spectrum Twente an optimal location to create a standardized procedure as the results are based on high expertise.

**Research question:** *Can per-operative 3D-TEE assist the surgeon in decision making during mitral valve plasty and thereby giving the procedure more standardization?*

## Thesis outline

This thesis consists of two separate concept papers. The first article is titled '*Three dimensional trans-esophageal echocardiography as a predictive tool to determine the annuloplasty ring size during mitral valve plasty*'. In this article it is tried to tackle the problem of low standardization during mitral valve plasty. This is done by per-operatively predicting the ring size in annuloplasty with the use of 3D-TEE. During this study the results of Philips segmentation software are retrospectively compared to the implemented ring sizes during surgery. On this data, a model is created which gives advice to the surgeon for predicting the ring size before surgery.

The second article has the title '*The use of pre-operative two dimensional echocardiography to identify patients at risk for systolic anterior motion*'. In this article parameters, which are associated with systolic anterior motion, are validated on 2D ultrasound datasets. This is done by comparing different parameters between a population suffering from SAM, and a healthy population. The anatomy, pathophysiology and technical background are limited explained in these articles. For a more detailed explanation the corresponding appendix can be referred.



# Chapter 2

## Three Dimensional Transesophageal Echocardiography as a Predictive Tool to determine the Annuloplasty Ring Size during Mitral Valve Plasty.

*R. Bruggink<sup>1,4</sup>, R. Lindeman<sup>4</sup>, C.H. Slump<sup>2</sup>, J.G. Grandjean<sup>3,4</sup>*

<sup>1</sup> Technical Medicine, University of Twente, Enschede, The Netherlands

<sup>2</sup> Department of Robotics and Mechnatronics, University of Twente, Enschede, The Netherlands

<sup>3</sup> Department of Biomechanical Engineering, University of Twente, Enschede, The Netherlands

<sup>4</sup> Department of Cardiothoracic Surgery, Medisch Spectrum Twente, Enschede, The Netherlands

### 2.1 Introduction

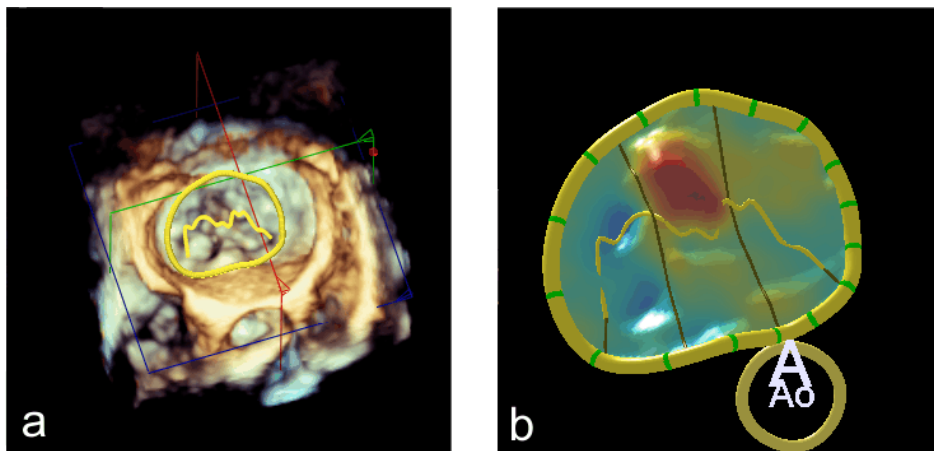
### 2.2 Methods and Materials

Patients who underwent MVP surgery at the department of cardio-thoracic surgery at the 'Medisch Spectrum Twente' hospital and had a pre-/per-operative mitral valve 3D-TEE dataset were included into this study. To prevent geometric changes the maximum delay between ultrasound and surgery was two months. Patient inclusion started retrospectively in January 2012 and continued until July 2015. Ultrasound data was acquired per-operatively with the iE33 xMatrix echocardiography system<sup>1</sup>. Each dataset contained a 4D image of the mitral valve with a minimal duration of one cardiac cycle. As calculations were performed on the late diastolic phase of the heart, minimal five frames had to be present in one cardiac cycle to minimize the

---

<sup>1</sup> Philips Electronics, The Netherlands

phase shifts between patients. Exclusion criteria were: prior cardiac surgeries, low quality of the echo-graphic data and per-operative conversion to MVR when MVP was not satisfying.



**Figure 2.1:** The results of the Mitral Valve Navigator (*Philips electronics, The Netherlands*). In A the annulus is drawn into the 3D-TEE data, creating a verification for the user. B shows the reconstructed mitral valve in which the commissures and coaptation plane are visible. Furthermore a bulged leaflet can be seen in P2.

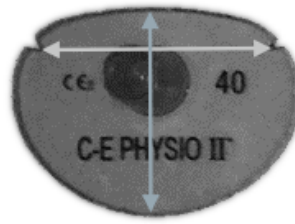
## Data Processing

The datasets were analysed with the use of Mitral Valve Navigator software (MVN)<sup>2</sup>, which semi-automatic segments the mitral valve. In this software the user selected the mitral valve annulus in a coronal and sagittal image whereupon the whole annulus was calculated. This annulus was manually checked, and adapted when location errors were present. The commissures were selected in transversal 2D images. For validation of these commissure locations, these were projected into the 3D image of the mitral valve. When the segmentation, as shown in figure 2.1, was finished, the MVN shows values of different mitral valve parameters, which were exported to Excel afterwards. A more detailed explanation of the MVN is presented in appendix 5.5 The mitral valves leaflet lengths can be determined by the MVN software, but due to the limitation, that it can not process over each other placed leaflets, it often gives a underestimation. A measuring tool for use in 4D images was created with Matlab<sup>3</sup>. In this tool the user selected a slice in a top projection of the mitral valve. This ensures that the measuring plane was perpendicular to, and in the middle of the coaptation plane. The resulting slice contained the anterior and posterior leaflet at the height of P2/A2. The user could manually track the leaflet by clicking on it. When

<sup>2</sup>Philips Electronics, The Netherlands, Version 10.2 [32]

<sup>3</sup>Matworks Inc. Massachusetts, Version 2015b

finished, the leaflet lengths were calculated with respect to the pixel dimensions. Images of this tool are present in appendix 5.9.



**Figure 2.2:** The ring sizer of Edwards Physio II which corresponds with a size 40 annuloplasty ring. The horizontal line is the C-C distance and the vertical line corresponds with the AML length.

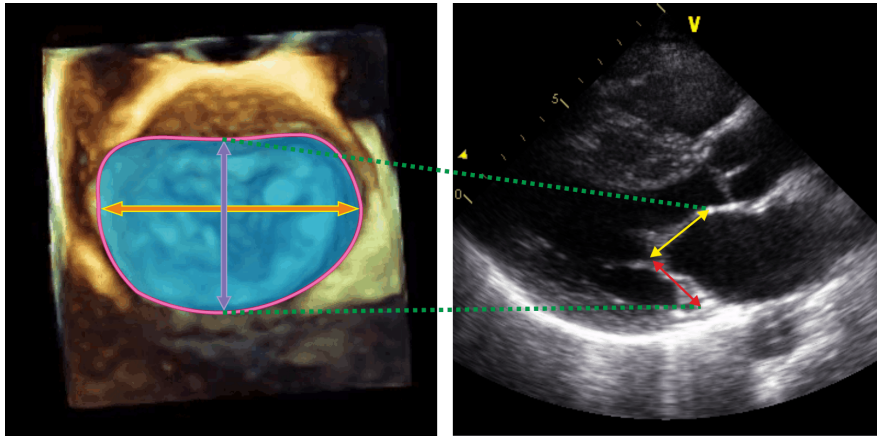
### Ring size prediction model

Results of each segmented dataset were collected and stored in a database. SPSS statistics software<sup>4</sup> was used for statistical analysis. Geometric parameters were tested on correlation with the implemented ring size. The commissure to commissure diameter (C-C) is the distance between the two commissures in the mitral valve. This distance corresponds with the long axis of the mitral valves orifice. [34] Some of the current sizers, including the Edwards Physio II sizers, as shown in figure 2.2, have two notches in their platform which must correspond to this C-C to determine the initial ring size during surgery. [26] The anterior leaflet (AML) is used in conventional sizing for fine-tuning the initial ring size determined by the C-C. When the AML is larger as the sizers platform, a larger ring size is chosen. A large sized posterior leaflet (PML) is a risk factor for SAM as it can induce an anterior shift of the coaptation plane. [35] The mitral valve structure can roughly be described as an ellipse. As shown in figure 2.3 the anterior to posterior diameter (AP) corresponds with the minor axis and the antero-lateral to postero-medial diameter (ALPM) with the major axis. These ellipsoid diameters with the area and the circumference of this ellipse were included to this study as well. In Carpentier et al. [31] it is advised to oversize the ringsize when the anterior leaflet is significant longer in comparison of the height of the sizer. However, as there is no good consensus, the model did not takes this f. Dilatation of the mitral valve causes an increase in several parameters. Correction for annular dilatation was applied to compensate for enlarged geometrics of the mitral valve. [36, 37] This was done by under-sizing the predicted ring by one ringsize.

The ring implanted was a Edward Physio II or a St. Jude Sequin ring, which both have sizes between 26 to 40 with steps of 2. Each dataset was analysed twice, so

---

<sup>4</sup>IBM, USA, Version 23 [33]



**Figure 2.3:** The basic geometrics of the mitral valve. The arrows correspond with: ALPM (orange), AP (purple), AML (yellow) and PML (red). The circumference is accented by pink and the area by cyan.

the intraclass correlation (ICC) could be determined. For parameters which correlated significant with the ring size univariate linear regression models were created to predict the ring size independently. Additionally these predictors were used to produce a multiple linear regression model. Parameters in the multiple regression model were excluded if their significance was higher than 0.10. Predicted ring sizes were rounded to the closest existing ring size. When sizes between the predicted and implemented ring differed two or more ring sizes it was interpret as a failed calculation. The models were tested on their goodness of fit with Pearson's  $r^2$  test.

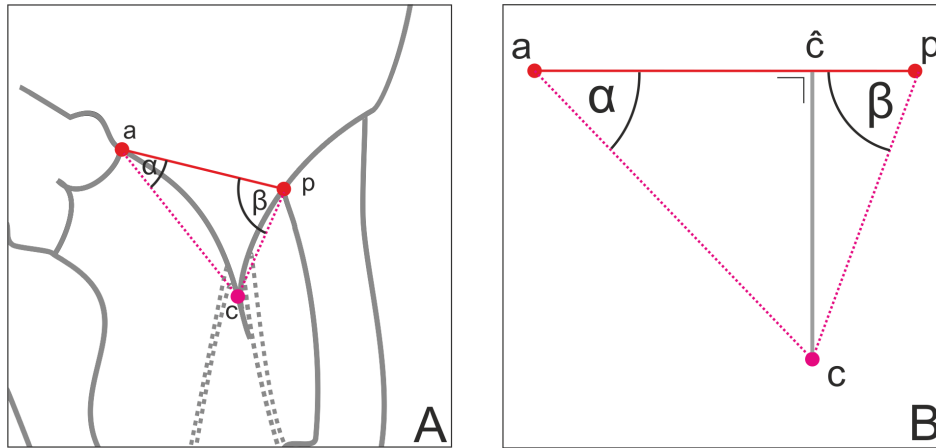
### Model Validation

To create more clarity about the feasibility of a predictive model a preliminary validation study was performed. Patients were included with the same criteria as the model population. Inclusion time was from August to October 2015. For each patient the ring size was determined pre- or per-operatively, thereby informing the surgeon about the predicted ring sizes. The surgeon determined afterwards the ring size conventionally with the Physio Edwards II ring sizers combined with his expertise. Both predictions were tested on agreement by Pearson correlation. Scatter plots were use to find systematic errors of the prediction model, as the Pearson test does not take these errors in account.

### Leaflet prediction model

When the diameter of the annulus is decreased due to annuloplasty, the geometry and especially the lengths of the leaflets are altered. [30] This alteration can induce risk factors for SAM, and should be monitored and preferably predicted. Two of the, in literature described, risk factors are a posterior leaflet length exceeding 15mm and

an anterior-posterior leaflet length ratio smaller than 1.3. [38] To help the surgeon managing these risk factors, a model was made to predict the leaflet behaviour after annuloplasty. As seen in figure 2.4 the model was based on the anterior to posterior length (AP) of the mitral valve. As the mitral valve consist out of two mostly parallel located leaflets, the leaflet coaptation is most changed in the anterior to posterior diameter. Therefore, to simplify the prediction model, the change in width of the mitral valve was initially neglected. In summary the extra predicted leaflet coaptation after surgery were calculated with the following steps:



**Figure 2.4:** The rationale behind the leaflet prediction model. Point  $a$ ,  $p$  and  $c$  correspond respectively to the anterior annulus point, posterior annulus point and the coaptation point.

- The coaptation point ( $c$ ) are calculated by determine the intersection of the two circles which can be formed with the annulus points ( $a$  and  $b$ ) as centre and the leaflet lengths ( $\bar{ac}$  and  $\bar{pc}$ ) as radius.
- Angles  $\angle\alpha$  and  $\angle\beta$  are calculated with the known points
- The decrease in length of  $\bar{ap}$  due to the annuloplasty ring is relatively distributed between  $\bar{ac}$  and  $\bar{pc}$
- The distances  $\bar{ac}$  and  $\bar{pc}$  are calculated again with the new known diameter
- The increase of leaflet coaptation length is calculated by the difference between the new and old leaflet lengths

### Application developement

The integration of the model into an application is crucial for optimal use in the clinical environment. An application tool can help the surgeon to use the model in a

fast and user friendly manner. To increase the supported platforms it was chosen to use a web application. This tool can be used with every platform which has access to the internet and a browser, e.g. smartphones and personal computers. The web application had to met the following requirements:

- **Safety** The application must only be accessed by rightful users
- **Costs** The cost of the tool must be as low as possible without compromising its safety.
- **User friendly** The tool must contain a minimum number of input boxes and buttons
- **Complexity** The user should be able to use the tool without first reading the manual

## 2.3 Results

28 patients were included for creating the model. Reasons for exclusion were: low quality datasets (6) and prior cardiac surgery (1). Patient characteristics are visualized in table 2.1. The mean age of the patients was 69.9 +/- 8.9 years and 21 were male. Furthermore, 8 patients had annular dilation. The MVN was able to segment the mitral valve including the annulus in 26 datasets, manual segmentation had to done in two datasets. An example of the segmentation is shown in figure 2.1.

### Prediction model

As shown in table 2.2, the C-C, circumference and area of the mitral valve are significant, strong correlated, predictors of the implemented ring size ( $r^2$  is respectively 0.69, 0.68 and 0.69). The ICC of these parameters are acceptable (respectively 0.89, 0.9 and 0.92) which indicates a fair intra-observer variability. The AP, AML and PML are significant put have poor predictive value for the ring size and were therefore not used to create a model. The correlation between each of the significant predictors was high ( $> 0.9$ ) and therefore no multiple linear regression model could be established due to multicollinearity. [39] However three univariate linear models are created which can strengthen the predictive value of the total model if they mutually correspond.

Univariate linear regression was used to create models with the C-C (2.1), circumference (2.2) and area (2.3) of the mitral valve. To create a model which takes each parameter into account a new model was created. This model takes the average of the three independent predictions. The results are shown in table 2.3. predicted ring

**Table 2.1:** Patient Characteristics (n = 28)

| Characteristic |                 | N/ $\mu$ | %/ $\sigma$ |
|----------------|-----------------|----------|-------------|
| Age            |                 | 69.9     | 8.9         |
| Implanted Ring |                 | 31.6     | 3.6         |
| Sex            |                 |          |             |
| -              | Male            | 21       | 75%         |
| -              | Female          | 7        | 25%         |
| MR severity    |                 |          |             |
| -              | Moderate        | 3        | 10%         |
| -              | Severe          | 25       | 90%         |
| Cause          |                 |          |             |
| -              | Prolapse PML    | 14       | 50%         |
| -              | Malcoaptation   | 8        | 29%         |
| -              | Restrictive PML | 1        | 4%          |
| -              | Other           | 5        | 17%         |

**Table 2.2:** Model setup: correlation between the parameters and the implemented ring size, with the ICC of each parameter

| Predictor      | Correlation coefficient ( $r$ ) | Pearson $r^2$ | Standard error of estimate ringsize (mm) | ICC  | CI 95%    |
|----------------|---------------------------------|---------------|------------------------------------------|------|-----------|
| C-C distance*  | 0.83                            | 0.69          | 1.96                                     | 0.87 | 0.74-0.94 |
| Circumference* | 0.83                            | 0.68          | 1.88                                     | 0.93 | 0.85-0.97 |
| Leaflet area*  | 0.83                            | 0.69          | 1.98                                     | 0.95 | 0.89-0.97 |
| AP*            | 0.69                            | 0.48          | 2.35                                     | 0.89 | 0.77-0.95 |
| AML*           | 0.54                            | 0.29          | 2.73                                     | 0.85 | 0.70-0.93 |
| PML*           | 0.60                            | 0.35          | 2.61                                     | 0.85 | 0.70-0.93 |

size are plotted against the implemented ring size in figure 5.17 located in appendix 5.8. Their Pearson correlations ( $r^2$ ) were higher then 0.74 with a standard error of estimate of around 1.8mm.

$$\text{Ringsize (C-C)} = 2 \left\| \frac{(0.6698x) + 11.15}{2} \right\| \quad (2.1)$$

$$\text{Ringsize (circumference)} = 2 \left\| \frac{(0.1561x) + 10.52}{2} \right\| \quad (2.2)$$

$$\text{Ringsize (area)} = 2 \left\| \frac{(0.0078x) + 21.14}{2} \right\| \quad (2.3)$$

**Table 2.3:** Model setup: correlation between the predicted and implemented ring size

| Predictor     | Correlation coefficient ( $r$ ) | Pearson $r^2$ | Standard error of estimate (mm) |
|---------------|---------------------------------|---------------|---------------------------------|
| C-C distance  | 0.87                            | 0.76          | 1.80                            |
| Circumference | 0.86                            | 0.74          | 1.83                            |
| Leaflet area  | 0.86                            | 0.74          | 1.83                            |
| Mean model    | 0.88                            | 0.77          | 1.73                            |

In table 2.4 the prediction differences are shown. In 50% of the cases the model was able to predict the same size as the surgeon choose during MVP. Two predictions have failed as they exceeded the maximum deviation of one ring size. The predictors independently show almost the same trend, but small deviations are present.

**Table 2.4:** Model setup: the agreement between the prediction and the implemented ring size.

| Difference | Advice   | C-C      | Circumference | Area     |
|------------|----------|----------|---------------|----------|
| 0          | 14 (50%) | 14 (50%) | 12 (43%)      | 13 (46%) |
| 2          | 7 (25%)  | 7 (25%)  | 8 (29%)       | 8 (29%)  |
| -2         | 5 (18%)  | 4 (14%)  | 6 (21%)       | 5 (18%)  |
| 4          | 1 (4%)   | 1 (4%)   | 1 (4%)        | 1 (18%)  |
| -4         | 1 (4%)   | 2 (7%)   | 1 (4%)        | 1 (4%)   |

### Validation of the prediction model

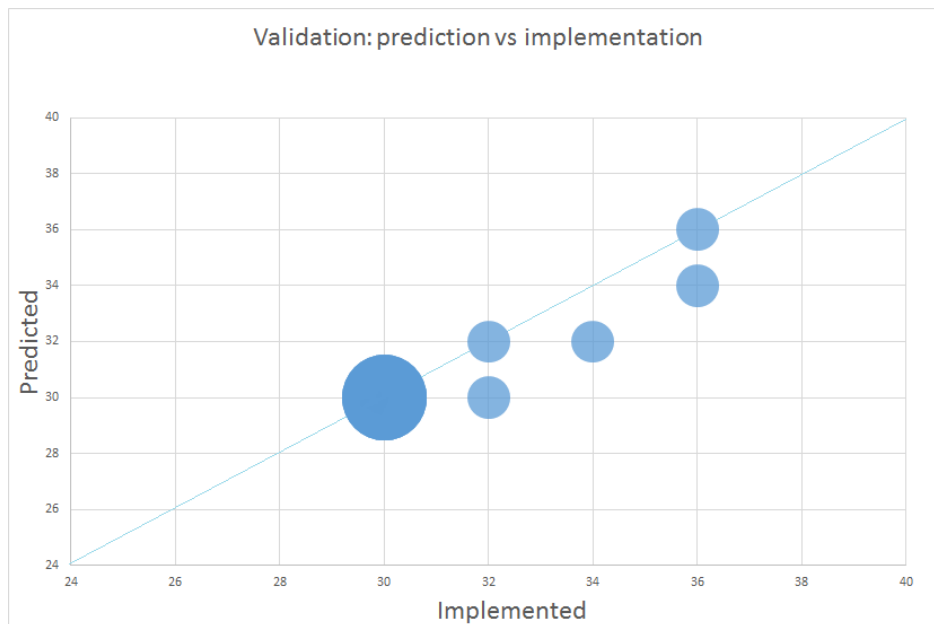
During the including period 11 patients had a 3D-TEE during MVP. Two were excluded due to low quality datasets. 10 were included to validate the prediction model, age ( $62.3 \pm 7.9$ ). The cause of MR was in 8 cases PML prolapse and in 1 patients there was annulus dilatation. The validation results are shown in table 2.5. The predictive power, calculated with the Pearsons  $r^2$ , is 0.85 for the advice model. This coefficient was not much different for the independent predictors C-C, circumference and area (respectively 0.78, 0.78 and 0.85). The corresponding scatter plot for the advice model is shown in figure 2.5.

### Application development

The linear prediction models based on the C-C, circumference and area were implemented into a web application. These models calculate the ring size per parameter independently, so three prediction values are present in the output. When they mutually differ more than one ring size the user is alerted as the likelihood of

**Table 2.5:** Validation model: correlation between the predicted and implemented ring size

| Model         | Correlation coefficient ( $r$ ) | Pearson $r^2$ | Standard error of estimate (mm) |
|---------------|---------------------------------|---------------|---------------------------------|
| C-C distance  | 0.89                            | 0.78          | 1.42                            |
| Circumference | 0.88                            | 0.78          | 1.27                            |
| Leaflet area  | 0.92                            | 0.85          | 1.06                            |
| Mean model    | 0.92                            | 0.85          | 1.06                            |



**Figure 2.5:** Validation model: the prediction plotted against the implemented ring. A larger circle at coordinate [30,30] represents 4 measurements.

a failed prediction is increased. A switch to indicate annular dilatation is present, which causes a ring size smaller in the prediction. The application does meet the requirements in the following aspects: For safety the application is user and password protected, which protects the saved data from unauthorized persons. Additionally a SSL certificate is implemented to encrypt the communication between the user and the server. The application works from a raspberry pi computer, which is a cheap and very power convenient platform. The total costs are listed in table 2.6 but can be considered as negligible. The tool is designed to work with minimal user clicks, to make it faster and more user-friendly. Optionally the leaflet prediction model can be used, however this requires three extra parameters to be inserted, i.e. AML, PML and the AP length of the annulus. In the result screen the surgeon can interactively change between the ring sizes. The prediction of extra coaptation length is shown

in real-time.

**Table 2.6:** Costs of the webapplication.

| Section                 | Costs (€) | Note    |
|-------------------------|-----------|---------|
| Raspberry Pi 2 computer | ± 50,-    | one-off |
| Power consumption       | ± 10,-    | annual  |
| SSL certificate         | ± 10,-    | annual  |

\*Based on numbers deriving from October 2015

## 2.4 Discussion

With internal validation, the model was able to predict a ring size equal or with one size difference in 26 cases (93%) and exact in 14 cases (50%). In three cases the prediction differed two ring sizes in comparison with the implanted rings. In one case this difference could be explained by severely dilated ventricle and annulus, in which the model will choose a larger ring, while the annulus was smaller before it became dilated. The model chooses to apply under-sizing of one size when annular dilation is present, however surgeons can choose for an even smaller ring size when they expect that the coaptation is still not sufficient. [40] The rationale behind this is to increase leaflet coaptation by decreasing the annular diameter. [31, 41] In the other two cases no significant abnormalities in the heart could be found. Furthermore, the anterior leaflet lengths were not much larger as the sizer, which means no over-sizing was needed. The difference in ringsize could be explained by calculation error by the model. However, as ring sizing is not fully standardized, deviation in chosen ring sizes could be present as well. A suboptimal ring size could be chosen per-operatively without inducing complications, as a size smaller or larger ring does not cause complications in all cases. Additionally, a surgeon can choose for a smaller ring, and use leaflet resection to cope with the increased leaflet lengths as well. At this moment it is not clear if the deviated predicted ring sizes are due to a failed prediction or to per-operatively decision making by the surgeon. With this in mind it can be concluded that the surgeon should only use this model to give advice and not as the definitive answer until thorough external validation is done.

The ICC of the used parameters are good but not optimal because small fluctuations can change the predicted ring size. With a 2mm increase in C-C distance, the model will predict a larger ring size. The lower ICC of 0.87 for the C-C parameter was expected as the commissures are often hard to identify in the MVN software. In this software the commissures points are chosen manually in a 2D transversal image, in which often, both commissures are not present in the same slice. Additionally,

# MVPadvisor

creating more standardization for mitral valve plasty.

Determining the correct ring size in annuloplasty of the mitral valve can be challenging as often the surgeon has to cope with low visibility of the valve. Furthermore to increase the standardization of the mitral valve plasty process a new tool is developed. This tool predicts the needed ringsize based on 3D-TEE ultrasound. After the 3D-TEE dataset is processed by the Mitral Valve Navigator, developed by Philips electronics, the resulting parameters can be filled in this application. The application calculates the predicted ring size indepently from three parameters and compares their outcome for agreement.

C-C distance

Circumference

Area

Enable leaflet prediction



A-P distance

AML length

PML length

Annulus dilatation



Calculate

## Annuloplasty Prediction Model

|                             |           |
|-----------------------------|-----------|
| Determined by C-C           | 32        |
| Determined by Circumference | 32        |
| Determined by Area          | 32        |
| <b>Advised Ringsize</b>     | <b>32</b> |

## Leaflet Prediction Model

|                      |      |
|----------------------|------|
| Increase of AML (mm) | 20.3 |
| Increase of PML (mm) | 10.1 |
| Leaflet ratio        | 2    |

## Adapt ring size



Update

**Figure 2.6:** The web application interface, which let the user assess the ring size prediction interactively. The three independent calculated ring sizes are showed as differences are easily detected. The conclusive advice is highlighted below the other predictions. The surgeon can choose to enable the leaflet prediction model by clicking on the corresponding switch. The ring size slider can be used to see the change in parameters when another ring size is chosen.

exact identification of the commissures is hard as good spatial perception is missing. Though the MVN software shows the location of the chosen commissures in a 3D projected volume, this volume can not be used to alter the commissures directly. For future development a better selection method for the commissures should be implemented.

The high Pearson coefficient of 0.87 for the advice model results is most likely caused by the circumference model prediction ( $r^2 = 0.89$ ). This indicates that, if there is a mismatch between the predictors, the circumference should be the best parameter to follow. However, the number of subjects were limited in the validation study and therefore no hard conclusions on the predictive values of each parameter can be made. More patients should be included into the validation study to see if the current trends are still valid in a larger population. The circumference is, in the MVN software, the most reliable parameters due to three reasons: at first the annulus is easily identified as in most cases it is the bending point of the leaflets. Secondly the area can be under estimated as when the leaflets overlap, e.g. due to prolapse, parts of the leaflets are not calculated into the area. At last the C-C can be, as said before, sometimes hardly recognized in the 3D data.

The leaflet prediction model is introduced in this study, but it has not been validated. First the leaflet lengths of the tool should be compared with in situ measurements to see if there are differences between the ones from the Matlab tool. If these correspond, more accurate and reproducible measurements of the leaflet lengths can be performed. This removes the disadvantage that the echocardiologist must try to reproduce the exact same slice in follow-up, as the slice can be selected from the 3D ultrasound dataset. Furthermore these values can be used to determine risk factors for SAM like a large posterior leaflet or a low ratio between the AML and PML, in which the surgeon has to perform PML resection.

The quality of the ultrasound images is important for the performance of the MVN. Poor quality decreases the accuracy of the initial MVN estimation. Manual alteration of the suboptimal prediction can be performed, but due to the quality the distinctiveness can be atrocious. In some datasets artefacts in the mitral valve were present which causes mismatches between the data and the actual mitral valve. In this study these artefacts were not present in the parts of the mitral valve which were used for measurements but it has to be kept in mind in future extension of this study.

## 2.5 Conclusion

This study shows a promising new tool which can be used to standardize the current annuloplasty sizing technique. Better measuring techniques to determine the CC have to be created for a more precise and less user dependent determination of this

parameter. Furthermore, validation should be continued to create more certainty about the predictive values of the tool.

## **2.6 Acknowledgements**

I would like to thank the anaesthesiologists of the Thorax Centrum Twente for creating the possibility to perform this research by acquiring the needed 3D-TEE data. Furthermore I would like to thank my fellow colleagues for the interesting and inspiring conversations, which helped me greatly in this research.

## **2.7 Disclosures**

The authors have no conflict of interests and nothing to disclose.



# Chapter 3

## The use of Pre-operative Two Dimensional Echocardiography to Identify patients at Risk for Systolic Anterior Motion

*R. Bruggink<sup>1,2</sup>, C.H. Slump<sup>1,2</sup>, J.G. Grandjean<sup>1,2</sup>*

<sup>1</sup> University of Twente, Enschede, The Netherlands

<sup>2</sup> Department of Cardiothoracic Surgery, Medisch Spectrum Twente, Enschede, The Netherlands

### 3.1 Introduction

Systolic Anterior Motion (SAM) is a phenomenon in which the mitral valve moves anterior towards the inter ventricular septum during systole, causing a left ventricular outflow obstruction (LVOTO). This can be a life treating condition which often results in severe mitral regurgitation (MR). The severity of SAM differs from minimal LVOTO to a severe MR which causes haemodynamic instability, low cardiac output and hypotension. [42, 43] SAM often occurs when the patients suffers from a hypertrophic obstructive cardiomyopathy (HOCM). In HOCM the left ventricular outflow tract (LVOT) is narrowed by a hypertrophic intra ventricular septum (IVS). Consequently, the distance between the IVS and the mitral valve is decreased making it easier for the leaflet to block the LVOT. [44, 45]. The two main mechanisms for causing SAM are the 'Venturi' and the 'drag' effect. [46] During systole the blood can push the mitral valve directly into the LVOT, this is called the drag-effect. When the LVOT is narrowed, higher blood velocities are facilitated. These higher velocities create lower local pressures, as the law of Bernoulli indicates. This lower pressure can suck the anterior leaflet of the mitral valve (AML) into the LVOT. This phenomenon is called the Venturi-effect. For a long time it was thought the Venturi effect was the main cause of SAM but more recent literature concluded an increased involvement of the drag-

effect. [47] MR is when blood flows from the left ventricle (LV) into the left atrium (LA) during systole, thereby compromising the function of the mitral valve. [48] Untreated MR can lead to pulmonary hypertension and ultimately to heart failure. [49] The treatment with the most proven efficiency is surgery. [8–15] Two different surgical methods are present as the valve can be repaired or replaced. In mitral valve plasty (MVP) it is tried to regain mitral valve functionality while preserving the leaflets. In contrast with repair (MVR) the mitral valve is removed and replaced by a biological or mechanical valve. For most patients MVP is preferable, as it is associated with low rates of thromboembolism, resistance to endocarditis, high durability and no need for anticoagulation. [5, 16–18] SAM is a possible complication after MVP and occurs between 5 to 10% of the surgeries and can increase to 27% in patients suffering from Barlows disease. [38, 50, 51] Multiple studies already suggested predicting factors for SAM like the ratio between the mitral valve leaflet lengths, the distance between septum and the coaptation point and the aorto-mitral angle. [35, 50, 52] In this study it is tried to verify these parameters between the healthy population and patients suffering from SAM. Furthermore the angle of attack, which indicates the angle between the coaptation plane and the outflow is tested. The results of this study can help to highlight patients before MVP which have an increased risk of SAM.

## 3.2 Methods and Materials

Two dimensional transthoracic echocardiography (TTE) images in patients are analysed. Patients are allocated into two groups, patients suffering from SAM and healthy control patients. Images are acquired in the Medisch Spectrum Twente (MST). It was tried to select the control population based on the age distribution present in the SAM cohort. All patients must be above 18 years old and a fully completed echo-cardiograph examination must be performed. Patients were excluded if the patient had prior cardiac surgery or if the dataset is of poor quality.

Data analysis is done with custom made software created with Matlab<sup>5</sup> in which the user is able to select reference points interactively. The parameter selection tool is visualized in figure 3.7. The used parameters are listed below and in table 3.7:

**C-sept** When the distance between the mitral valve and the IVS decreases, the diameter of the outflow tract gets more narrow. This can lead to increased blood velocities and thereby creating a local drop in pressure and increasing the risk of SAM following the Venturi hypothesis. [53] This parameter is calculated by taking the shortest distance between the leaflets coaptation point and the IVS.

**LVOT** As said above, the Venturi effect increases when the outflow tract is narrowed.

---

<sup>5</sup>Matworks Inc. Massachusetts, Version 2015b

**Table 3.7:** The parameters determined by the tool

| Parameter                       | Abbreviation |
|---------------------------------|--------------|
| <u>Distances</u>                |              |
| Coaptation - septum distance    | C-sept       |
| LVOT diameter                   | LVOT         |
| IVS thickness                   | S-thickness  |
| Length of the anterior leaflet  | AML          |
| Length of the posterior leaflet | PML          |
| <u>Angles</u>                   |              |
| Aortomitral angle               | ∠Ao-Mi       |
| Angle of Attack                 | ∠AoA         |
| <u>Ratios</u>                   |              |
| leaflet length ratio            | ALPM         |

This parameter is calculated by taking the smallest distance of the LVOT.

**AML and PML** When the length of the leaflets is increased, it has more freedom to move into the LVOT and thereby increasing the risk of SAM. [54] The length of the leaflets is determined by clicking on its attachment on the annulus and the coaptation point.

**S-thickness** The thickness of the septum is an indicator for HOCM which is a large risk factor for SAM as the blood flow more posterior. [55] This parameter is calculated by measuring the thickest part of the IVS.

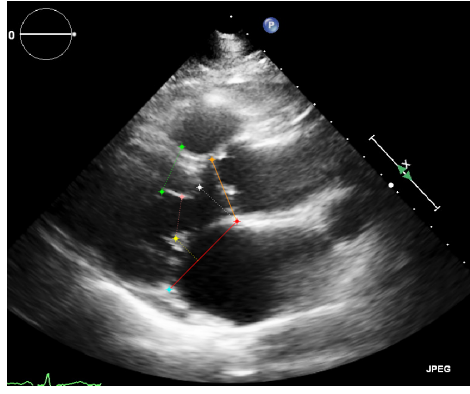
**Aortomitral angle** When the angle of the aorta and mitral valve increases, blood flow is directed more behind the mitral leaflets, increasing the chance of pushing them into the LVOT. [56] The aorto-mitral angle is calculating by taking the angle between the perpendicular lines of the mitral valve and the Aortic valve.

**Angle of attack** As a bulging septum changes the blood flow to posterior as well, it increases the risk of leaflet jibbing. The AoA is calculated by the angle between the perpendicular lines of the mitral valve and LVOT. [56, 57]

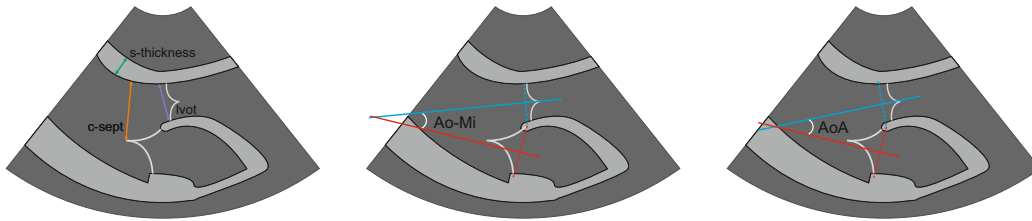
**ALPM** As the PML gets relatively larger to the AML, the coaptation point will alter towards the IVS, decreasing the distance of the leaflets and the LVOT.

Data analysis is performed with SPS<sup>6</sup>. Differences of each parameter between the groups were tested on significance. To see intra-observer variability each dataset was measures twice to determine the intra-class coefficient (ICC).

<sup>6</sup>IBM, USA, version 23 [33]



**Figure 3.7:** An example of a measurement done with Matlab.



**(a)** The distance parameters: C-sept, LVOT and the septum thickness **(b)** The aorto-mitral angle (Ao-Mi) indicating the angle between in and outflow **(c)** The Angle of attack (AoA) which indicates the angle of outflow

**Figure 3.8:** The three functional types of mitral regurgitation

### 3.3 Results

A total of 35 patients suffering from SAM were included into this study (mean age  $65.1 \pm 15$  years, 50% male). 18 patients without cardiac diseases were included as a control group (mean age  $64.2 \pm 12$  years, 63% male). The age and sex distributions were not different between the groups ( $p > 0.05$ ). The Matlab tool was able to process all the datasets and the results between the groups were successfully tested on significant differences. The results are displayed in table 3.8. Significant results are indicated with an asterisk ( $p < 0.05$ ). The parameters C-sept, septum thickness, LVOT diameter, AoA and Aortomitral angle are significantly different between the groups. The ICC of the parameters are moderate, indicating that there were some differences between the two measurements.

**Table 3.8:** Differences between the SAM and the control population. Significant parameters are indicated with an asterisk ( $p < 0.05$ )

| Parameter        | Control |          | SAM    |          | sign. | ICC  | CI 95%     |
|------------------|---------|----------|--------|----------|-------|------|------------|
|                  | $\mu$   | $\sigma$ | $\mu$  | $\sigma$ |       |      |            |
| C-sept (cm)      | 3.2     | 0.4      | 1.9    | 0.4      | 0.00* | 0.76 | 0.46-0.90  |
| S-thickness (cm) | 1.3     | 0.2      | 2.3    | 0.4      | 0.00* | 0.64 | 0.26-0.85  |
| LVOT (cm)        | 4.8     | 0.5      | 4.2    | 0.7      | 0.00* | 0.68 | 0.32-0.87  |
| AMVL (cm)        | 2.5     | 0.5      | 2.6    | 0.5      | 0.59  | 0.49 | 0.05-0.78  |
| PMVL (cm)        | 0.9     | 0.4      | 0.8    | 0.4      | 0.65  | 0.52 | 0.08 -0.79 |
| ALPL (ratio)     | 1.4     | 0.2      | 1.3    | 0.2      | 0.44  | 0.42 | -0.05-0.73 |
| AoA (deg)        | 154°    | 4.9      | 146.4° | 6.4      | 0.00* | 0.60 | 0.20-0.83  |
| Ao-Mi (deg)      | 160°    | 5.7      | 152.1° | 6.7      | 0.00* | 0.66 | 0.29-0.86  |

### 3.4 Discussion

The results show multiple significant differences between patients suffering from SAM and the control population. The thickness of the septum, LVOT diameter and C-sept are significant parameters, which are all indicators for HOCM. This suggests, as literature states, the major role of HOCM in the development of SAM. The significant LVOT diameter suggest that the role of the Venturi-effect could still be present as a local pressure drop is created when the diameter of the LVOT decreases. In addition the drag-effect is supported by significant angles AoA and aorto-mitral angle, which are larger in the SAM population, indicating that the blood is pushed out the heart under a larger angle. When this happens a larger partition of the blood is pushed posterior the mitral valve, thereby increasing the pressure toward the LVOT.

The significant difference between the C-sept and aorto-mitral angle is in agreement to earlier literature. In Maslow et al [35] the C-sept in SAM patients was  $1.9 \pm 0.4$  cm is found, which is in agreement with  $2.3 \pm 0.5$  cm found in this study. However the AL/PL ratio found significant in their study could not be reproduced in this study. This can possible be explained by the difference in the acquisition method. Maslow et al. used transesophageal images which are from better quality in comparison with the TTE images, which makes it easier to distinct leaflet tissue from chordae. The transition between the chordae and leaflet tissue is in most cases hardly seen, and often assumptions have to be made to select the end of the leaflet. However, TTE images are less invasive and available for most patients. Furthermore images with 2D ultrasound are from a cross section of the heart on a particular time, which can be hard to reproduce. This results in differences between parameters when these do not agree between patients, e.g. when the C-sept is calculated in the centre of

the heart it will be larger than measured more lateral. To overcome this problem, 3D images can be made from the left ventricle which help with more reproducible measurements. [58, 59]

The ICC values for the intra-observer variability are not high, with a maximum of 0.76 for the C-sept distance. The coaptation plane of the leaflets can in most cases be identified by follow the leaflets in time, even with bad quality images. The inner septum wall is in most cases identifiable as well, which can explain the higher ICC for the C-sept. The lower mitral and upper aortic annulus were not clear in low quality images, corresponding with the low ICC values in the other parameters.

The most of the patients which have SAM suffer from HOCM. This can explain the large differences of the C-sept and AoA between the control and SAM population. It was tried to create an additional group of patients suffering only from HOCM to see if these parameters are still different between the HOCM and SAM population. However, it was not succeeded to include enough HOCM patients to create a new cohort as most of these patient had suffered from SAM as well. For further research it can be tried to substituted the HOCM group with a not obstructive hypertrophic cardiomyopathy (HCM) group. These patients are larger in number and are lower correlated with SAM. However, as HCM comes in different degrees of severity, a good selection has to be made to decrease intra-population variability.

### **3.5 Conclusion**

The parameters C-sept and aorto-mitral angle are, in agreement with literature, significant different between the cohorts. In addition the AoA and the LVOT diameter differ as well, increasing the list of SAM predictors. These parameters can be used for pre-operative screening of patients before MVP, decreasing the change of developing SAM after the surgery as the surgeon can apply different techniques. Although multiple prediction studies are done, they do not always agree, creating different cut-off values. A large multi-centre cohort study can be done to determine these cut-off values with more precision.

### **3.6 Disclosures**

The author has no conflict in interests and nothing to disclose.

# Chapter 4

## General discussion and future perspectives

### 4.1 Introduction

3D-TEE had already proven its abilities to give the surgeon an optimal view of the structures and lesions in the heart. With this study a start is made for the 3D-TEE to give the surgeon advice about the course of the MVP surgery. With the parameters deriving from the datasets a pre-operative planning can be made, which will give more standardization of the whole process. While the tool is still in development and needs more validation, the results are promising.

### 4.2 Back to the aim of this study

In the begin of this Master thesis the following question is formulated: *'Can per-operative 3D-TEE assist the surgeon in decision making during mitral valve plasty and thereby giving the procedure more standardization?'*. Almost every surgeon has his own strategy in choosing the ring size during annuloplasty based on their observations and expertise. The first article described a method in which the 'observation' is taken over by an application based on linear models. The results of this model are promising as it was able to predict the correct ring size or with one deviation in most patients. Despite this result, two outliers were present in the data, which suggests that the model is not completely fool proof and should always be compared with the surgeons knowledge and expertise. Answering the question, per-operative 3D-TEE can be used to give the surgeon advice which ring size should be optimal in a specific patient. This advice gives the surgeon scientific rationale for its choice, making it more standardized.

## 4.3 Future perspectives

The first steps of creating a guiding environment for the surgeon are made. However much improvements and additions could still be made. In this section the authors vision enhanced with current literature is used to show which future perspectives are present in this topic.

### 4.3.1 3D visualization

Two dimensional ultrasound have a large disadvantage, as these images only visualize a single slice in the three dimensional volume of the mitral valve. This makes it harder to mentally visualise the pathology and measurements of the mitral valve. [60] 3D ultrasound enables to skip the mental visualization part, by creating a 3D moving object which the user can interact (moving and rotating) with it. As proposed in the first article, addition of 3D visualization into the application will help the surgeon to properly understand specific mitral valve. 3D visualization is not new, as the newer ultrasound stations already have implemented this feature. But with the addition of CAD models into this visualization, it will give the surgeon the possibility to 'try' the different annuloplasty ring sizes in this specific mitral valve. Implementing this into the application will create an single environment for the surgeon to prepare the MVP surgery. However this requires good collaboration between the surgeons and anaesthetists as the data must be acquired and processed before.

### 4.3.2 Augmented reality

In addition to 3D visualization is the use of augmented reality. With augmented reality the user sees the real world around him through e.g. a pair of glasses in which certain objects and screens are superimposed upon. This enables to put extra information into the surgeons view, without the need of extra monitors and therefore space. [61, 62] An example is superimposing an ultrasound mitral valve above the patients, which makes enables a quick view to the heart in physiological circumstances and use it as per-operative reference material. Additionally measurement values like, the saturation, blood pressure and temperature can be projected. A possible candidate for this could be the 'Dragonfly' manufactured by Thales<sup>1</sup>. The Dragonfly is a tool which monitors the position of the surgeon, and where he is looking. Knowing of this information can then be used to project the things describe above in a particular place in the view of the surgeon. Furthermore, Chu et al. [63] investigated the use of augmented reality to show important, with TEE calculated,

---

<sup>1</sup>Thales Group, developed by the USA division

intra-cardiac landmarks on the patient. The results are promising as they claim to reduce damage nearly a 40-fold to other intra-cardiac structures.

### **4.3.3 Software Fusion**

In the hospital, dozens of different software packages are present. As multiple programs have to be opened and used, the whole process becomes less clear. Additionally more programs which has to be used simultaneously affects the user-friendliness as the user has to switch between a lot of programs. At this moment the tool is a separate platform, meaning that another additional program has to be used during the process. By trying to implement the models into already existing programs like MVN, additional annoyance and devious work can be prevented. Validation and good contact with manufacturers can help for this implementation.

### **4.3.4 Multi-center collaboration**

In the Medisch Spectrum Twente hospital around 70 MVP surgeries are performed each year which initially can be used to validate this tool. Collaborating with other hospitals makes it possible to increase the number of patients, making the validation process faster. Additionally, this will test the inter-center variability and helps to gain useful feedback about the model and software. Before this can be done the MVN software must be adapted to cope with the limitations described in this thesis.

## **4.4 Final comment**

In this thesis a new, 3D-TEE based, method to predict the ring size during annuloplasty was presented. This will give the surgeon more scientific rationale for his actions, and gives awareness when there are patients at risk. The three way verification of this tool decreases the number of false positives, as the ring size must be predicted with use of three dependent prediction. With this method the scientific rationale and therefore the standardization of MVP surgeries is increased, hopefully lowering the border for surgeons to consider repair over replacement when possible.



# Chapter 5

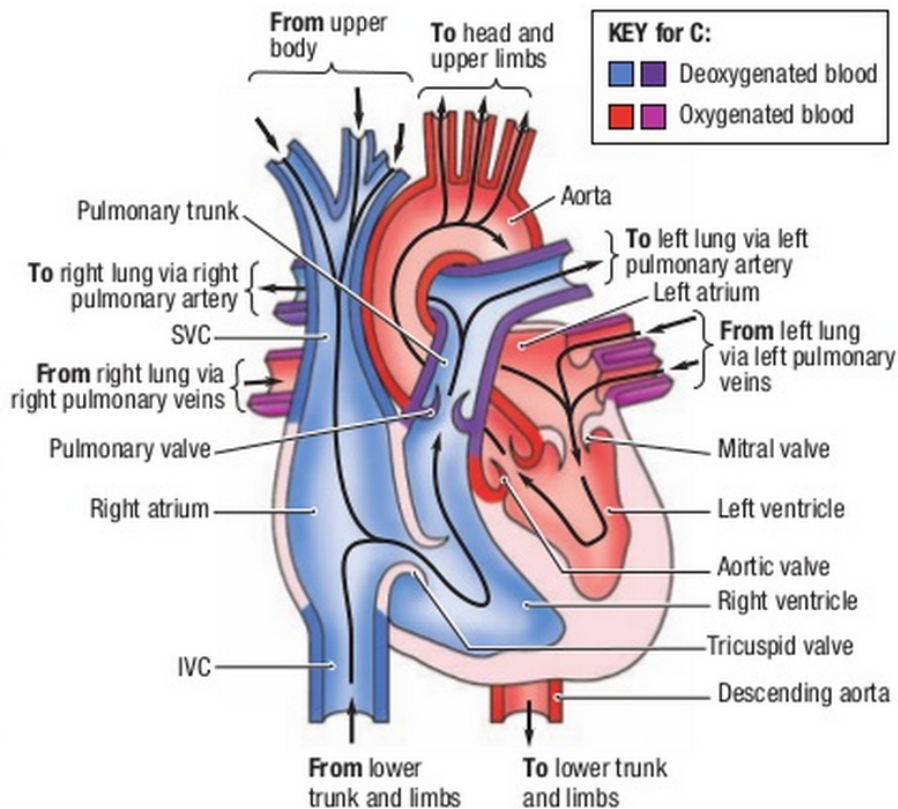
## Appendix

### 5.1 Anatomy

The human heart is a double chambered suction and pressure pump which propels blood thorough the human body. The right side of the heart receives venous blood from the IVC and SVC and pumps it through the pulmonary trunk to the lungs for oxygenation. In the left atria this oxygenated atrial blood is collected allowing the left ventricle to pump it through the Aorta to supply the body with oxygen and nutrients. The anatomy of the heart can be seen in figure 5.1 [64].

To prevent back-flow into the different compartments four valves are present, i.e. the aortic, mitral, pulmonary and the triscupid valve. The mitral valve is located between the left atrium and ventricle and consist out of two noticeable different leaflets, the anterior leaflet (AML) and the posterior leaflet (PML). The AML, often referred as the aortic leaflet, is in general longer, has a trapezoidal shape, a smoother surface than the PML and no distinctive fissures between its segments. From base to end of the leaflet two zones can be seen. The proximal zone, called the atrial zone, is translucent, smooth, regular and thin. In contrast the distal zone, called the rough or coaptation zone, is irregular and thick due to the attached chordae tendinae. The AML is approximately attached on a third of the mitral annulus. The free part is divided in three scallops by two indentations, called 'clefts'. These identification are supported by multiple chordae which facilitates a larger opening of the leaflet at diastole. Like the AML the PML is divided in a smooth and rough zone likewise. The mitral valve contains two commissures: the AC and the PC. At the commissures the leaflets transit to each other. To prevent regurgitation the leaflets must have righteous coaptation. In general the coaptation length is about 7 to 9mm in the middle but become less at the commissures. [5,31]

A widely used classification to distinguish the components of the mitral valve is the Carpentier classification which is shown in figure 5.2. Both leaflets are divided into

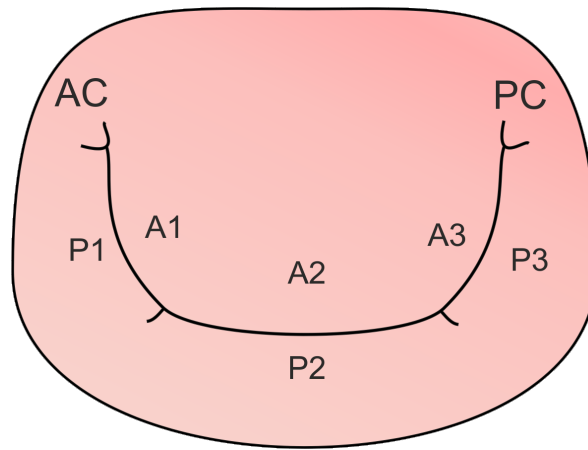


**Figure 5.1:** Anatomy of the human heart, copied from Grants, atlas of anatomy [65].

three segments based on the scallops present in the posterior leaflet. The segments of the posterior are called: P1 (anterolateral), P2 (middle) and P3 (posteromedial). The corresponding segments of the anterior leaflet are classified respectively as A1, A2 and A3. The commissures of the valve are labelled as the anterior commissure (AC) and the posterior commissure (PC). Their function is to create a continuity and full coaptation between the leaflets at their junction. Each commissure is supported by one or two 'fan-like' chordae. [31,66]

The annulus is the junctional zone which separates the left atrium and ventricle and gives attachment to the mitral leaflets. The annulus is shaped as a oval ring is able to change shape during the cardiac cycle. The aortic valve has a fibrous continuity with the AML, which gives a fibrous structure to this part of the leaflet. This makes this part less prone for dilatation. The other, mainly muscular, parts are more seen dilated in significant MR

The mitral valve is part of the sub-valvular apparatus and can not function on its own. The sub-valvular apparatus, meaning the papillary muscles and chordae tendinae, but also the ventricular geometry, is crucial to retain normal valve functionality. The



**Figure 5.2:** Carpentier classification of the mitral valve. A: anterior, P: posterior, AC: anterior commissure and PC: posterior commissure

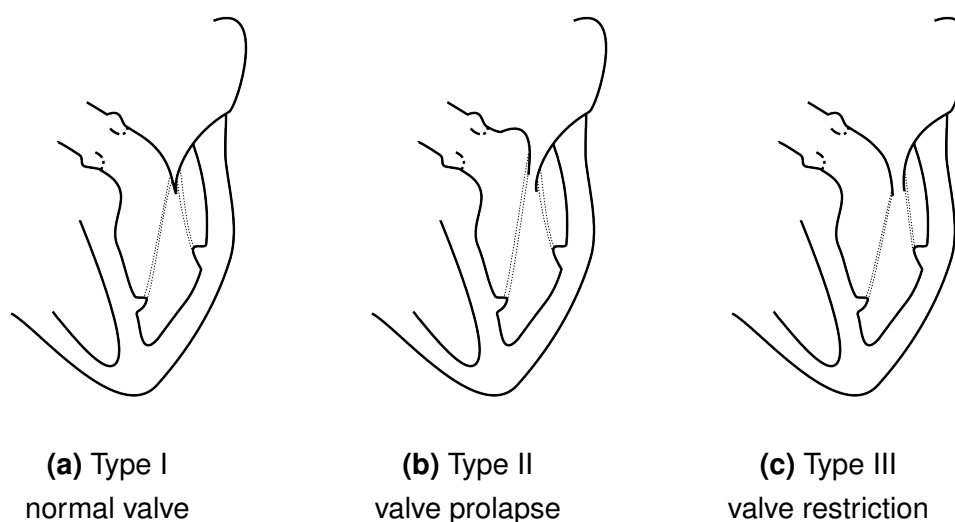
papillary muscles and chordae act like parachute cords during systole, preventing the leaflets (the parachute) from prolapsing, therefore preventing regurgitation.

## 5.2 Pathophysiology

### 5.2.1 Mitral Valve Regurgitation

Mitral valve regurgitation (MR) or mitral insufficiency is a condition in which the mitral valve does not close properly, causing blood to leak into the LA during systole. It can have several causes, as defects of each part of the mitral apparatus can lead to a dysfunctional valve. [41] The main cause is mitral valve prolapse, in which one or both leaflets tip into the atrium during systole. [67] Other causes are rheumatic fever, valve infection or heart remodelling after a heart attack. [68]

Mitral valve regurgitation (MR) or mitral insufficiency is a condition in which the mitral valve does not close properly, causing blood to leak into the LA during systole. Regurgitation can occur in several diseases, e.g. mitral valve prolapse, damage due a heart attack, rheumatic fever, valve infection or heart remodelling. A common cause of MR is ventricular dilatation. When the heart is prolonged exposed to a high blood pressure or intoxication, left ventricular enlargement can occur causing the mitral annulus to expand. When the diameter of the annulus increases, the coaptation of the leaflet becomes less as the leaflets are pulled from each other, resulting in mal-coaptation. Another cause of ventricular enlargement is chronic leakage of the mitral valve which causes a vicious circle. The heart response to prolonged MR is expansion of the left ventricle and atrium, which increases the regurgitation gradation. [68]



**Figure 5.3:** The three functional types of mitral regurgitation

According to Carpentier et al. [31] MR can be divided into three functional classes as seen in figure 5.3. Type I means normal leaflet motion, in type II there is re-

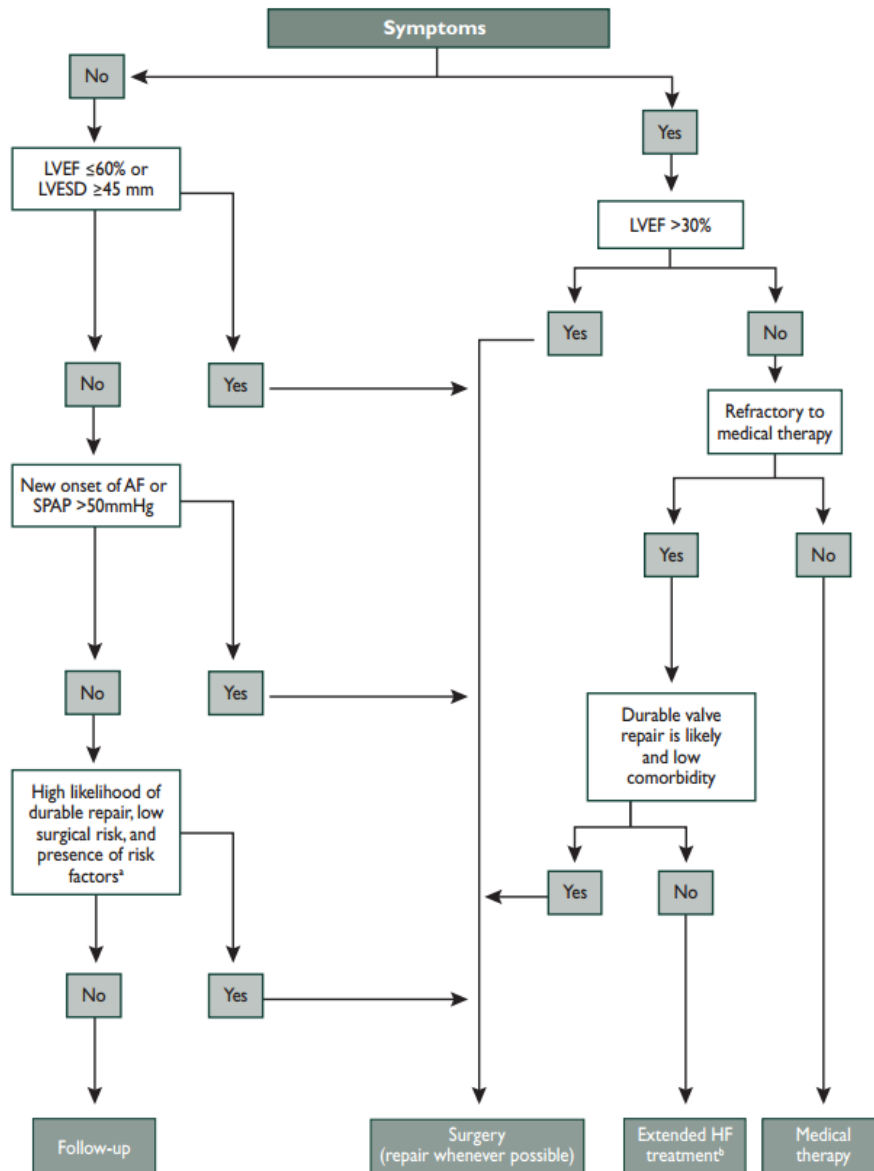
gurgitation due to leaflet prolapse and type III indicates regurgitation due to leaflet restriction. In the last type there are two subtypes: IIa and IIB, which indicates respectively restricted opening and restricted closure. Each functional class be the cause of several pathological diseases and lesions which are listed into table 5.1. Besides the Carpentier classification MR can be primary or secondary. Primary MR covers all the diseases which have their affection on the mitral apparatus, e.g. chordae ruptures. In secondary, or functional MR the mitral apparatus is intact but its distorted by environmental en geometrical factors, like ventricular dilatation due cardiac remodelling.

**Table 5.1:** Causes of valvular dysfunction [31]

| Class            | Valve lesion / disease                                                           |
|------------------|----------------------------------------------------------------------------------|
| <b>Type I</b>    | Annular dilatation<br>Perforation<br>Tear vegetation                             |
| <b>Type II</b>   | Chordae/papillary muscle rupture<br>Chordae/papillary muscle elongation          |
| <b>Type IIIa</b> | Leaflet thickening<br>Commisural fusion<br>Chordae thickening or fusion          |
| <b>Type IIIb</b> | Calcification<br>Ventricular aneurysm / dilatation<br>Ventricular fibrous plaque |

As the pressure in the left atrium and pulmonary veins increases (pulmonary hypertension) symptoms like breathless, fatigue and chest pain can occur. These symptoms can be limited relieved with use of blood pressure decreasing medication like nitrates, diuretics and  $\beta$ -blockers. Surgery is the only long-term solution to prevent dilatation and solve the MR and should be performed before the heart is weakened too much. The ECS developed a flowchart for MR management which can be seen in figure 5.4. Asymptomatic patients with a decreased left ventricle ejection fraction ( $LVEF \leq 60\%$ ) This chart shows that surgery is indicated when the preferred when the patient is symptomatic and  $LVEF > 30\%$  or asymptomatic and  $LVEF > 60\%$

The first clues of the presence of MR can be found with physical examination. The intensity and duration of the systolic murmur or a presence of a third heart sound can indicate MR. Ultrasound is the imaging modality of choice to confirm the diagnosis, and is used in almost every patient showing a murmur. Additionally the MR serverity and prognosis can be assessed, with relatively low costs.



**Figure 5.4:** Guidelines for the management of mitral regurgitation, copied from ESC 2012.

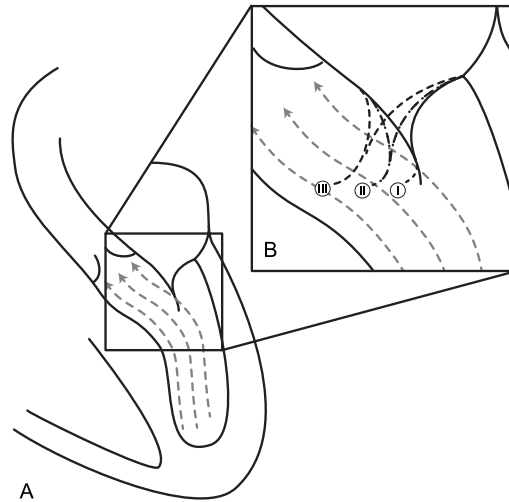
## 5.2.2 Systolic Anterior Motion

Systolic anterior motion (SAM) is a possible lethal phenomenon in which the distal portion of the anterior leaflet is dragged toward the septum during systole [43, 69]. The leaflet remains in this position until end systole, blocking a part of the LVOT. This results in a decreased stroke volume and an increased gradient over the LVOT [21, 70, 71]. Initially SAM was considered to be specific to hypertrophic cardiomyopathy (HCM), a disease in which the intra ventricular septum (IVS) is thickened, but it is now recognised in all settings which alter the complex dynamic anatomy of the left ventricle. Some examples are valve surgery, myocardial infarction and hypertensive

heart disease [72, 73]. The exact mechanism for SAM is not fully understood but literature describes two possible mechanisms: the 'Venturi' effect and the drag effect. The Venturi effect, called after Giovanni Venturi (1746-1822) who described a pressure drop when the velocity in a tube increases, explains a pulling force on the mitral valve during systole. This effect occurs when a part of the LVOT is obstructed e.g. in HOCM where the septum is thickened, thereby decreasing the diameter of the LVOT. Consequently the local bloodflow increases and due to Bernoulli's law the pressure drops. This pressure drop creates a suction force which should pull the mitral valve into the LVOT [56, 74]. The other hypothesis describes the 'drag' effect. When blood is pumped from the LV to the LVOT, it can apply force to the lateral part of the PML, thereby pushing it and consequently the AML towards the septum [54, 56]. Initially it was thought the 'venturi' effect was the major factor for SAM but current research concluded that this effect is overrated and the 'drag' effect is the dominant hydrolic force to push the AML towards the septum [21]. In both principles HOCM can be described as a risk factor for SAM as shown in figure 5.5. In the 'Venturi' effect, the HOCM decreases the LVOT diameter, thereby increasing the suction force and in the 'drag' effect the flow angle is altered which positions the flow more behind the mitral valve. Other risk-factors include a narrow aorto-mitral angle, excessive PML, small AML/PML ratio, a low septum - coaptation length and a too small implanted annuloplasty ring after MVP [75]. The incidence of SAM after MVP is between 2 and 16% despite recent developments in the procedure [75]. Detection of SAM is done with use of ultrasound, in which the leaflets can be monitored, the gradient over the LVOT can be determined and the presence of MR can be seen [43]. Management of SAM is dependent on its severity and can involve surgical interventions which may include subaortic membrane removal, IVS myectomy and leaflet resection. Ibrahim et al. created a management scheme for treating SAM, which can be seen in addendum C.

### 5.2.3 Mitral Stenosis

As closing is the problem with MR, valve opening is the problem in mitral stenosis (MS). The valvular apparatus becomes an obstruction to the left ventricular inflow, as the valvular orifice area decreases. This increases the gradient over the valve, which can cause a lowered cardiac output, an increased atrial pressure and consequently pulmonary hypertension. A normal healthy mitral valve has an orifice area of around 4 to 6 cm<sup>2</sup> and can decrease to 2.25cm<sup>2</sup> without expressing any symptoms like dyspnea. Severe MR occurs when the orifice area becomes smaller than 1cm<sup>2</sup> and results in a subnormal cardiac output which fails to adapt during exercise [77]. The main cause of MS is rheumatic fever but can also be congenital. Diseases like



**Figure 5.5:** A: The influence of a bulging septum on the LVOT flow. B: The process of SAM, In I the coaptation plane is pushed into the LVOT, as in II & III this process is continued until the valve is blocking the LVOT. [76]

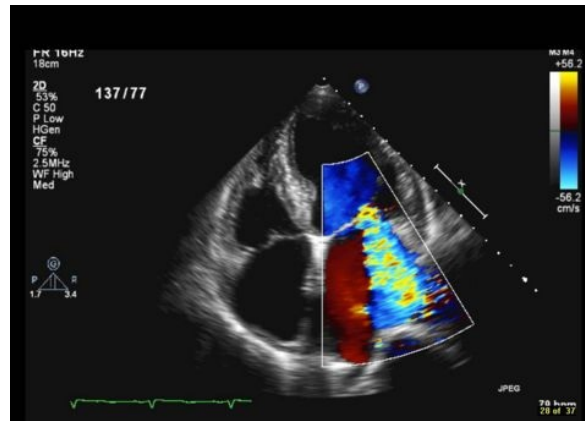
annulus calcification, endocarditis en left atrial myxoma can mimic the physiology of MS. The latency time between rheumatic fever and MS is around the 20 to 40 years and once the symptoms develop it can take about 10 years before they become disabling. The major part of the mortality is due heart failure, other causes include embolisms and infections. Treatment often consist out of surgery (MVR), percutaneous mitral commissurotomy and the use of medication [78].

## 5.3 Ultrasound

Ultrasound is a minimally invasive technique for imaging of internal tissues. The images are based on reflection of sound waves which are emitted by the ultrasound probe and can be compared to the sonar which bats use to navigate. Ultrasound can be used to visualize the heart internal structure and function in real-time without using invasive techniques or ionizing radiation. Additionally ultrasound is fast and portable, which enables quick use in emergency situations. Conventional transthoracic echocardiography (TTE) is used for routine cardiac imaging. Another US technique is transoesophageal echocardiography (TEE) where a ultrasound transducer mounted gastroscope is inserted into the oesophagus. This gives a unobstructed view of the cardiac structures and vessel with superior quality over TTE. However, TEE is semi-invasive and causes patient discomfort and the procedure risk are comparable with normal gastroscopy which include puncture lesions [79]. In the MST, TEE is used in cardio-thoracic surgery as a pre-operative safety check and as a monitoring/validation tool to verify e.g. the function of the new mitral valve. The advantage of TEE during surgery is getting superior image quality while the patient comfort is, due to the anaesthetics, not affected.

The use of 2D ultrasound has three main disadvantages over 3D ultrasound: First the operator has no total overview of the structure, which increases the chance of missing a diagnosis. At second, the volume calculations are based on 2D measurements in two orthogonal views, which has a lot of assumptions and interpolations. At last the repeatability of follow up measurements is hard, as the slice must be on the same location and angle as the previous measurements. In summary it makes it hard to perform precise, repeatable, measurements with use of 2D ultrasound. [60, 80]

MR can be diagnosed with use of the Doppler effect in ultrasound. As moving particles change the frequency of waves, the blood flow direction in the heart can be monitored. Flow over the mitral valve during systole, indicate regurgitation of the mitral valve, which can be seen in figure 5.6. As many people have a physiological MR it is important to differentiate it from pathological. Therefore guidelines are made to scale MR into four different gradations, i.e.: none, mild, moderate and severe. [81]



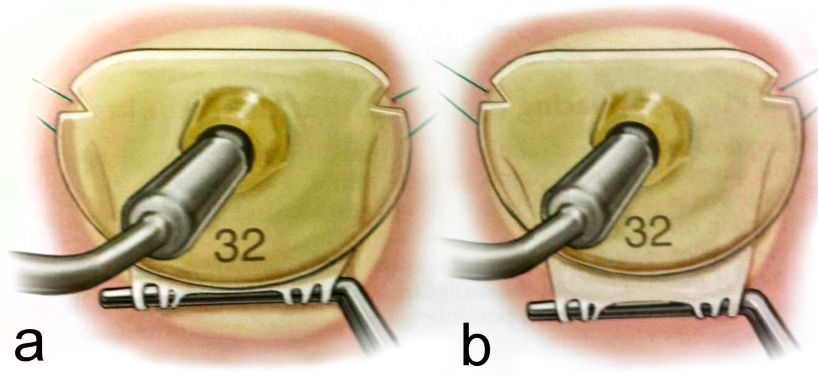
**Figure 5.6:** A somewhat turbulated jet into the left atrium during systole suggests mitral regurgitation. This flow is visualized with use of Doppler ultrasound

## 5.4 Mitral Valve Plasty

Mitral valve plasty (MVP), is the procedure of restoring the mitral valves function without replacing it with a new valve. The first reported MVP was by Bailey et al. [82] in 1951. The modern era of MVP started in 1971 by A. Carpentier which proposed the anatomical changes in patients suffering from MR. This created a foundation for a more systematic and reproducible MVP. [83] In the cardio-thoracic territory he is often called the father of modern valve repair. [84] To perform a successful MVP, four critical components must be satisfied: first the surgeon should have a clear knowledge of the mechanism of the valvular dysfunction; second a consistent and excellent exposure of the mitral valve is achieved; as third the repair techniques are performed precisely and last the result of the repair should be assessed intra-operatively [83]. There are several anatomic approached to get to the mitral valve, like median or right sternotomy or the anterolateral thoracotomy, in which the surgeon uses a minimal invasive technique through the right flank. [85] To get to the mitral valve in the heart, there are multiple approached as well. the most common way is through the left atrium. Further, less used, approaches are through the left ventricle or aortic root.

Several techniques to repair MR are described in the literature. Which technique is used is dependent on the cause of the MR, and is often patient specific. [86] The three most used techniques are annuloplasty, leaflet resection and chordal placement. [87] In annuloplasty a ring is attached on the mitral annulus, changing its diameter. A smaller diameter will result in more leaflet coaptation and can cure MR solely in some cases. Furthermore, annuloplasty stabilizes the annulus, preventing future dilatation. Research has shown that patients who had annuloplasty during MVP are less likely to develop recurrent MR. [34] When a small ring is chosen, mitral stenosis can develop. But is the gradient is around 4 to 6 mmHg, this stenosis is of less importance than the recurrent MR. In leaflet prolapse, caused by elongated or ruptured chordae, new artificial chordae can be implanted. [31, 87]

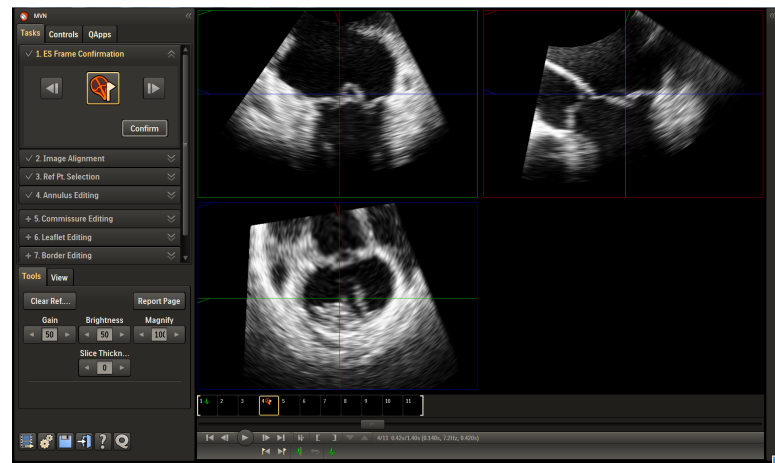
The conservative technique to determine the annuloplasty size is the use of 'annuloplasty sizers', which can be seen back in figure 2.2 and figure 5.7. As said, the annuloplasty ring reduces the annulus diameter, which causes a larger coaptation of the leaflets. The ring size is determined with use of the notches which should correspond with the commissures in the mitral valve and is called the intercommissural distance. Fine-tuning is done by measuring the AML and PML length. When the AML length exceeds the sizer as shown in figure 5.7, a larger ring size is recommended. When the PML length of any segment is greater then 20mm, resection of this segment is advised to prevent SAM. [31].



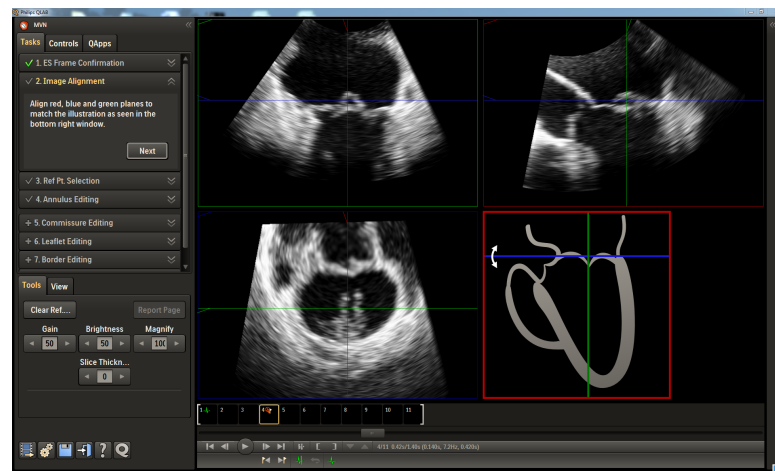
**Figure 5.7:** A: The conventional measurement to determine the ring size, the notches must fit the commissures. B: if the AML exceeds the sizer, a larger ring size is advised. Image adapted from Carpentier et al. [31]

## 5.5 Mitral Valve Navigator

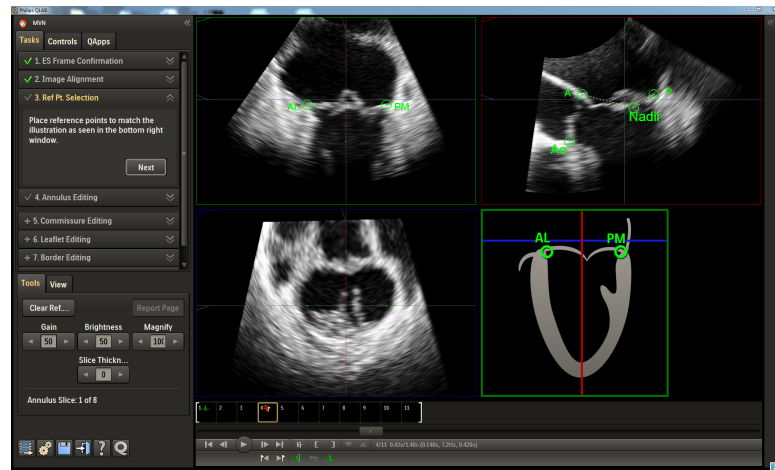
The MVN software semi-automatically segments the mitral valve from a 3D TEE dataset. With the buttons in the left screen the user can change the gain, brightness, slice-thickness and the zoom of the 3D volume. The gain can be used to make the valve more visible by removing the low echo-dense structures before its location. The segmentation is done in seven steps, which are explained by the figures below:



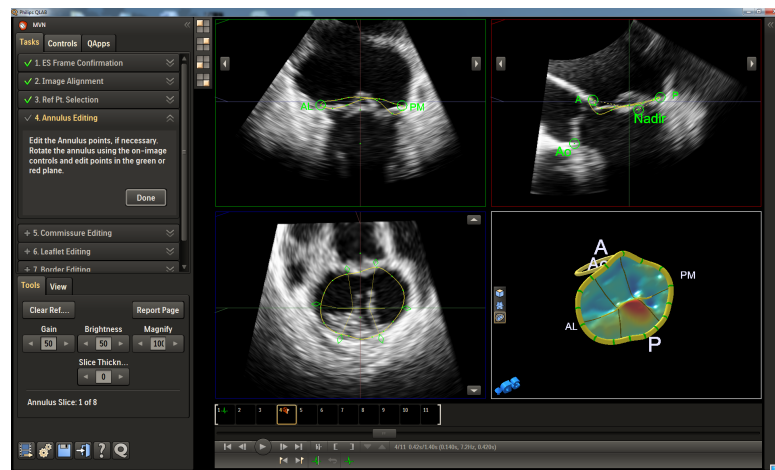
**Figure 5.8:** Step 1, validation if the right frame is chosen. The correct frame is the early diastolic frame, just before opening of the mitral valve.



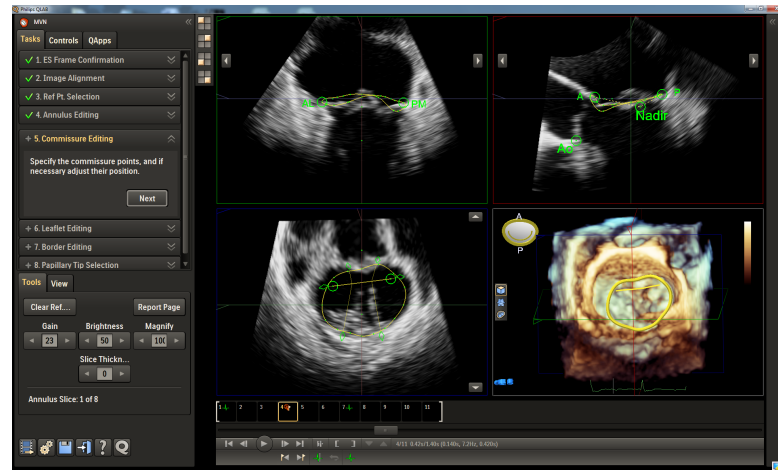
**Figure 5.9:** Step 2, By rotating the volumes and moving the middle point to the locations which are shown in the right lower box, the tool get information about the location of different needed structures. E.g. the tool now knows that the aorta is present at the left in the upper right image.



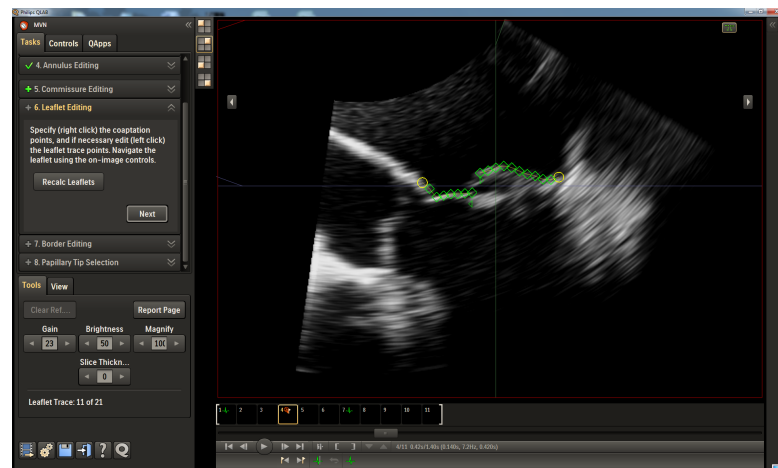
**Figure 5.10:** Step 3, Initial points are needed to make an atlas based estimation of the annulus. This is done by moving the indicator points to the annulus. Furthermore the nadir (coaptation point) and the lower aortic annulus must be marked which are used to calculate different parameters.



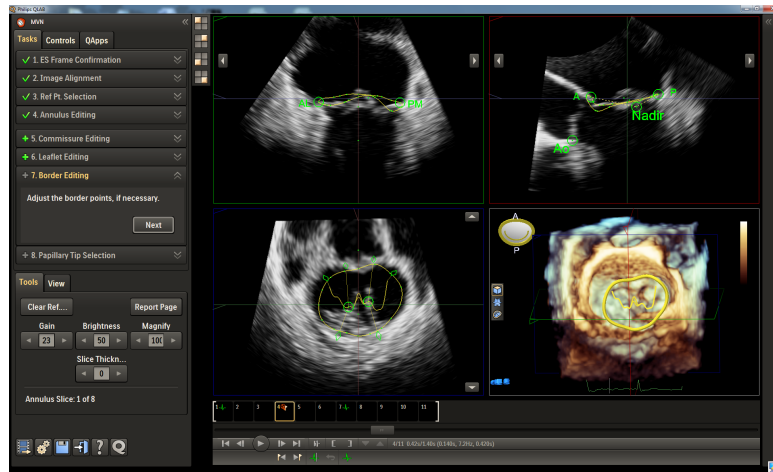
**Figure 5.11:** Step 4, After the estimation is finished, the annulus points must be manual checked and, if needed, adapted to their right location



**Figure 5.12:** Step 5, The two commissure points have to be manually placed. This can best be done with help of the 3D volume projection in the lower right box.



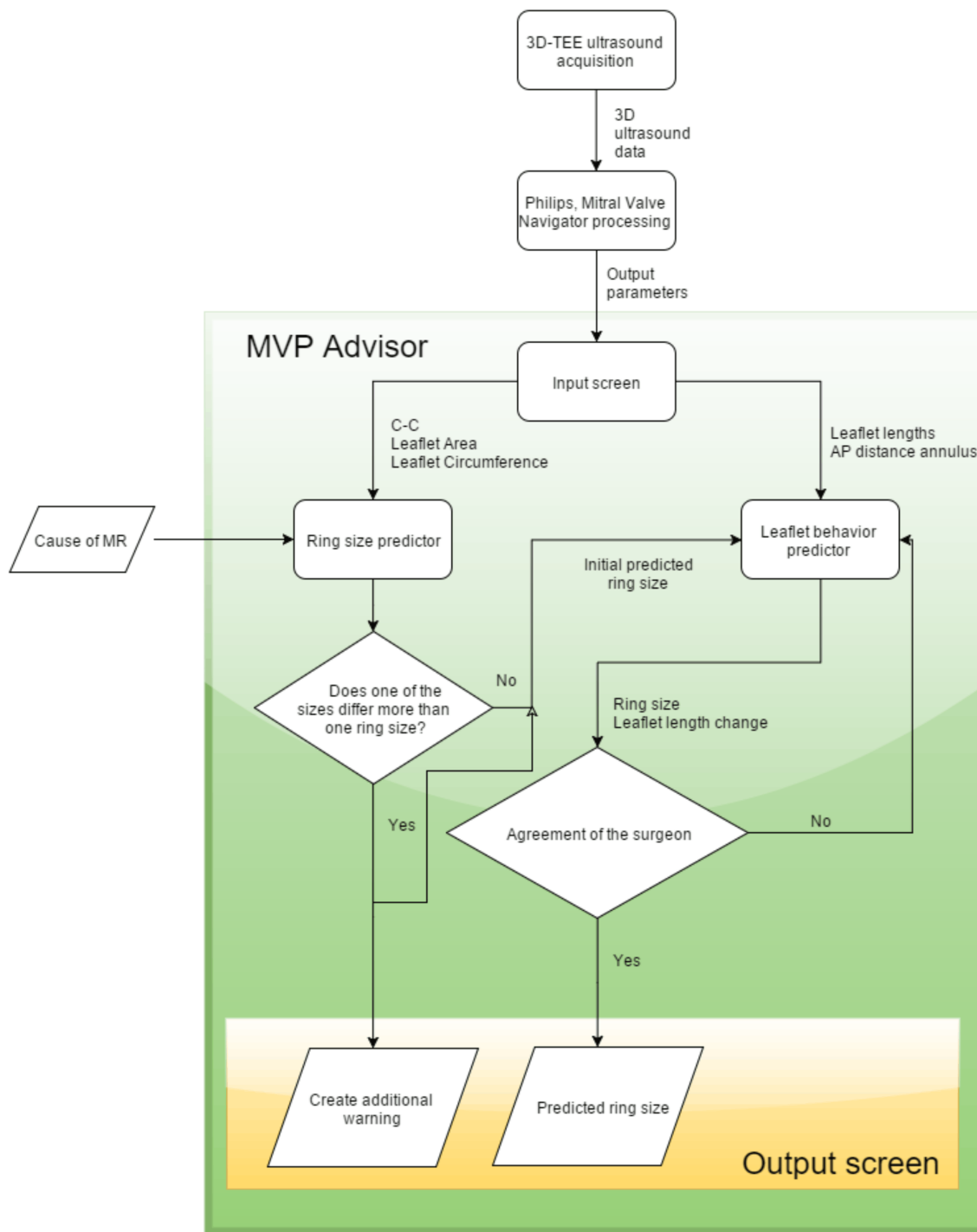
**Figure 5.13:** Step 6, To determine the area of the leaflets, their location and curvature must be known. MVN first estimates the contour of the leaflets, which can be altered by clicking with the mouse on another location. In most cases this is not needed as the estimation is in general good. With the right mouse button the border between the two leaflets is selected, which is used to distinate the leaflet area to the AML or PML area. In this figure the limitation of the tool is seen as the prolapse of the PML can not be added to the lenght of the PML



**Figure 5.14:** Step 7, The border between the valvular segments can be assigned by dragging the diamond to their right locations. When this is not done properly, the area and lengths of each leaflet segment is not accurate, and can not be used.

## 5.6 Prediction Tool

The current model can be described by the flowchart present in figure 5.15. The 'MVP advisor' application is visualized by the green box in the middle in which multiple processed are present. The whole process starts with the acquisition of the 3D-TEE data by the anaesthetist. The mitral valve is semi-automatic segmented and analysed with use of the MVN software developed by Philips. The resulting parameters of this program is exported and loaded into the MVP advisor. With use of three independently predicting parameters the ring size is calculated. If one of the three parameter differs one of more sizes, an alert is created on the result page. As literature advises to apply 'under-sizing' when the MR is caused by dilatation, the resulting size is reduced by one size. With use of the calculated ring the change in leaflet lengths, after implementation, is approximated with the 'leaflet behavior predictor'. When the surgeon disagrees with the result, the predicted ring size can be manually changed, triggering the 'leaflet behaviour predictor' to update the changed leaflet values. For validation, the results are saved into a database. This records the patient characteristics, input parameters, predicted ring sizes and the implemented ring sizes. These values can later be used to see the accuracy and additional value of this tool in the clinical setting.



**Figure 5.15:** A flowchart describing the working of the model

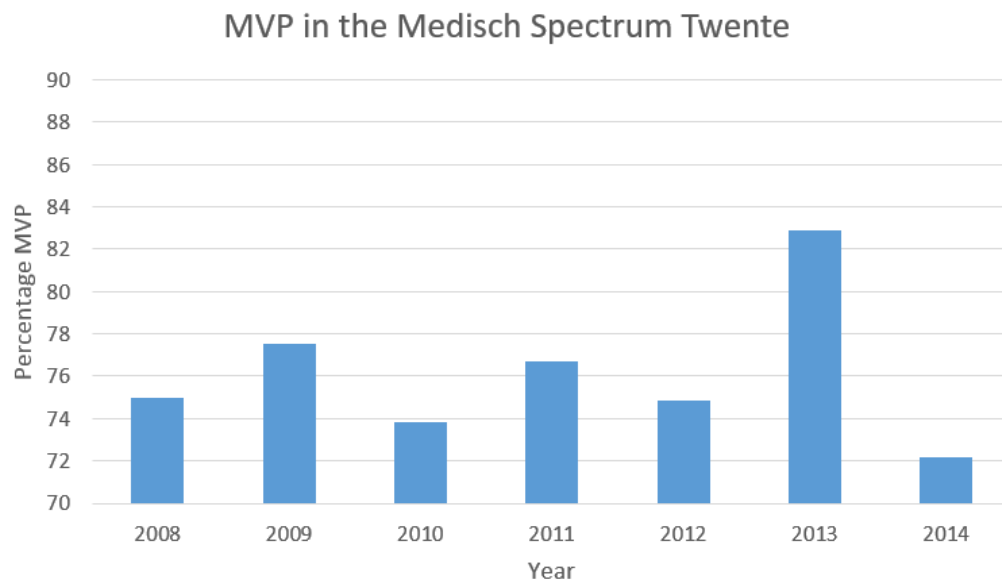
## 5.7 MVP/MVR ratio's in the Medisch Spectrum Twente hospital

To assess the MVP/MVR ratio in the Medisch Spectrum Twente hospital, data of mitral surgeries between July 2008 to December 2014 were collected. The data was grouped by MVP and MVR, in which the MVP can further be divided into: only annuloplasty, mitral reconstruction and annuloplasty and reconstruction. In total of 1327 patient had mitral surgery 40.8% male, age  $67 \pm 11.1$  and Euroscore<sup>1</sup>  $9.2 \pm 10.5$ . Other characteristics are shown in table 5.2. The results can be seen in figure 5.16. The mean MVP/MVR ratio was 76.1%. This percentage did not differ much through the years with exception of the year 2013, in which 83% of the patients who underwent mitral surgery had their mitral valve repaired. The Euroscore was significantly lower in the MVP groups ( $7.8 \pm 8.2$  vs  $16.2 \pm 16.1$ ), indicating that patients with a higher Euroscore are more likely to get a total replacement. However, redo surgeries were not taken into account, which possibly can explain a part of this difference. The Euroscore increases by three points when the patient had prior cardiac surgery and as it is more likely for a patient to get a MVR in a redo-surgery the Euroscore is increased in this group.

**Table 5.2:** Patient characteristics of the patients who underwent mitral valve surgery. Parameters marked with an asterisk are significant different between the groups

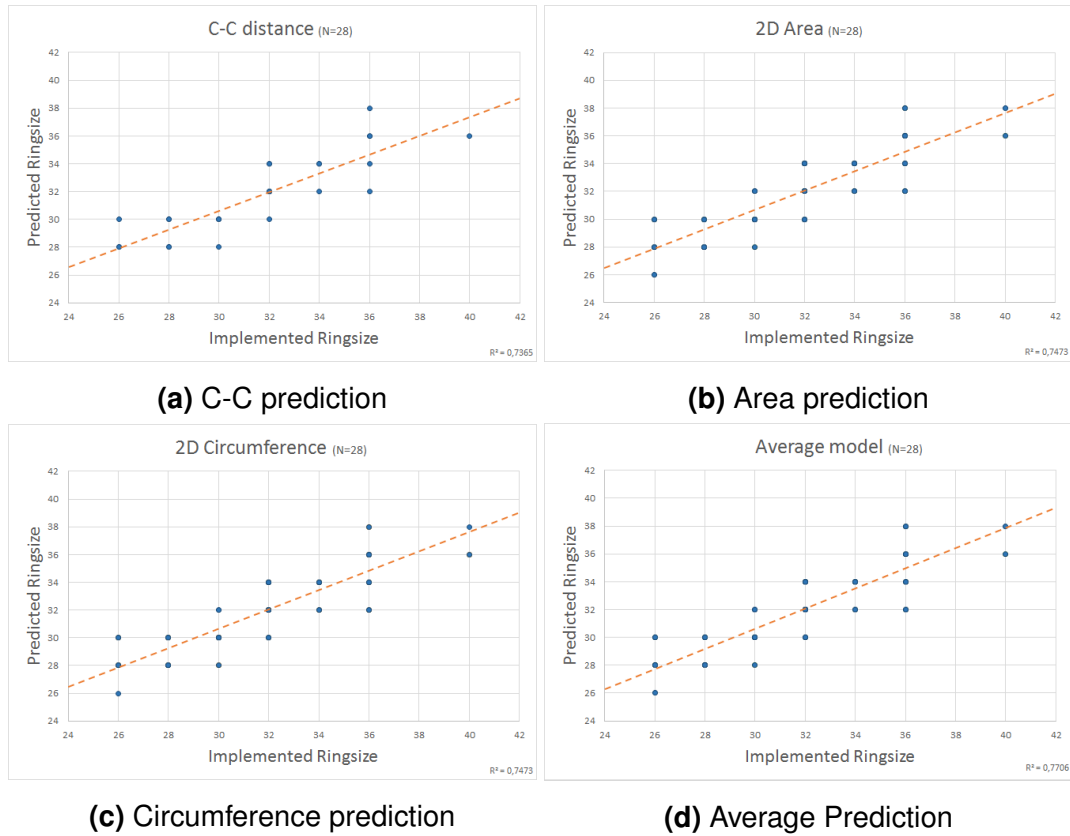
| Charateristic         | MVR (n=251)      | MVP (n=1076)     | Sign  |
|-----------------------|------------------|------------------|-------|
| Age                   | $66.7y \pm 11.2$ | $67.1y \pm 11.1$ | 0.65  |
| Sex (percentage male) | 46%              | 64%              | 0.00* |
| BMI                   | $27.0 \pm 8.3$   | $26.4 \pm 4.3$   | 0.11  |
| Euroscore I           | $15.0 \pm 15.5$  | $7.85 \pm 8.35$  | 0.00* |
| Severity              | $3.2 \pm 1.22$   | $3.2 \pm 1.22$   | 0.62  |

<sup>1</sup>The euroSCORE I, used for calculate the risk of death in heart surgery [88]



**Figure 5.16:** The percentage of MVP during mitral valve surgeries.

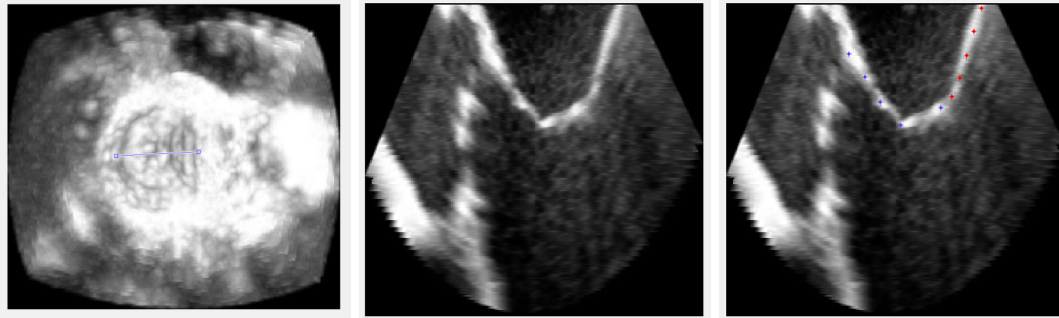
## 5.8 Additional model graphs



**Figure 5.17:** The ring size predictions vs the actually implanted ring.

## 5.9 4D volume measuring tool

Until no sufficient solution is implemented into the MVN software, the custom made Matlab tool can be used to determine the lengths of the AML and PML. This tool works in two simple steps. In the first (figure 5.18a) step the user has to draw a line perpendicular on and in the middle of the coaptation plane. At this location the leaflets have their longest length in most cases. This line will be used to calculate a slice which is shown in figure 5.18b. In step two (figure 5.18c) the user is now able to measure the leaflet lengths by putting five points on it, which gives more accuracy in curved leaflets in comparison a single line measurement.



**(a)** Selection of the needed slice **(b)** Resulting slice, in which the A2 and P2 are visible **(c)** Manual tracking of the leaflets

**Figure 5.18:** The three functional types of mitral regurgitation

# Bibliography

- [1] W Y Kim, P G Walker, E M Pedersen, J K Poulsen, S Oyre, K Houlind, and a P Yoganathan. Left ventricular blood flow patterns in normal subjects: a quantitative analysis by three-dimensional magnetic resonance velocity mapping. *Journal of the American College of Cardiology*, 26(1):224–38, July 1995.
- [2] Tomasz a Timek, David T Lai, Paul Dagum, Frederick Tibayan, George T Daughters, David Liang, Gerald J Berry, D Craig Miller, and Neil B Ingels. Ablation of mitral annular and leaflet muscle: effects on annular and leaflet dynamics. *American journal of physiology. Heart and circulatory physiology*, 285(4):H1668–74, October 2003.
- [3] Akinobu Itoh, Gaurav Krishnamurthy, Julia C Swanson, Daniel B Ennis, Wolfgang Bothe, Ellen Kuhl, Matts Karlsson, Lauren R Davis, D Craig Miller, and Neil B Ingels. Active stiffening of mitral valve leaflets in the beating heart. *American journal of physiology. Heart and circulatory physiology*, 296(6):H1766–73, June 2009.
- [4] Blase A Carabello. The current therapy for mitral regurgitation. *Journal of the American College of Cardiology*, 52(5):319–26, July 2008.
- [5] Karen P McCarthy, Liam Ring, and Bushra S Rana. Anatomy of the mitral valve: understanding the mitral valve complex in mitral regurgitation. *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology*, 11(10):i3–9, December 2010.
- [6] Maurice Enriquez-Sarano, Cary W Akins, and Alec Vahanian. Mitral regurgitation. *Lancet*, 373(9672):1382–94, April 2009.
- [7] Bernard lung and Alec Vahanian. Epidemiology of acquired valvular heart disease. *The Canadian journal of cardiology*, 30(9):962–70, September 2014.
- [8] Giovanni B Pedrazzini, Francesco Faletra, Giuseppe Vassalli, Stefanos Demertzis, and Tiziano Moccetti. Mitral regurgitation. *Swiss medical weekly*, 140(3-4):36–43, January 2010.

- [9] Catherine M Otto. Chronic Mitral Regurgitation. *The New England Journal of Medicine*, 345(10):740–746, 2001.
- [10] Louis P. Perrault, Alan J. Moskowitz, Irving L. Kron, Michael a. Acker, Marissa a. Miller, Keith a. Horvath, Vinod H. Thourani, Michael Argenziano, David a. D'Allessandro, Eugene H. Blackstone, Claudia S. Moy, Joseph P. Mathew, Judy Hung, Timothy J. Gardner, and Michael K. Parides. Optimal surgical management of severe ischemic mitral regurgitation: To repair or to replace? *The Journal of Thoracic and Cardiovascular Surgery*, 143(6):1396–1403, November 2011.
- [11] Ottavio Alfieri and Michele De Bonis. Mitral valve repair for functional mitral regurgitation: is annuloplasty alone enough? *Current Opinion in Cardiology*, 25(2):114–118, March 2010.
- [12] Damien J LaPar and Irving L Kron. Should all ischemic mitral regurgitation be repaired? When should we replace? *Current opinion in cardiology*, 26(2):113–7, March 2011.
- [13] Jen-Ping Chang. Reparative surgery for degenerative mitral valve regurgitation. *Formosan Journal of Surgery*, 44(6):211–214, December 2011.
- [14] Janne J Jokinen, Mikko J Hippeläinen, Otto a Pitkänen, and Juha E K Hartikainen. Mitral valve replacement versus repair: propensity-adjusted survival and quality-of-life analysis. *The Annals of thoracic surgery*, 84(2):451–8, August 2007.
- [15] Mir Wasif Ali and Steven F Bolling. Mitral valve repair: What the ACORN Trial taught us. *Current cardiology reports*, 12(2):116–21, March 2010.
- [16] Lieng H Ling, Maurice Enriquez-Sarano, James B Seward, A Jamil Tajik, Hartzell V Schaff, Kent R Bailey, and Robert L Frye. Clinical outcome of mitral regurgitation due to flail leaflet. *New England Journal of Medicine*, 335(19):1417–1423, 1996.
- [17] Maurice Enriquez-sarano, Hartzell V Schaff, Thomas A Orszulak, A Jamil, Kent R Bailey, and Robert L Frye. Valve Repair Improves the Outcome of Surgery for Mitral Regurgitation. pages 1022–1028, 1995.
- [18] Rakesh M Suri, Hartzell V Schaff, Joseph a Dearani, Thoralf M Sundt, Richard C Daly, Charles J Mullany, Maurice Enriquez-Sarano, and Thomas a Orszulak. Survival advantage and improved durability of mitral repair for leaflet prolapse subsets in the current era. *The Annals of thoracic surgery*, 82(3):819–26, September 2006.

- [19] James S Gammie, Shubin Sheng, Bartley P Griffith, Eric D Peterson, J Scott Rankin, Sean M O'Brien, and James M Brown. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *The Annals of thoracic surgery*, 87(5):1431–7; discussion 1437–9, May 2009.
- [20] Paul W M Fedak, Patrick M. McCarthy, and Robert O. Bonow. Evolving concepts and technologies in mitral valve repair. *Circulation*, 117(7):963–974, 2008.
- [21] Mark V Sherrid, C K Chu, Ernest Delia, Allen Mogtader, and Edward M Dwyer. An Echocardiographic Study of the Fluid Mechanics of Obstruction in Hypertrophic Cardiomyopathy. *Journal of the American College of Cardiology*, 22(3):816–825, 1993.
- [22] Ruth K. Petrone, Heinrich G. Klues, Julio A. Panza, Elfriede E. Peterson, and Barry J. Maron. Coexistence of mitral valve prolapse in a consecutive group of 528 patients with hypertrophic cardiomyopathy assessed with echocardiography. *Journal of the American College of Cardiology*, 20(1):55–61, July 1992.
- [23] Francesco Maffessanti, Nina a. Marsan, Gloria Tamborini, Lissa Sugeng, Enrico G. Caiani, Paola Gripari, Francesco Alamanni, Valluvan Jeevanandam, Roberto M. Lang, and Mauro Pepi. Quantitative Analysis of Mitral Valve Apparatus in Mitral Valve Prolapse Before and After Annuloplasty: A Three-Dimensional Intraoperative Transesophageal Study. *Journal of the American Society of Echocardiography*, 24(4):405–413, 2011.
- [24] Edward B Savage, T Bruce Ferguson, and Verdi J DiSesa. Use of mitral valve repair: analysis of contemporary United States experience reported to the Society of Thoracic Surgeons National Cardiac Database. *The Annals of thoracic surgery*, 75(3):820–5, March 2003.
- [25] B lung. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *European Heart Journal*, 24(13):1231–1243, July 2003.
- [26] Wolfgang Bothe, D Craig Miller, and Torsten Doenst. Sizing for mitral annuloplasty: where does science stop and voodoo begin? *The Annals of thoracic surgery*, 95(4):1475–83, April 2013.
- [27] Mauro Pepi, Gloria Tamborini, Anna Maltagliati, Claudia Agnese Galli, Erminio Sisillo, Luca Salvi, Moreno Naliato, Massimo Porqueddu, Alessandro Parolari, Marco Zanobini, and Francesco Alamanni. Head-to-head comparison of two-

- and three-dimensional transthoracic and transesophageal echocardiography in the localization of mitral valve prolapse. *Journal of the American College of Cardiology*, 48(12):2524–30, December 2006.
- [28] B lung. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *European Heart Journal*, 24(13):1231–1243, July 2003.
- [29] A Marc Gillinov, Eugene H Blackstone, Edward R Nowicki, Worawong Slisatkorn, Ghannam Al-Dossari, Douglas R Johnston, Kristopher M George, Penny L Houghtaling, Brian Griffin, Joseph F Sabik, and Lars G Svensson. Valve repair versus valve replacement for degenerative mitral valve disease. *The Journal of thoracic and cardiovascular surgery*, 135(4):885–93, 893.e1–2, April 2008.
- [30] Ronald a. Kahn, Alexander J. C. Mitnacht, and Anelechi C. Anyanwu. Systolic Anterior Motion as a Result of Relative Undersizing of a Mitral Valve Annulus in a Patient with Barlows Disease. *Anesthesia & Analgesia*, 108(4):1102–1104, 2009.
- [31] Alain Carpentier, David H Adams, and Farzan Filsoufi. *Reconstructive Valve Surgery*. Saunders Elsevier, 2010.
- [32] Philips Healthcare. Mitral Valve Navigator version 10.2, 2014.
- [33] SPSS inc. SPSS 23 for Windows, 2015.
- [34] Manuel K Rausch, Wolfgang Bothe, John-Peder Escobar Kvitting, Julia C Swanson, D Craig Miller, and Ellen Kuhl. Mitral valve annuloplasty: a quantitative clinical and mechanical comparison of different annuloplasty devices. *Annals of biomedical engineering*, 40(3):750–61, March 2012.
- [35] A D Maslow, M M Regan, J M Haering, R G Johnson, and R a Levine. Echocardiographic predictors of left ventricular outflow tract obstruction and systolic anterior motion of the mitral valve after mitral valve reconstruction for myxomatous valve disease. *Journal of the American College of Cardiology*, 34(7):2096–104, December 1999.
- [36] Srilakshmi Adhyapak and Srilakshmi M. Adhyapak. *Ventricular Geometry in Post-Myocardial Infarction Aneurysms: Implications for Surgical Ventricular Restoration*. Springer Science & Business Media, 2012.
- [37] J. Kwan. Geometric Differences of the Mitral Apparatus Between Ischemic and Dilated Cardiomyopathy With Significant Mitral Regurgitation: Real-Time

Three-Dimensional Echocardiography Study. *Circulation*, 107(8):1135–1140, 2003.

- [38] Robin Varghese, Anelechi C Anyanwu, Shinobu Itagaki, Federico Milla, Javier Castillo, and David H Adams. Management of systolic anterior motion after mitral valve repair: an algorithm. *The Journal of thoracic and cardiovascular surgery*, 143(4 Suppl):S2–7, April 2012.
- [39] Jacob Cohen, Patricia Cohen, Stephen G. West, and Leona S. Aiken. *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*. 2013.
- [40] Matthew a Romano and Steven F Bolling. Update on mitral repair in dilated cardiomyopathy. *Journal of cardiac surgery*, 19(5):396–400, 2004.
- [41] Pravin M Shah. Current concepts in mitral valve prolapse—diagnosis and management. *Journal of cardiology*, 56(2):125–33, September 2010.
- [42] Ottavio Alfieri and Elisabetta Lapenna. Systolic anterior motion after mitral valve repair: where do we stand in 2015? *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*, 48(3):344–6, September 2015.
- [43] Michael Ibrahim, Christopher Rao, Hutan Ashrafian, Umar Chaudhry, Ara Darzi, and Thanos Athanasiou. Modern management of systolic anterior motion of the mitral valve. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*, 41(6):1260–70, June 2012.
- [44] H Reul, N Talukder, and EW Müller. Fluid mechanics of the natural mitral valve. *Journal of biomechanics*, 14(5):361–372, 1981.
- [45] E D Wigle, Z Sasson, M a Henderson, T D Ruddy, J Fulop, H Rakowski, and W G Williams. Hypertrophic cardiomyopathy. The importance of the site and the extent of hypertrophy. A review. *Progress in cardiovascular diseases*, 28(1):1–83, 1985.
- [46] P Spirito and B J Maron. Patterns of systolic anterior motion of the mitral valve in hypertrophic cardiomyopathy: assessment by two-dimensional echocardiography. *The American journal of cardiology*, 54(8):1039–46, November 1984.
- [47] Mark V Sherid. Pathophysiology and treatment of hypertrophic cardiomyopathy. *Progress in cardiovascular diseases*, 49(2):123–51, 2006.
- [48] Elaine N Marieb, Jon Mallat, and Patricia Brady Wilhelm. Heart Valves. In *Human Anatomy*, chapter The Heart, pages 537–540. Pearson Benjamin Cummings, San Francisco, fifth edition, 2008.

- [49] Parveen Kumar and Michael L. Clark. *Kumar & Clark Clinical Medicine*. 2002.
- [50] Takashi Miura, Kiyoyuki Eishi, Shiro Yamachika, Kouji Hashizume, Shiro Hazama, Tsuneo Ariyoshi, Shinichiro Taniguchi, Kenta Izumi, Wataru Hashimoto, and Tomohiro Odate. Systolic anterior motion after mitral valve repair: predicting factors and management. *General thoracic and cardiovascular surgery*, 59(11):737–42, November 2011.
- [51] Morgan L Brown, Martin D Abel, Roger L Click, Ronald G Morford, Joseph a Dearani, Thoralf M Sundt, Thomas a Orszulak, and Harzell V Schaff. Systolic anterior motion after mitral valve repair: is surgical intervention necessary? *The Journal of thoracic and cardiovascular surgery*, 133(1):136–43, January 2007.
- [52] Robin Varghese, Shinobu Itagaki, Anelechi C Anyanwu, Paula Trigo, Gregory Fischer, and David H Adams. Predicting systolic anterior motion after mitral valve reconstruction: using intraoperative transoesophageal echocardiography to identify those at greatest risk. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*, 45(1):132–7; discussion 137–8, January 2014.
- [53] Christopher M Walker, Gautham P Reddy, Tan-Lucien H Mohammed, and Jonathan H Chung. Systolic anterior motion of the mitral valve. *Journal of thoracic imaging*, 27(4):W87, July 2012.
- [54] L Jiang, R a Levine, M E King, and a E Weyman. An integrated mechanism for systolic anterior motion of the mitral valve in hypertrophic cardiomyopathy based on echocardiographic observations. *American heart journal*, 113(3):633–44, March 1987.
- [55] Sameh M Said, Hartzell V Schaff, Rakesh M Suri, Kevin L Greason, Joseph a Dearani, and Rick a Nishimura. Bulging subaortic septum: an important risk factor for systolic anterior motion after mitral valve repair. *The Annals of thoracic surgery*, 91(5):1427–32, May 2011.
- [56] Mark V Sherid, David Z Gunsburg, Sonja Moldenhauer, and Gretchen Pearle. Systolic anterior motion begins at low left ventricular outflow tract velocity in obstructive hypertrophic cardiomyopathy. *Journal of the American College of Cardiology*, 36(4):1344–1354, October 2000.
- [57] Ehud Schwammental and Robert A Levine. Dynamic Subaortic Obstruction: A Disease of the Mitral Valve Suitable for Surgical Repair? *JACC*, 28(1):203–206, 1996.

- [58] Kambiz Shahgaldi, Cristina da Silva, Magnus Bäck, Andreas Rück, Aristomenis Manouras, and Anders Sahlén. Transesophageal echocardiography measurements of aortic annulus diameter using biplane mode in patients undergoing transcatheter aortic valve implantation. *Cardiovascular ultrasound*, 11(1):5, January 2013.
- [59] Judy Hung, Roberto Lang, Frank Flachskampf, Stanton K Shernan, Marti L McCulloch, David B Adams, James Thomas, Mani Vannan, and Thomas Ryan. 3D echocardiography: a review of the current status and future directions. *Journal of the American Society of Echocardiography official publication of the American Society of Echocardiography*, 20(3):213–33, 2007.
- [60] Bernhard L Partik, Alfred Stadler, Stephan Schamp, Anke Koller, Martin Voracek, Gertraud Heinz, and Thomas H Helbich. 3D versus 2D ultrasound: accuracy of volume measurement in human cadaver kidneys. *Investigative radiology*, 37(9):489–95, September 2002.
- [61] Ronald Azuma and Ronald Azuma. A survey of augmented reality. *Presence: Teleoperators and Virtual Environments*, 6(4):355–385, 1997.
- [62] Jeffrey H Shuhaiber. Augmented reality in surgery. *Archives of surgery (Chicago, Ill. : 1960)*, 139(2):170–4, February 2004.
- [63] Michael W A Chu, John Moore, Terry Peters, Daniel Bainbridge, David McCarty, Gerard M Guiraudon, Chris Wedlake, Pencilla Lang, Martin Rajchl, Maria E Currie, Richard C Daly, and Bob Kiaii. Augmented reality image guidance improves navigation for beating heart mitral valve repair. *Innovations (Philadelphia, Pa.)*, 7(4):274–81, January.
- [64] Keith Moore, Package Lww, Moore, and Patrick Doc. *Clinically Oriented Anatomy, 6th Ed. + Anatomy: a Regional Atlas of the Human Body, North American Edition*. Lippincott Williams & Wilkins, 2012.
- [65] A. M. R. Agur and Arthur F. Dalley. *Grant's Atlas of Anatomy*. Lippincott Williams & Wilkins, 2009.
- [66] Pravin M. Shah. Current concepts in mitral valve prolapse-Diagnosis and management. *Journal of Cardiology*, 56(2):125–133, 2010.
- [67] Julia C Swanson, Gaurav Krishnamurthy, Akinobu Itoh, John-Peder Escobar Kvitting, Wolfgang Bothe, D Craig Miller, and Neil B Ingels. Multiple mitral leaflet contractile systems in the beating heart. *Journal of biomechanics*, 44(7):1328–33, April 2011.

- [68] Zoltan G Turi. Cardiology patient page. Mitral valve disease. *Circulation*, 109(6):e38–41, March 2004.
- [69] Robin Varghese, Anelechi C Anyanwu, Shinobu Itagaki, Federico Milla, Javier Castillo, and David H Adams. Management of systolic anterior motion after mitral valve repair: an algorithm. *The Journal of thoracic and cardiovascular surgery*, 143(4 Suppl):S2–7, April 2012.
- [70] Edward L Yellin, Srdjan Nikolic, and Robert W M Frater. Left Ventricular Filling Dynamics and Diastolic Function. *Progress in cardiovascular diseases*, XXXII(4):247–271, 1990.
- [71] M V Sherrid, D Z Gunsburg, S Moldenhauer, and G Pearle. Systolic anterior motion begins at low left ventricular outflow tract velocity in obstructive hypertrophic cardiomyopathy. *Journal of the American College of Cardiology*, 36(4):1344–54, October 2000.
- [72] Michael Ibrahim, Christopher Rao, Hutan Ashrafian, Umar Chaudhry, Ara Darzi, and Thanos Athanasiou. Modern management of systolic anterior motion of the mitral valve. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*, 41(6):1260–70, June 2012.
- [73] M Luckie and R S Khattar. Systolic anterior motion of the mitral valve—beyond hypertrophic cardiomyopathy. *Heart (British Cardiac Society)*, 94(11):1383–5, November 2008.
- [74] Lynn M Charls. SAM-systolic anterior motion of the anterior mitral valve leaflet post-surgical mitral valve repair. *Heart & lung : the journal of critical care*, 32(6):402–6, January 2003.
- [75] Andrew D. Maslow, Meredith M. Regan, J.Michael Haering, Robert G. Johnson, and Robert A. Levine. Echocardiographic predictors of left ventricular outflow tract obstruction and systolic anterior motion of the mitral valve after mitral valve reconstruction for myxomatous valve disease. *Journal of the American College of Cardiology*, 34(7):2096–2104, December 1999.
- [76] R. Bruggink, S.A.J. Engelhard, T.M. Fabius, and B.J.M. Hermans. Multi Disciplinary Assignment Technical Medicine Plan of approach Introduction. 2012.
- [77] C Dima and K Desser. Mitral Stenosis: Background, Pathophysiology, Epidemiology, 2014.

- [78] Alec Vahanian, Ottavio Alfieri, Felicita Andreotti, Manuel J. Antunes, Gonzalo Barón-Esquivias, Helmut Baumgartner, Michael Andrew Borger, Thierry P. Carrel, Michele De Bonis, Arturo Evangelista, Volkmar Falk, Bernard Iung, Patrizio Lancellotti, Luc Pierard, Susanna Price, Hans Joachim Schäfers, Gerhard Schuler, Janina Stepinska, Karl Swedberg, Johanna Takkenberg, Ulrich Otto Von Oppell, Stephan Windecker, Jose Luis Zamorano, Marian Zembala, Jeroen J. Bax, Claudio Ceconi, Veronica Dean, Christi Deaton, Robert Fagard, Christian Funck-Brentano, David Hasdai, Arno Hoes, Paulus Kirchhof, Juhani Knuuti, Philippe Kolh, Theresa McDonagh, Cyril Moulin, Bogdan a. Popescu, Željko Reiner, Udo Sechtem, Per Anton Sirnes, Michal Tendra, Adam Torbicki, Ludwig Von Segesser, Luigi P. Badano, Matjaž Bunc, Marc J. Claeys, Nikša Drinković, Gerasimos Filippatos, Gilbert Habib, a. Pieter Kappetein, Roland Kassab, Gregory Y H Lip, Neil Moat, Georg Nickenig, Catherine M. Otto, John Pepper, Nicolo Piazza, Petronella G. Pieper, Raphael Rosenhek, Naltin Shuka, Ehud Schwammenthal, Juerg Schwitter, Pilar Tornos Mas, Pedro T. Trindade, and Thomas Walther. Guidelines on the management of valvular heart disease (version 2012). *European Heart Journal*, 33(19):2451–2496, 2012.
- [79] W. G. Daniel, R. Erbel, W. Kasper, C. A. Visser, R. Engberding, G. R. Sutherland, E. Grube, P. Hanrath, B. Maisch, and K. Dennig. Safety of transesophageal echocardiography. A multicenter survey of 10,419 examinations. *Circulation*, 83(3):817–821, March 1991.
- [80] A Fenster, D B Downey, and H N Cardinal. Three-dimensional ultrasound imaging. *Physics in medicine and biology*, 46(5):R67–R99, 2001.
- [81] William a. Zoghbi, Maurice Enriquez-Sarano, Elyse Foster, Paul a. Grayburn, Carol D. Kraft, Robert a. Levine, Petros Nihoyannopoulos, Catherine M. Otto, Miguel a. Quinones, Harry Rakowski, William J. Stewart, Alan Waggoner, and Neil J. Weissman. Recommendations for Evaluation of the Severity of Native Valvular Regurgitation with Two-dimensional and Doppler Echocardiography. *Journal of the American Society of Echocardiography*, 16(7):777–802, 2003.
- [82] C.P. Bailey, T.J.E. O'Neill, R.P. Glover, W.L. Jamison, and H.P.R. Ramirez. Surgical repair of mitral insufficiency. *Diseases of the chest*, 19(2):125–37, February 1951.
- [83] A. Marc Gillinov and Delos M. Cosgrove. Mitral Valve Repair. *Operative Techniques in Thoracic and Cardiovascular Surgery*, 3(2):95–108, May 1998.

- [84] Tues Wed, Edition Annual, Tirone E David, and William G Williams. AATS Daily News, Tuesday s Simultaneous David predicts Nabel clear on NHLBI vision :. *AATS Daily News*, pages 11–14, 2005.
- [85] R.G.C. Inderbitzi, Melfi Schmid, R.A., and R.P. Casula. *Minimally Invasive Thoracic and Cardiac Surgery: Textbook and Atlas*. Springer Science & Business Media, 2012.
- [86] Patrick Perier, Wolfgang Hohenberger, Fitsum Lakew, Gerhard Batz, and Anno Diegeler. Minimally invasive repair of posterior leaflet mitral valve prolapse with the "respect" approach. *Annals of cardiothoracic surgery*, 2(6):833–8, November 2013.
- [87] Donald D. Glower. Surgical Approaches to Mitral Regurgitation. *Journal of the American College of Cardiology*, 60(15):1315–1322, 2012.
- [88] Samer a M Nashef, Francois Roques, Bradley G Hammill, Eric D Peterson, Philippe Michel, Frederick L Grover, Richard K H Wyse, and T Bruce Ferguson. Validation of European System for Cardiac Operative Risk Evaluation (EuroSCORE) in North American cardiac surgery. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*, 22(1):101–5, 2002.