

# UNIVERSITY OF TWENTE.

Faculty of Science & Technology

## CircAdapt: Model validation and prediction of anatomical and haemodynamic parameters for patients with mitral insufficiency

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## Abbreviations

|       |                                        |
|-------|----------------------------------------|
| CO    | Cardiac Output                         |
| EOA   | Effective Orifice Area                 |
| ERO   | Effective Regurgitant Orifice          |
| EROA  | Effective Regurgitant Orifice Area     |
| LA    | Left Atrium                            |
| LV    | Left Ventricle                         |
| LVEDV | Left Ventricular End Diastolic Volume  |
| LVEF  | Left Ventricular Ejection Fraction     |
| MET   | Metabolic Equivalent of Task           |
| MI    | Mitral Insufficiency                   |
| mLAP  | mean Left Atrial Pressure              |
| MRI   | Magnetic Resonance Imaging             |
| MUMC  | Maastricht University Medical Centre   |
| MV    | Mitral Valve                           |
| PISA  | Proximal Isovolemic Surface Area       |
| RA    | Right Atrium                           |
| RV    | Right Ventricle                        |
| RVEDV | Right Ventricular End Diastolic Volume |
| VC    | Vena Contracta                         |
| VCA   | Vena Contracta Area                    |

## Abstract

**Introduction:** It is still unclear which of the many treatment options for a mitral insufficiency (MI) would give the best result for each individual patient. Patient specific simulations in haemodynamic circulation models could be the solution. The aim of this study is to take a step towards the validation of the CircAdapt model and to gain knowledge about the different aspects that could play a role in MI.

**Method:** Simulations of the heart and circulatory dynamics in patients with MI are done with the CircAdapt mathematical model. Validation of CircAdapt with exercise capacity and left ventricular ejection fraction (LVEF) was done with patient data from Maastricht University Medical Centre (MUMC). The influence of the effective regurgitant orifice area (EROA), effective orifice area (EOA) and cavity dilatation on the exercise capacity of MI patients was examined. Also, the effect of the MitraClip was simulated.

**Results:** The data regarding exercise capacity cannot be used to validate CircAdapt. The simulated LVEF resembles the trend in the patient data. Out of all the cavities, right ventricular (RV) function has the greatest influence on the exercise capacity of MI patients. EOA has a bigger influence on the exercise capacity for smaller EROAs.

**Conclusion:** For further validation studies and patient specific simulations, the measurement and handling of the necessary data has to be improved. CircAdapt cannot be validated with restricted patient data. The simulation results are in line with the expectations based on known physiology and pathology. Furthermore, a prospective study with a homogeneous population should be considered. It is interesting to examine the function and mechanics of the RV further. Relationships between single input parameters need to be further researched and adopted into CircAdapt for a better representation of reality.

**Keywords:** Mitral Insufficiency, CircAdapt, Effective Regurgitant Orifice Area, Exercise, MitraClip

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# 1 Introduction

## 1.1 Introduction

Mitral insufficiency (MI) is the most common heart valve disease and its prevalence increases with age. From the people above the age of 75, 1 out of 10 suffers from MI. Because of the heavy link between age and degenerative heart diseases, it is very likely that there will be increasingly more MI interventions in the future as the average age of the population is getting higher. [1]

There are plenty of treatments to treat MI. At the moment surgical procedure is the golden standard. In the past, complete replacement of the mitral valve (MV) was very common. Recently other surgical options to treat MI have become available like valvular resection, ring annuloplasty or by using the Alfieri stitch. [2] However, for some patients the advantages of surgery will not outweigh its risks. Some patients therefore, do not undergo treatment at all.

A less invasive option is placing a MitraClip via a catheter, which grips the two leaflets of the MV together. This makes those leaflets close better and decreases MI. This intervention is percutaneous and less invasive than the surgical procedure. [3, 4] Interventions to help patients with MI are however not always successful for every patient. Additionally, it is still unclear which of the many treatment options for a MI would give the best result for each individual patient. Lastly, valve treatments are the most expensive and risky of all heart operations, making the correct choice regarding treatment options vital. [5]

Patient specific simulations in haemodynamic circulation models could be extremely valuable in the solution for this problem. If the effects of the treatment options can be simulated for every individual patient, then that could help with determining which procedure would be the best for each patient. Simulations of the cardiovascular mechanics and haemodynamics can already be done with CircAdapt, which is a mathematical model of the heart and circulation. [6] This model has been validated for the normal circulation and in various other applications. [7] It however, has not been validated for MI yet. The aim of this study is to validate CircAdapt regarding MI. This will be done with the help of patient data from the Maastricht University Medical Centre (MUMC), obtained from Doppler echocardiography and the results of ergometry tests.

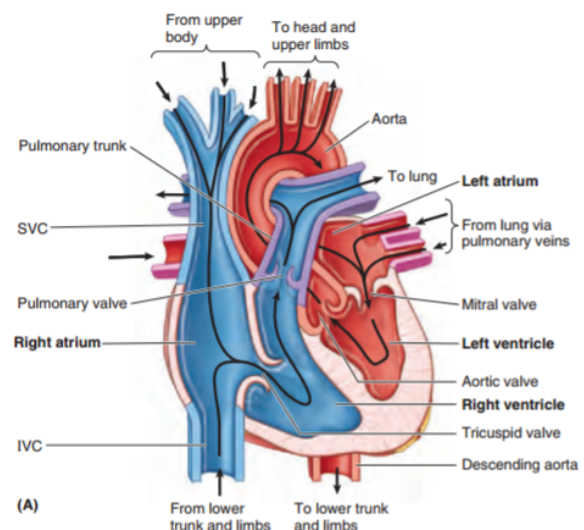
Besides attempting to validate the model with the patient data, the effect of certain parameters on the cardiac function in case of MI will be simulated. These simulations will provide insight in which parameters are possibly important for haemodynamic performance of a patient with MI and which parameters could be promising to target in treatments. The simulation results could be clinically validated in further research to advance the validation of CircAdapt.

This study may be a first step towards the validation of patient specific simulations in CircAdapt for patients with MI and may give an insight in what parameters could be interesting to examine further. More research after this study is needed before it can be clinically useful. The results and findings of this study using patient data from MUMC may contribute to answer the following overall main question:

Is CircAdapt valid for patient specific simulation of patients with mitral insufficiency during exercise and rest so predictions can be made on what treatments would lead to the best results?

## 1.2 Background

### 1.2.1 Anatomy



**Figure 1:** Anatomical overview of the frontal section of the heart. [8]

The heart can be divided into four cavities which are separated by walls and valves (Figure 1). The right side of the heart consists of the right atrium (RA) and right ventricle (RV), with the tricuspid valve positioned in between the two cavities. Connected to the RA are the superior and inferior vena cava that provide the heart with the

venous return from the rest of the body. The left side of the heart consists the left atrium (LA) and left ventricle (LV), with the MV separating them. [8]

The wall of each ventricle consists of three layers. These are, from the inside to the outside, the endocardium, which covers the heart valves, myocardium and epicardium. The epicardium is a thin external layer. The myocardium is the thickest layer and consists of muscles. The ventricles are primarily muscular, because they have to deliver the most work during the blood circulation. [8]

The myofibers are connected to the cardiac skeleton. The four cavities of the heart are separated by the four fibrous rings of the heart (*annulus fibrosus cordis*) and are all part of the cardiac skeleton. These four rings surround the orifices of all the valves. [8] The cardiac skeleton and its fibrous rings provide structure and support to the heart and enables opening of the valves. Especially the atrioventricular ring of the MV needs to be supportive, because of the thickness of the LV. The skeleton also provides attachment to the valve leaflets. Additionally, electric signals generated by the heart are isolated so impulses can reach the atria and ventricles separately, which ensures independent contraction. [9]

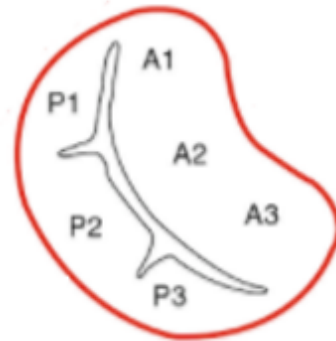
The MV is a complex structure consisting of the LA, LV, valve leaflets, the wall of the LV, the chordae tendineae and the papillary muscles. United, all these structures are called the MV apparatus. [10]

The mitral annulus is a structure shaped like a horse saddle, consisting of connective tissue and muscle tissue. Muscle tissue can mainly be found in the posterior part of the annulus, which enables the annulus to contract. The valve leaflets are connected to the annulus, so contraction of the annulus leads to closure of the valve.

The MV consists of an anterior and posterior leaflet. The anterior leaflet can functionally be divided into three parts, A1, A2 and A3. The posterior leaflet can be divided into P1, P2 and P3 (Figure 2). [11]

The MV leaflets consist out of three layers surrounded by an outer collagenous elastic endothelial layer. The first layer is the atrialis, originating from the LA endocardium. The second layer, the fibrosa is an extension of the fibrocollagenous tissue of the annulus. It contains colla-

gen and elastin fibres. The final layer is the spongiosa which contains a lot of collagen. This layer is in between the atrialis and fibrosa. [12, 13]



**Figure 2:** Schematic overview of the anterior and posterior leaflets of the mitral valve. The anterior leaflet is divided in A1, A2 and A3. The posterior leaflet is divided in P1, P2 and P3. [11]

The chordae tendineae prevent prolapse of the leaflets into the LA. The chordae tendineae are tendon threads connected to the two papillary muscles. In total there are about 25 chordae tendineae connected to 60 points of the MV apparatus.

There is a posteromedial and an anteromedial papillary muscle, which both originate from the corresponding side of the free wall of the LV. Every papillary muscle is connected to both valve leaflets with chordae tendineae. If one of the muscles is damaged, both leaflets will be affected.

Damage to the chordae can lead to MI. It is important that the chordae stay extended to prevent prolapse of the MV. This is accomplished by keeping the distance between the annulus and papillary muscle at a constant length. This is done by simultaneous contraction of the papillary muscles with the LV. [14]

### 1.2.2 Physiology

The function of the heart is to provide the body with oxygen, by circulating blood. During atrial systole the blood flows from the LA to the LV. The pressure in the LA exceeds the pressure in the LV, causing the MV to open. The chordae tendineae are relaxed when the MV is open. Subsequently the ventricular systole takes place during which the LV contracts. The oxygenated blood flows into the aorta and is circulated

through the rest of the body. Because the pressure in the LV rises above the LA pressure, the MV closes, preventing the blood from flowing back into the LA. After the systole comes the diastole of the heart during which the heart is relaxed. The pressure gradient causes the blood to flow passively from the LA into the LV, with an open MV. The diastole is directly followed by the atrial systole and the cardiac cycle starts over again.

With normal valvular function, the amount of blood flowing into the aorta every minute is called the cardiac output (CO). The CO is defined as the stroke volume multiplied by the heart rate. At rest the heart rate is 71 beats per min and the CO is 5 L/min, but this can increase to 200 bpm and 25 L/min during exercise. Eventually there is the diastole of the heart during which the heart is relaxed. The pressure gradient causes the blood to flow passively from the LA into the LV, with an open MV. [15, 16]

### 1.2.3 Pathology

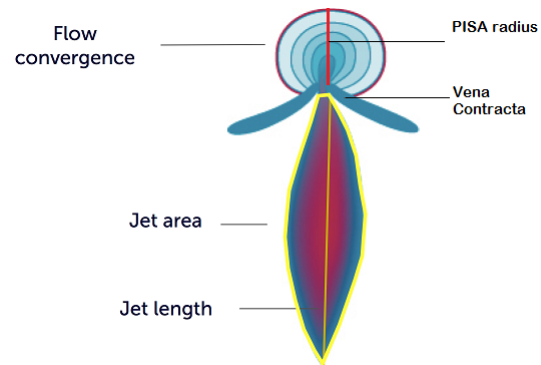
The MV is the most often associated with valvular heart diseases because of its complexity. [17] In case of MI, the anterior and posterior leaflet do not close completely during ventricular systole. This causes backflow of blood from the LV to the LA, which leads to a reduced blood flow through the systemic circulation. To compensate for the leakage, the LV starts to contract stronger to pump more blood into the aorta. Due to this, dilatation and hypertrophy of the LV will occur and the pump function of the heart can deteriorate. [18]

To estimate the severity of MI, the effective regurgitant orifice area (EROA) is used. This is the area of the effective regurgitant orifice (ERO) between the MV leaflets during systole. A mild MI is defined by an EROA of less than  $0.2 \text{ cm}^2$ , moderate by an EROA of  $0.2\text{-}0.4 \text{ cm}^2$  and severe MI is defined by an EROA of more than  $0.4 \text{ cm}^2$ . Healthy subjects have almost no EROA. [19]

The EROA can be calculated from the regurgitant flow and the flow velocity through the orifice. The velocity can be measured with Doppler echocardiography, but for the regurgitant flow, the radius of the proximal isovelocity surface area (PISA) is needed (Figure 3). The PISA is a 3D surface area where the flow converges on the orifice in layers of equal velocity. The pressure gradient created by the orifice causes the flow to converge, which creates the PISA.

The principle is that if the regurgitation is mild,

only the blood nearer to the orifice will accelerate towards the orifice whereas in severe regurgitation, blood from farther away from the orifice will start accelerating towards it. The radius of the PISA indicates how far away from the orifice the blood starts accelerating towards the orifice. A larger PISA radius leads to more regurgitant flow and a larger EROA.



**Figure 3:** Jet flow of the regurgitation. Definition of PISA, vena contracta and other echocardiographic parameters. [20]

Another way to estimate the severity of MI is by using the vena contracta (VC). The VC is defined as the narrowest width of the proximal regurgitant jet just below the orifice and can be measured with Doppler echocardiography. [21] The VC is smaller than the ERO.

There are different possible causes for MI. A distinction can be made between structural and functional MI. When the valve is structurally abnormal, such as in a prolapse, the MI is considered structural. If the valve is structurally normal, but leaks because of the remodelling of the heart, the MI is considered functional. [22, 23]

Even though there are two distinct causes of MI, it is clinically hard to discover whether the origin of the MI was structural or functional. Functional changes in the LV geometry can create structural defects in the mitral apparatus. Vice versa, structural errors can induce functional changes.

MI is dynamic, because of changes dependent on loading conditions and the phase of cardiac cycle. [24] The effective orifice area (EOA) is the anatomical area of the MV orifice during diastole. The EOA can be determined with Doppler echocardiography and corresponds to the location of the smallest cross-sectional area through the valve during diastole. [25] If the EOA is narrowed, this could result in impairment of filling



of the LV in diastole. Such a narrowing can lead to MV stenosis.

#### 1.2.4 CircAdapt

CircAdapt is a mathematical model of the heart and circulation developed by the Department of Biomedical Engineering of MUMC. [6] With this model, real time beat-to-beat simulation of the haemodynamics of the cardiovascular system during physiological and pathophysiological situations can be performed. This model consists of a network of four modules that represent the main elements of the closed-loop cardiovascular system, including the heart compartments, the blood vessels, the valves and the periphery resistances in the pulmonary and systemic circulation. The core of the model consists of a system of differential equations in state variables with respect to time. Examples of these state variables are the volumes, pressures and flows in all compartments of the model. The model records all these state variables for every heartbeat as function of time. [7] The model is coded in MATLAB, where all the variables that are used in the equations can be altered. [26]

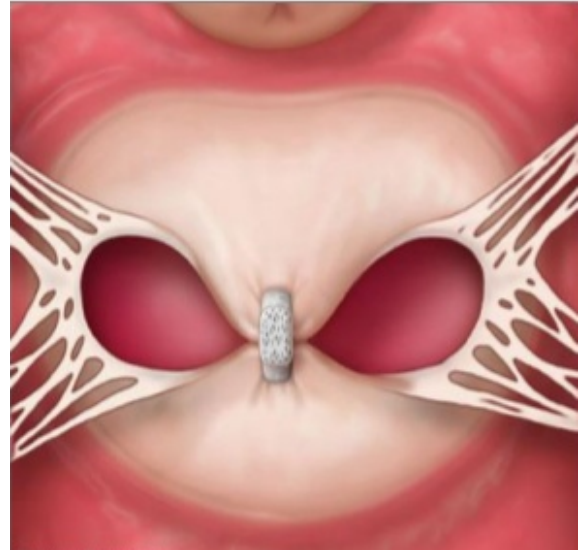
The model takes CO and heart rate as input to simulate exercise. CircAdapt interprets the two inputs as the exercise level it should reach. By altering the vascular resistance and the total volume of blood, CircAdapt can increase the venous return and mean pressure inside the RA which ultimately leads into an increase of the CO. The model is asked to make the necessary adaptations to reach the specified CO and is even capable of making adaptations outside the physiological domain to reach its goal.

#### 1.2.5 Mitral surgery and MitraClip

Surgical approaches to treat functional MI are considered the golden standard. The leak can be surgically fixed through partial resection of the valve leaflets, chordal repair or by central sewing of the leaflets with an Alfieri stitch. All surgical approaches are mostly accompanied with ring annuloplasty to prevent the annulus from further dilating as this could revert the effects of the surgery.

When the MV is too damaged, the aforementioned surgery options will not be successful and replacement of the MV has to be considered. Surgical replacement of the MV can be done with either a mechanical or biological valve, both of which have their strengths and weaknesses.

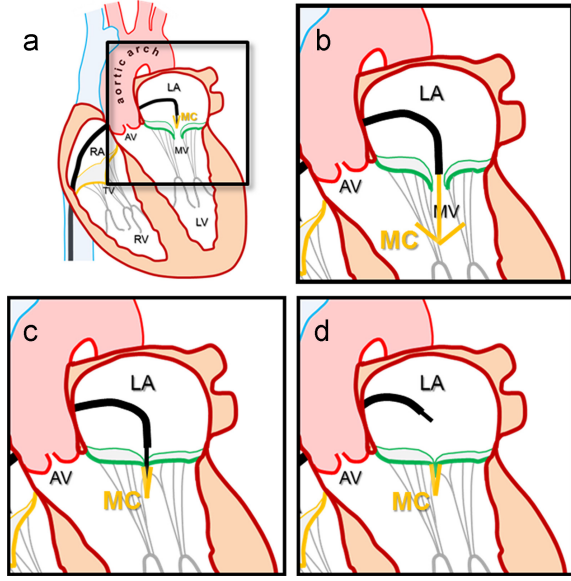
Placing a MitraClip via a catheter is another common option to treat functional MI. With this device, a double-orifice valve is created by clipping together the leaflets (Figure 4). The leaflets are clipped together so the EROA gets reduced. MitraClip has been used in patients with functional, degenerative and mixed MR. Not all patients can be treated with a MitraClip, as there are some contraindications such as pre-existing mitral stenosis and active endocarditis. [27] MitraClip have been shown to reduce MR, but to a lesser degree than surgery does. [28]



**Figure 4:** Mitral valve leaflets with MitraClip during diastole. A double orifice is created by clipping the anterior and posterior leaflet together. [29]

The MitraClip has two grippers above a dual arm structure. The grippers secure the MV leaflets to assist with the capture of the leaflets while the heart is beating. [27, 30], The procedure is performed with the patient under general anaesthesia. [30] To be eligible for a MitraClip procedure, the morphology of the valve should meet certain requirements from the EVEREST criteria which are listed in Appendix E. [31] The delivery and placement of the MitraClip is shown in Figure 5. The arms and grippers are covered with polyester fabric, a material which introduces tissue ingrowth. [30]





**Figure 5:** Schematic drawing of the placement of a MitraClip. [32]

- a) Access of the MitraClip device into the left atrium, through trans-septal puncture.
- b) MitraClip insertion into the left ventricle.
- c) MitraClip positioning across the mitral orifice and closure of the arms.
- d) The delivery system is retracted.

### 1.3 Hypotheses

The regurgitating blood in MI leads to a decreased cardiac function. During exercise, patients with MI will experience symptoms such as shortness of breath much sooner than healthy individuals, making it harder for the patients with MI to reach the same exercise levels as healthy individuals. [33] The severity of MI also plays a role in exercise capacity as it affects how much blood is being regurgitated. It is assumed that with increasing severity of MI, the patients become more symptomatic, the filling pressures within the heart increase and cardiac function worsens. With this in mind, the following hypothesis for Simulation 1 is made:

**Hypothesis 1** *Increasing severity of MI decreases the exercise capacity.*

Cardiac function is largely based on the function of the LV, which is defined as the left ventricular ejection fraction (LVEF). The LVEF is one of the most used parameters when it comes to classifying the grade of LV dysfunction and it is also used in the decision-making whether or not surgery should be performed on patients with MI. [34] Additionally, the popularity of LVEF as a clinical parameter also comes from its prognostic value as determinant of mortality in pa-

tients with heart failure. [35]

Despite its clinical importance, the LVEF is a poor measure of LV function because of load dependence, measurement errors and observer variability. The LVEF is calculated from the left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV respectively) which is in reality more a measure of chamber function rather than myocardial function. [36] This can be an issue in MI as favourable loading conditions can preserve LVEF even though the myofibers of the LV have become damaged because of the structural changes in the LV due to MI. [37]

Additionally, LVEF does not take into consideration the direction of the blood flow. In patients with MI the total afterload of the LV is diminished even though the systemic afterload stays the same. The MV leakage is directly responsible for the decrease of the total afterload. The decreased total afterload leads to a seeming increase of the total stroke volume. However, the effective stroke volume entering the systemic circulation is still the same or diminished because a portion of the total stroke volume empties into the LA due to the leaking MV. [38]

Despite all of its flaws, LVEF is still used because it is widely available and easy to measure. When LVEF is defined by using LVEDV and LVESV only, the following equation is used:

$$LVEF = \frac{LVEDV - LVESV}{LVEDV} \times 100\% \quad (1)$$

The LVEF increases for higher stroke volumes (LVEDV-LVESV). Due to the diminished total afterload and the volume overload of the LV because of the increased filling pressures, the total stroke volume and LVEF is expected to be higher for increasing severity of MI. [39] This holds true for acute MI, but for chronic MI the LV function deteriorates even further as the contractility decreases due to the increased filling pressures and the LV remodelling. Therefore, the LVEF will decrease for increasing severity of chronic MI.

CircAdapt produces acute results after a parameter change has been simulated. Therefore:

**Hypothesis 2** *Increasing the severity of MI influences the LVEF in CircAdapt.*

In Simulation 3, loss of contractility of the myofibers due to dilated cardiomyopathy is simulated. Dilatation causes a reduced wall contractility of the cavities. This can result in a reduced

exercise capacity. [40] As previously stated, MI causes volume overload in LA and LV which leads to dilatation of both cavities. LA enlargement is a good predictor for disadvantageous cardiac events. [41, 42] An increase in LA pressure, following a volume overload, causes pulmonary oedema, which subsequently leads to an increase of the RV afterload and ultimately, RV dilatation. RV failure combined with pulmonary hypertension can ultimately cause the RA to dilate. [43]

Over the years the increasing importance of the function of the right side of the heart has been recognized. Recently, new imaging techniques have been developed to study the anatomy and physiology of the RV and RA. Still not very much research has been done to the right side of the heart. The complex shape and structure of the RV makes it very difficult to study. [44] Different studies however, have shown the prognostic value of the RV in cardiovascular diseases. [45, 46] The CircAdapt model makes it possible to examine the influence of anatomical parameters on the RV and RA without the need of any measurements done in patients.

The blood flows from the atria to the ventricles following a passive pressure gradient created by the suction of the ventricles, so the contraction of the ventricles is more important for the CO than the contraction of the atria. Because of that, the contractility of the ventricles is expected to have a bigger influence on the relationship between EROA and exercise capacity, compared to the contractility of the atria. The following hypothesis will be tested in CircAdapt:

**Hypothesis 3** *Independent dilatation of all the heart cavities decreases the exercise capacity, with the ventricles having a higher influence than the atria.*

The EOA of the MV is the area of the gap enclosed by the leaflets of the MV. The EOA at peak exercise is a predictor of the exercise capacity. [47] The size of the EOA influences the pressure gradient over the MV. For large EOA, the amount of effort needed to reach the same filling decreases. This leads to an increase of the maximum attainable LVEDV and subsequently stroke volume. This means that an increase of the EOA would result in an expected increase of the exercise capacity, which leads to the following hypothesis for Simulation 4:

**Hypothesis 4** *A larger EOA increases the exercise capacity.*

Placing a MitraClip is a commonly used option to treat a MI. With this device, a double-orifice valve is created by clipping together the leaflets. Placement of the MitraClip leads to a reduction in the EROA which ensures a reduction of mitral regurgitation. One of the risks attached to the MitraClip procedure is the possibility of developing a mitral stenosis. [48] Besides the reduction in EROA, a reduction of the EOA can be detected after MitraClip placement, which could possibly result in mitral stenosis. A compromise between the perfect reduction of the EROA and maintaining a large enough MV opening area is required for optimal recovery of the patient. [49, 50] The EOA influences the exercise capacity, as hypothesized in Simulation 4.

In Simulation 5 the influence of the EROA combined with the EOA on the exercise capacity is examined. Expected is that the largest opening area combined with the smallest EROA leads to the best result. [51]

**Hypothesis 5** *Reduction in EROA and reduction in EOA created by the MitraClip have a positive and negative effect on the exercise capacity, respectively.*

During exercise the CO is increased by raising the heart rate and stroke volume. Stroke volume can be increased by increasing the preload of the LV, which is an increase of the LVEDV. According to the Frank-Starling law of the heart, the myocardium contracts more forcefully as the myofibers are stretched because of the increase of the LVEDV. This results in a more powerful contraction of the heart and a bigger stroke volume. In simulation 2a the effect of lowered contractility due to dilated cardiomyopathy is analysed. The dilatation of the LV is a response of the myocardium to the volume and pressure overload in this cavity. Because exercise induces an increase in LVEDV, it is interesting to simulate it for different severities of MI to assess whether an increased severity of MI leads to a higher LVEDV. [15]

Because of the rising knowledge about the importance of the RV in cardiovascular diseases, it would also be interesting to assess the response of the right ventricular end diastolic volume (RVEDV) during exercise. During rest conditions, the RV does less work than the LV because of the lower afterload present in the pulmonary circulation compared to the systemic circulation. However when CO increases during exercise, the RV afterload may increase disproportionately more than LV afterload. This results in a higher relative change in RV wall stress

compared to the LV. [52] For an increased RV afterload, the only way stroke volume can increase is by raising the preload and therefore the RVEDV. In patients with MI, pulmonary hypertension will occur because of the blood regurgitation, which leads to an increase of the afterload as well. Therefore it is assumed that for increased severity of MI, the RVEDV becomes bigger and increases more rapidly during exercise. The hypotheses regarding the LVEDV and RVEDV during exercise for Simulation 6 can be summarized as followed:

**Hypothesis 6** *Increasing the severity of MI makes the LVEDV and RVEDV increase to higher levels.*

As previously stated, the regurgitating blood in MI leads to a decreased cardiac function. Patients with MI will experience symptoms like shortness of breath during exercise sooner than healthy individuals. Measuring data in patients with MI during rest can underestimate the influence of the MI. [53] Because the condition of the patient with MI can be estimated better in exercise, it is of interest what the influence of exercise is on the EROA.

In the CircAdapt model the EROA is defined as a static parameter. In reality the EROA is dynamic during every heartbeat and increases during exercise. These variations are not intrinsically simulated by the model. Exercise testing yields prognostic information which is not obtained in tests during rest. [54] To make the model resemble reality more accurately, a dependence of the EROA on the amount of delivered exercise has to be introduced. It is of interest to simulate the influence of exercise-dependent EROA on the exercise capacity.

These final simulations are done to show that there is clinical relevance in knowing what a dynamic EROA during exercise could do with the exercise capacity compared to only an independent EROA, measured in rest. It is also of interest to know the real relationship between EROA and exercise as the imposed one used in this simulation will have a expected negative effect on the exercise capacity. [55]

**Hypothesis 7** *For simulations with a stronger dependency of EROA on exercise, the exercise capacity will be lower compared to simulations without a dependency, for any given EROA in rest.*

**Table 1:** Overview of all the performed simulations with corresponding hypotheses.

| Simulation # | Hypothesis                                                                                                                                                                    |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Simulation 1 | Increasing severity of MI decreases the exercise capacity.                                                                                                                    |
| Simulation 2 | Increasing the severity of MI influences the LVEF in CircAdapt.                                                                                                               |
| Simulation 3 | Independent dilatation of all the heart cavities decreases the exercise capacity, with the ventricles having a higher influence than the atria.                               |
| Simulation 4 | A larger EOA increases the exercise capacity.                                                                                                                                 |
| Simulation 5 | Reduction in EROA and reduction in EOA created by the MitraClip have a positive and negative effect on the exercise capacity, respectively.                                   |
| Simulation 6 | Increasing the severity of MI makes the LVEDV and RVEDV increase to higher levels.                                                                                            |
| Simulation 7 | For simulations with a stronger dependency of EROA on exercise, the exercise capacity will be lower compared to simulations without a dependency, for any given EROA in rest. |

## 2 Method

### 2.1 Data

For this study, data of 46 patients with MI were analysed for the validation of CircAdapt regarding MI. Between April 2015 and January 2016 patient data were obtained. The data were collected from MUMC. A summary of the data can be seen in Table 2. Patients were excluded from analysis, in case of missing or extreme values for MET or EROA before treatment. All simulations and results are obtained in MATLAB. Any statistical analysis with the data from the database is performed in SPSS. [56]

**Table 2:** Patient data from Maastricht University Medical Centre. Variables with associated values.

| Variable                | #                    |
|-------------------------|----------------------|
| Patients [n]            | 46                   |
| Age [years]             | 70 [40 - 87]         |
| Male [n]                | 25                   |
| Female [n]              | 21                   |
| EROA [cm <sup>2</sup> ] | 0.29 [0.07 - 0.91]   |
| MET                     | 4.8 [1.4 - 10.5]     |
| LVEDV [mL]              | 111.7 [43.0 - 173.6] |
| LVEF [%]                | 50.4 [15.1 - 73.5]   |

#### 2.1.1 Bicycle ergometry

Values of the metabolic equivalent of task (MET) were obtained with a bicycle exercise test to reach maximum exercise and predict exercise capacity. Each 6 minutes, exercise intensity was increased until the predetermined wattage. The maximum amount of watts was determined by the formula:

$$W_{\max} = 3.33 \times (\text{Length in cm}) - 1.43 \times (\text{age}) - 312 - 47.1 \times (0=\text{male}/1=\text{female}) \quad (2)$$

Every 6 minutes, the amount of watts increased by 5, 10, 20 or 25 watts. During the exercise test, VO<sub>2</sub> intake and CO<sub>2</sub> production were measured. 1 MET equals 3.5 VO<sub>2</sub>/kg/min. [57]

#### 2.1.2 Transoesophageal Echocardiography

The data acquired from the images were put into a database from the Department of Cardiology of MUMC. 2D transoesophageal echocardiographic images were acquired using the Philips' IE33 ultrasound system. In these images, values for anatomical and haemodynamic parameters were determined. The images were further analysed with Philips' XCELERA image management system.

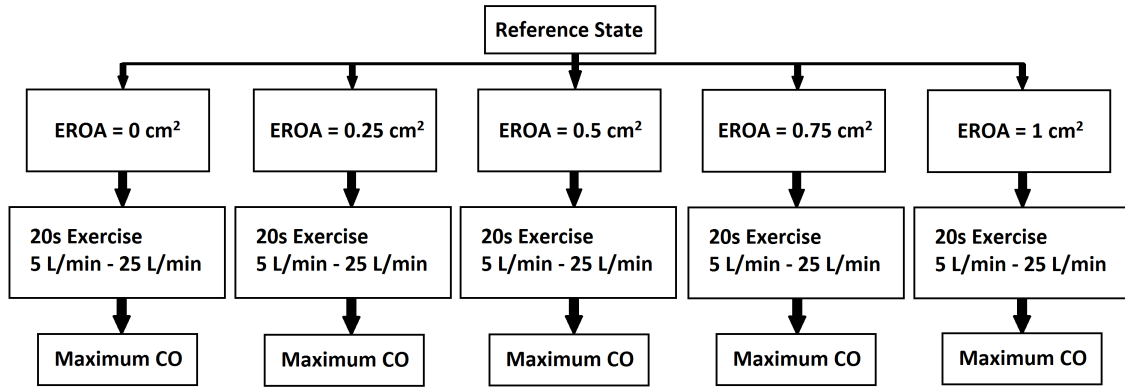
### 2.2 Simulations

Multiple sets of simulations were performed in order to test the hypotheses and to validate the model based on certain parameters and situations. Different sets of simulations were made in order to make predictions about the response of certain parameters during exercise and their effect on the exercise capacity. An overview of all the performed simulations can be found in Table 1. The graphs used to plot the results are found in the Appendix.

Exercise tests give important diagnostic information about the cardiac function. With these test, symptoms of cardiovascular disorders can be found that only occur during exercise. The maximum exercise level is a good measure of the condition of the patient. It can easily be compared between patients and over time. In order to perform exercise simulations in MATLAB, the heart rate and CO were increased to go from rest to intense exercise based on the relationship shown in Appendix F. [15] The mean arterial pressure was kept as 91 mmHg and a boundary was set for the mean LA pressure (mLAP) at 30 mmHg and represents the maximum mLAP in healthy patients. [58] When mLAP exceeds this boundary, pulmonary oedemas will occur at the alveolar level which limits subjects from reaching higher exercise levels. [59] The CO that corresponds to the moment mLAP exceeds 30 mmHg is defined as the CO<sub>max</sub>, which represents the maximum exercise capacity a subject can reach.

#### 2.2.1 Simulation 1

The MI can be simulated by altering the value of the parameter called *ALeak* within CircAdapt, which represents the EROA of the MV. To be able to compare the simulated exercise capacity to the patient data, a graph of the CO<sub>max</sub> with respect to the EROA is made. In order to accomplish that, many simulations at different exercise levels and different EROAs were done. The exact simulation protocol is illustrated in Figure 6. The other input variables that were used in the simulations were from the reference state available in CircAdapt. The corresponding CO<sub>max</sub> is determined for a single size of the EROA. This process is then repeated for different sizes of EROA. Ultimately, a graph of the CO<sub>max</sub> plotted against the EROA is made in which the influence of EROA on the achievable CO<sub>max</sub> can be seen. This graph will be compared to a graph of the patient data, if significant, where the MET is plotted against the EROA to test the validation of the model.



**Figure 6:** Schematic overview of the simulation protocol used in Simulation 1.

### 2.2.2 Simulation 2

The LVEF is defined in (1). In order to compute this in MATLAB, the LVEDV and LVESV have to be determined for every level of EROA. This can be done by respectively determining the maximum and minimum volume of the LV for a single cardiac cycle during steady state. This process is repeated for increasing levels of EROA. The used CO for this simulation is the rest situation, 5 L/min.

The contractility of the LV wall was lowered compared to the reference value, because MI patients mostly have weaker walls compared to healthy subjects. This is because these patients suffer from dilated cardiomyopathy which is associated with a loss of contractility. [40] Changing the value of the parameter  $Sf_{Act}$  alters the contractility of the walls of each cavity. [60] By lowering the contractility of each cavity wall, dilatation of the cavities can be mimicked in CircAdapt.

Ultimately a graph is made of the simulated LVEF plotted against the EROA. This graph will be compared to a graph of the patient data where the LVEF, determined with the biplane Simpson's method, is plotted against EROA to test the validity of the model.

### 2.2.3 Simulation 3

To evaluate the effect of dilatation of the heart cavities on the  $CO_{max}$  of patients with MI,  $Sf_{Act}$  is lowered. The process of Simulation 1 (Figure 6) is repeated but instead of using a single reference state, three states were used. The three states correspond to the three different values of wall contractility. The values used for  $Sf_{Act}$  are 50, 75 and 100 kPa for the free walls of the LV and RV and for the septal wall. The values 30, 45

and 60 kPa were used for the free walls of the LA and RA. Ultimately, three plots of  $CO_{max}$  with respect to EROA are produced for every cavity.

### 2.2.4 Simulation 4

EOA can be altered in CircAdapt by using the parameter  $AOpen$ . This parameter describes the opening area of the valve module during diastole in CircAdapt. To assess the effect of the size of EOA on the  $CO_{max}$  of patients with MI, the same simulation protocol introduced in Simulation 3 was used for  $AOpen$ . The three parameter values that are used are: 4 cm<sup>2</sup>, 6 cm<sup>2</sup> and 8 cm<sup>2</sup> respectively.

### 2.2.5 Simulation 5

To determine the success of the MitraClip, the effect of the change in both EROA and EOA has to be considered on  $CO_{max}$ . With the result of this simulation, it is possible to evaluate for one patient with a certain EROA and EOA before MitraClip placement, how much EROA and EOA need to be improved with the procedure to have a positive outcome on the  $CO_{max}$ .

The parameters of interest in CircAdapt are  $ALeak$  and  $AOpen$  with a resulting  $CO_{max}$ . For every increment of  $AOpen$  (EOA), a reference state is created. Each state will undergo the same simulation protocol introduced in Simulation 1. (Figure 6) The values used for  $ALeak$  range from 0 cm<sup>2</sup> to 1 cm<sup>2</sup> and the values for  $AOpen$  range from 8 cm<sup>2</sup> to 2 cm<sup>2</sup>. The end result is a dataset where a  $CO_{max}$  is computed for increasing size of EROA, for every increment of EOA. The result is plotted in a contour plot.

### 2.2.6 Simulation 6

The response of the LVEDV and RVEDV during exercise are examined further in this step. To analyse the effect of EROA on the exercise response, four simulations are made with as outcome the LVEDV and RVEDV plotted for increasing levels of CO. The four simulations represent the different test groups which are classified in Table 3. The LVEDV and RVEDV are determined by the maximum LV and RV volume of a single heartbeat during steady state. The different simulations were plotted in one graph. The different simulations end at the  $CO_{max}$  the virtual patient would physiological be able to reach. The  $CO_{max}$  can be determined by using the graph of Simulation 1.

**Table 3:** Classification of mitral insufficiency based on the size of EROA.

|                              | Healthy | Mild MI | Moderate MI | Severe MI |
|------------------------------|---------|---------|-------------|-----------|
| EROA size (cm <sup>2</sup> ) | 0       | <0.2    | 0.2-0.4     | >0.4      |

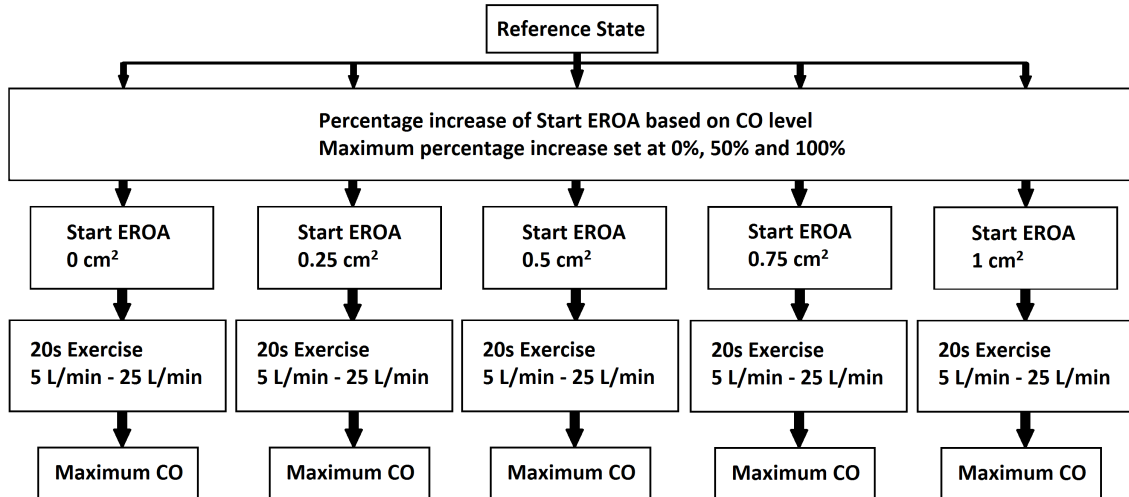
### 2.2.7 Simulation 7

To evaluate the effect of a dynamic EROA during exercise, the process of Simulation 1 is re-

peated but instead of using a static EROA shown in Figure 6, the EROA has been made dependent on the CO. The EROA has been made dynamic by multiplying the start EROA, which is the EROA in rest, with a gradually increasing percentage when CO rises up to the maximum simulated exercise level. At this level, the percentage increase caps at a predetermined value. During these simulations, the caps have been set at 0 % (static), 50 % and 100 %. EROA has been made dependent of CO by using the following formula:

$$EROA_{dynamic} = \left(1 + \frac{x \times CO}{25}\right) \times EROA_{start} \quad (3)$$

In equation (3), CO stands for the simulated CO level during exercise which starts from 5 L/min and increases up to the exercise cap of 25 L/min. To change the maximum percentage of increase for the EROA,  $x$  can be altered to make the dependency of EROA on CO 0 %, 50 % and 100 %. To get these predetermined percentages, the values 0, 0.5 and 1 have been filled in for  $x$  respectively. A brief overview of the simulation protocol is shown in Figure 7. The end result of these simulations is a graph where the  $CO_{max}$  is plotted against the EROA in rest for three different dependencies.

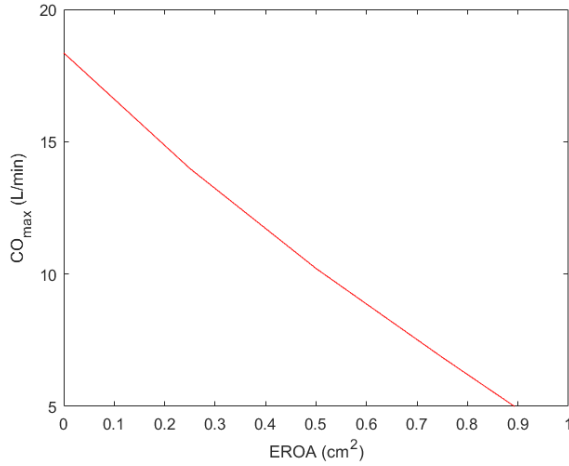


**Figure 7:** Schematic overview of the simulation protocol used in Simulation 7.

### 3 Results

#### 3.1 Simulation 1

When exercise is simulated in CircAdapt for increasing levels of EROA, a descending relationship can be noticed between the  $CO_{max}$  and EROA (Figure 8).

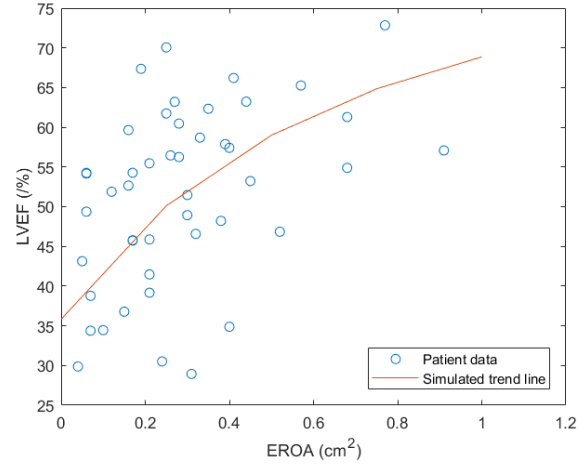


**Figure 8:** Maximum cardiac output with respect to EROA, simulated with CircAdapt.

Linear regression could not identify EROA as a significant determinant of  $MET_{max}$  ( $R^2 = 0.017$ ,  $p = 0.392$ ) regarding the data available from the database.

#### 3.2 Simulation 2

During rest, CircAdapt is capable of producing a simulated plot that can be fitted over the scattered data points available from the database regarding the LVEF (Figure 9). Linear regression identified EROA ( $R^2 = 0.189$ ,  $p = 0.003$ ) as a determinant of increased LVEF.

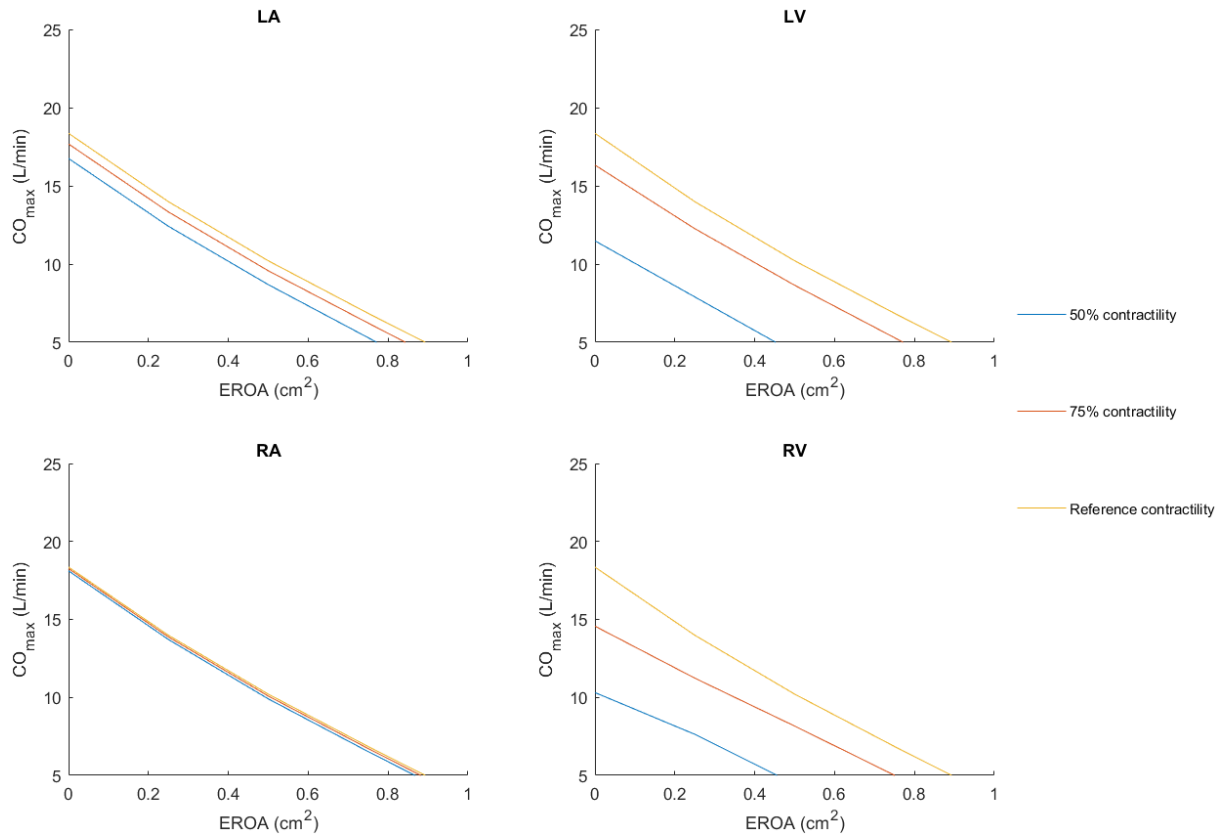


**Figure 9:** Scatter plot of patients with mitral insufficiency from the Maastricht University Medical Centre. Left ventricular ejection fraction with respect to EROA. Trend line simulated with CircAdapt plotted over data points.

#### 3.3 Simulation 3

In Figure 10 the simulation results of alternating the wall contractilities can be seen. First, the lower LA contractility the lower exercise capacity, represented by  $CO_{max}$ , becomes. The course of the line does not change for different LA contractilities. The influence of the LA is not very big compared to the influence of the ventricles. The influence of the RA contractility on the relationship between EROA and  $CO_{max}$  can be neglected. In the upper right graph can be seen that a decrease to 75 % LV contractility compared to the reference value leads to a smaller achievable  $CO_{max}$ . Further decrease of contractility to 50 % leads to a bigger decrease of  $CO_{max}$ . The first 25 % decrease in contractility leads to a smaller difference in  $CO_{max}$  compared to the second 25 % decrease. The decrease of  $CO_{max}$  for each LV contractility follows the same trend. The influence of the RV contractility can be seen in the bottom right graph. The line declines faster with an increasing EROA for a high RV contractility.

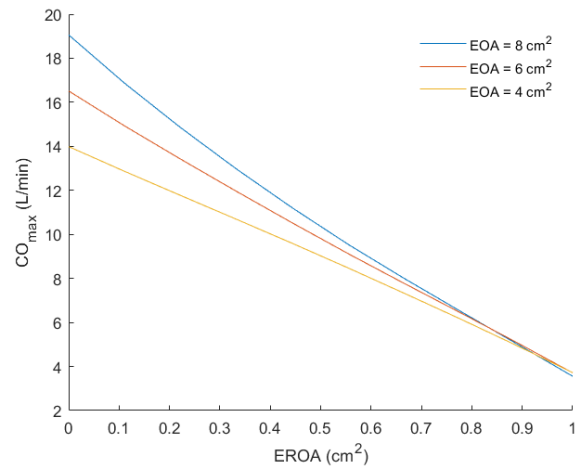




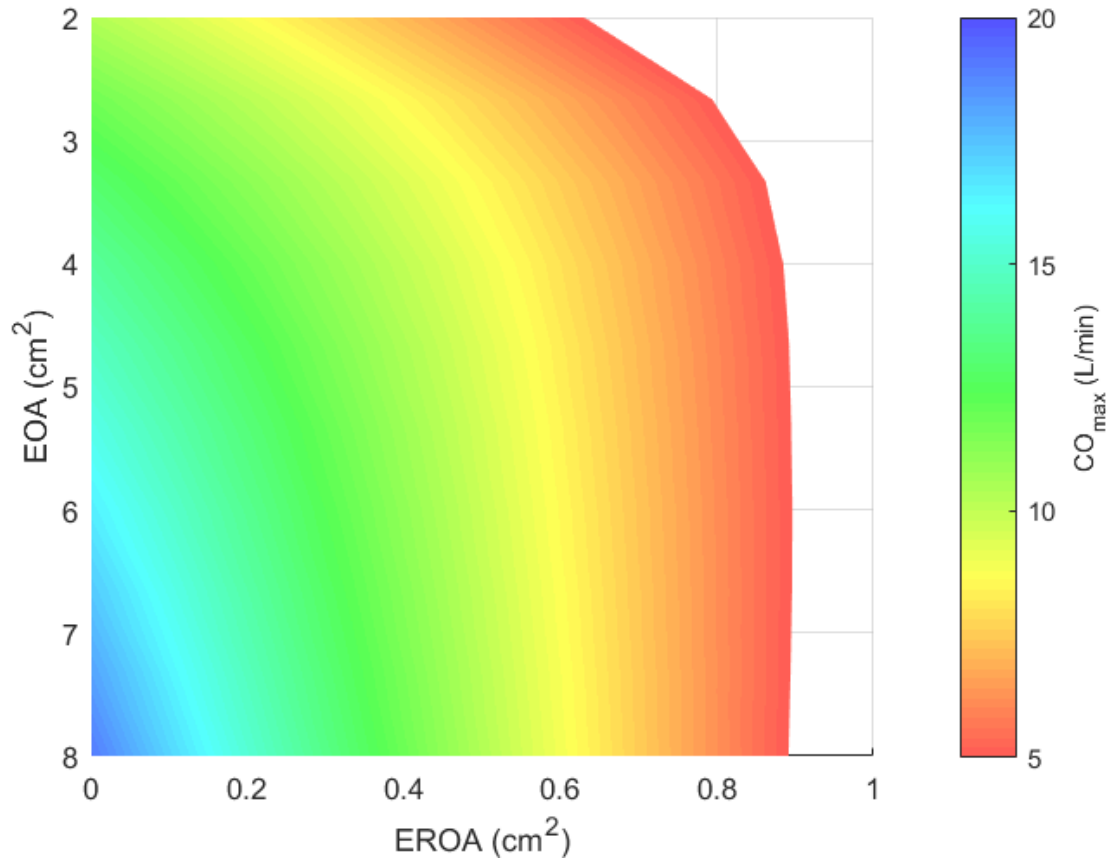
**Figure 10:** The effect of the wall contractility on the maximum cardiac output for increasing levels of EROA, for the left atrium, left ventricle, right atrium and right ventricle. Simulated for reference wall contractility, 50 % and 75 % of the reference wall contractility.

### 3.4 Simulation 4

In Figure 11 the graph in which the EOA is altered is shown. The  $CO_{max}$  declines faster with the increase of EROA for a larger EOA. There can be seen that the EOA has a greater influence on the  $CO_{max}$  for a smaller EROA. At an EROA of roughly  $0.8 \text{ cm}^2$  the lines for the three different sizes of EOA intersect. This means that for EROAs larger than  $0.8 \text{ cm}^2$ , EOAs from  $4$  to  $8 \text{ cm}^2$  do not affect the  $CO_{max}$ .



**Figure 11:** The effect of the effective orifice area simulated on the maximum cardiac output for increasing levels of EROA. Simulated for  $4 \text{ cm}^2$ ,  $6 \text{ cm}^2$  and  $8 \text{ cm}^2$ .



**Figure 12:** The simulated response of the maximum cardiac output to paired variance of the EROA and the effective orifice area. Maximum cardiac outputs lower than 5 L/min are not shown. EROA is determined during systole and the effective orifice area is determined during diastole.

### 3.5 Simulation 5

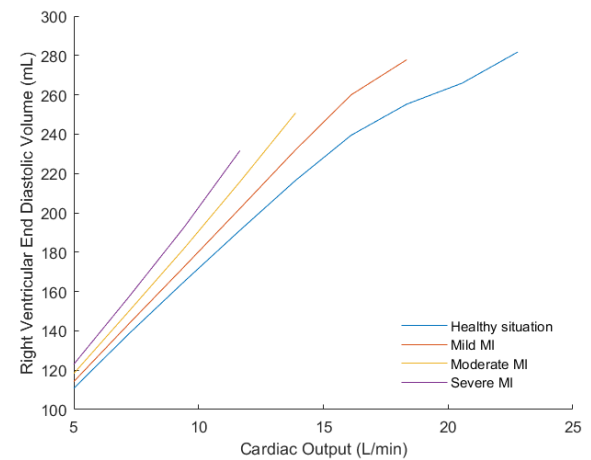
The paired variation of the EROA and the EOA produces the contour plot shown in Figure 12 where the different colours represent the different  $CO_{max}$  levels. An increase of the EROA influences the  $CO_{max}$  more than a decrease of the EOA will. EOA has a bigger influence on  $CO_{max}$  in case of a smaller EROA. For larger EROAs the influence of the EOA is negligible.

### 3.6 Simulation 6

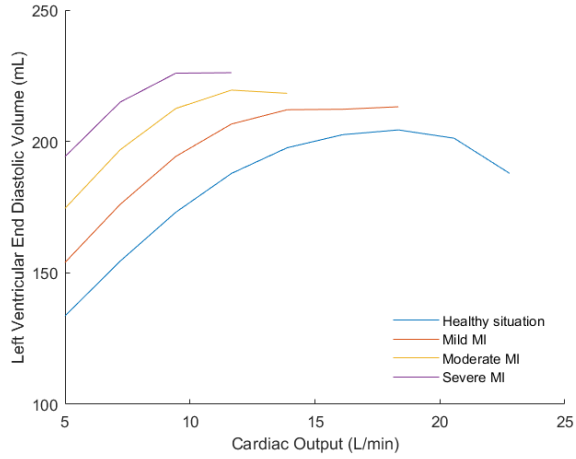
The RVEDV increases during exercise and an increased severity of MI raises the RVEDV across all CO levels. Figure 13 shows a healthy group and three groups of MI which are classified according to Table 3. Increased severity of MI also leads to an earlier cut-off point of the plot during exercise simulations.

The LVEDV shows a different response, as it appears to increase at first until it reaches a plateau and then starts to drop at higher levels of CO (Figure 14). MI severity seems to play a role

in how early and how high the LVEDV plateaus arise.



**Figure 13:** The response of the right ventricular end diastolic volume during exercise simulated for the healthy situation and different grades of MI.

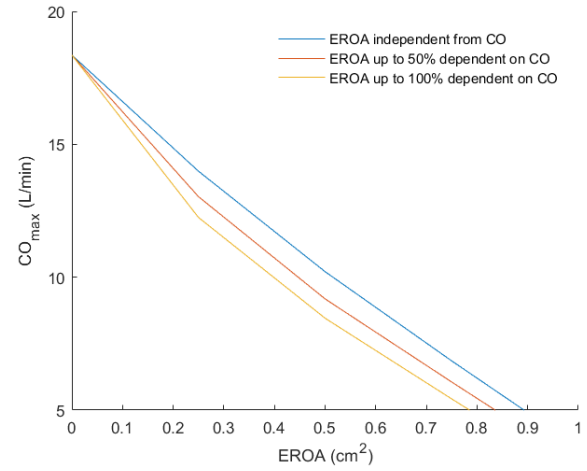


**Figure 14:** The response of the left ventricular end diastolic volume during exercise simulated for the healthy situation and different grades of MI.

### 3.7 Simulation 7

When EROA is made dependent on CO in equation (3), the exercise capacity decreases for in-

creasing levels of dependency when simulated (Figure 15). The amount it decreases is relatively low however.



**Figure 15:** The maximum cardiac output with respect to EROA simulated for different imposed dependencies of EROA on cardiac output. The plotted EROA is the EROA at rest.

## 4 Discussion

### 4.1 General

To make the CircAdapt model operable for patient specific simulations the most important aspect to improve are the measurements of the haemodynamic and anatomical parameters. The model follows the general response of the MI patient group, but a large study population is necessary to find a significant relationship in the data. The margin of error regarding the measurements of the anatomical and haemodynamic parameters is too high, which makes it for now, impossible to simulate patient specific situations.

A prospective study is recommended for further research. The study population has to be homogeneous to better estimate the influences of different parameters. Homogeneity will also lower the influence of comorbidities. Comorbidities could overestimate the influence of parameters regarding MI or cause wrong interpretation of relations between parameters.

CircAdapt doesn't account for comorbidities, which are common in MI patients. Treatment of MI might not lead to acute improvements to the heart, but it might alleviate some of those comorbidities. CircAdapt simulations might not directly indicate that the patient's condition has been improved. It only accounts for the possibly unchanged cardiac parameters even though the real patient's condition does show improvement because the comorbidities got treated. By treating one's comorbidities, the patient is instigated to exercise again which in the long term could lead to an improvement of their cardiac parameters and ultimately, their condition.

One of the benefits of the model is that it can show what the effect of a single parameter is, which can't be tested in living patients because of the cohesion between all the parameters. This also means that the results from CircAdapt from altering one parameter won't necessarily be representative for a real patient.

### 4.2 Simulation 1

The patient data regarding the MET and EROA were meant to be compared to the model outcome but could not be used to draw any conclusions regarding the validity of the CircAdapt model. In the simulation can be seen that the EROA influences at what CO the mLAP limit of 30 mmHg is reached. For patients with a larger EROA, this limit is reached for a smaller CO.

When the 30 mmHg limit is reached, the pulmonary pressure leads to pulmonary oedema so at this point the exercise capacity is reached. Despite the fact that no comparison with the data can be made, the simulation results are in line with expectations based on literature and the knowledge about physiology.

One of the reasons the patient data regarding the MET could not be used to draw conclusions about the validity of the model, is that MET cannot directly be compared to CO. CO is defined in L/min. 1 MET is equivalent to the consumption of 3.5 mL O<sub>2</sub> per kg body weight per minute. Also gender is taken into account when predicting the number of METs. Although those parameters for exercise capacity cannot directly be compared, there is a linear correlation between CO<sub>max</sub> and maximum oxygen consumption (L/min) in healthy subjects. [61] For validation the exact correlation between CO<sub>max</sub> and MET has to be taken into account.

There is no significant relationship between patient data of the EROA against the MET. This can be due to several causes. First of all, the EROA was wrongly determined in the patients. This is because using the measured diameter of the ERO to calculate the EROA is not entirely right. The actual shape of the EROA during systole is not a perfect circle, which makes the calculation of the surface area unreliable. It would be more accurate to determine the EROA by tracing the shape of the ERO. Moreover, the measured diameters of the EROs in different patients are prone to a lot of observer bias because it is difficult to consistently measure the diameter of the ERO. This adds to the unreliability of the determined EROA.

Instead of the EROA measured with 2D Doppler echocardiography, the vena contracta area (VCA) measured with 3D Doppler echocardiography should be used. [21] The VCA could be better than the EROA, because the position of the VC can be determined more accurately. However, VCA is not a perfect substitute for EROA, therefore it cannot be inserted for *ALeak* in CircAdapt.

The lack of significant correlation can also be caused by the influence of other parameters on the exercise capacity. The patient group is not homogeneous when it comes to parameters such as age, length, weight, heart size, annulus diameter, comorbidities etc. which can be confounders. It is recommended to do a prospective investigation for future validation studies, in which the patients for the database can be se-

lected and a homogeneous group can be created. Another possibility is to do in vivo testing in animal models, in which the desired MI can be created. [62] Both of these would make further validation studies of CircAdapt regarding MI more valuable.

A final note that has to be made is about the simulation. The assumption is made that the  $CO_{max}$  is reached when the mLAP exceeds 30 mmHg. This is an assumption based on literature. The exact value may vary between different patients and is influenced by different factors.

### 4.3 Simulation 2

The LVEF does indeed increase for higher EROAs simulated in CircAdapt as well as for the patient data. The correlation found in the patient data is significant. However, the correctness of the graph is doubtful. As stated previously, the EROA is not a trustworthy measure for the leak. The LVEF is determined by the LVEDV and the LVESV and volumes are difficult to determine with echocardiography, because of the low resolution. Images made with magnetic resonance imaging (MRI) have a better resolution and give a more accurate volume because the trabeculae of the heart cavity are taken into account. Furthermore, MRI images have a low bias and higher accuracy. For future use of LVEF in validation studies of CircAdapt, MRI or other operator independent imaging modalities should be used over echocardiography in acquiring data.

Despite all these shortcomings, CircAdapt is capable of producing a result that is similar to the observed data. LVEF is a commonly used parameter to judge LV function, despite its error prone-ness. The fact that the result from CircAdapt resembles the patient data means that the model is qualitatively validated for this parameter in patients with MI. To assess the value of this validation, more reliable values for LVEF are needed. Additionally, the usage of the total stroke volume (LVEDV-LVESV) in patients with MI has its flaws. Therefore it would be interesting to use a LVEF where the forward stroke volume has been used, for further validation studies of CircAdapt.

### 4.4 Simulation 3

Reducing the contractility of the different cavities has a negative effect on the  $CO_{max}$ . A few remarkable aspects can be noticed.

The contractility of the ventricles has a bigger influence on the relationship between EROA and  $CO_{max}$ , compared to contractility of the atria. The contraction of the ventricles is more important for the CO than the contraction of the atria, because the blood flows passively from the atria to the ventricles following a pressure gradient created by the suction of the ventricles.

The difference in contractility has a bigger influence on  $CO_{max}$  in the RV than in the LV. This shows that the RV is a possible limiting factor in obtaining maximum exercise. [63] This finding could warrant for more research into the function of the RV. This could be clinically useful in predicting the prognosis of a patient.

The effect of  $Sf_{Act}$  on the relationship between EROA and  $CO_{max}$ , shows a linear response up to a reduction to 70 % of the reference state. When the  $Sf_{Act}$  is reduced further, the response becomes non-linear. This explains the position of the lines in Figure 10. The lines of the reference contractility and 75 % contractility are closer to each other than the lines of 75 % and 50 % contractility despite the fact that the difference in both cases is the same.

### 4.5 Simulation 4

In a healthy situation, the  $CO_{max}$  is higher in patients with a larger EOA. [64] The same can be seen in the simulation with CircAdapt.

At a large EROA there is an intersection point at a low  $CO_{max}$  for the different values of EOA. This means that the three lines have different slopes. For higher EROA values, the EOA has a lower influence on the  $CO_{max}$ . This probably can be explained by the fact that EROA has a big influence on  $CO_{max}$  and takes over at greater EROAs. This result shows that when having a big EROA, the condition of the patient is very bad. At that point it does not matter what the EOA is. So treatment by just adjusting the EOA is not beneficial for this patient.

The CircAdapt model has various shortcomings which make these simulation results less representative of reality. Namely, CircAdapt makes use of a static EOA for predicting the  $CO_{max}$ . However, the EOA increases during exercise, because of an increasing anterior leaflet opening angle. [65] Literature shows that the EOA at peak exercise in particular, is the predictor of the exercise capacity, instead of the EOA during rest which is measured in patients. [47] For a better representation of reality, a dynamic EOA

during exercise should be introduced into CircAdapt.

Additionally, CircAdapt is a simplified model of the heart. Predictions of the  $CO_{max}$  are made with the EOA and EROA as two single inputs, but they could also have influence on each other. This relation could be clinically tested in order to define EOA and EROA better as inputs for CircAdapt.

#### 4.6 Simulation 5

Separate reduction of the EROA and EOA have a positive and negative influence on the exercise capacity, respectively, as can be seen in Simulation 1 and 4. Simulation 5 shows the same effect. A reduction of the EOA has a smaller negative influence on the  $CO_{max}$  compared to the benefits from a reduction of the EROA. Therefore treatment with for example a MitraClip should primarily target to reduce the EROA.

As previously stated in the Simulation 4, the EOA and EROA may have influence on each other. Also, both parameters have influence on the  $CO_{max}$ . When predicting the results of MitraClip, it could be important to know what the exact relation is between EOA and EROA. Further research is necessary.

In literature is found that a reduction in anteroposterior annulus diameter caused by placement of the MitraClip, is correlated with better mid-term results of the procedure. The forces placed on the MV leaflets are responsible for the changes in the geometry of the MV. [66] A given hypothesis is that an adequate change in the geometry of the MV, namely a reduction in anteroposterior annulus diameter, induces reverse LV remodelling for patients with secondary MI. [67] The effect of this reverse LV remodelling is not taken into account in this simulation. A reduced EOA has a negative effect on the exercise capacity directly after the procedure. However, a change in the EOA might be correlated with traction on the MV. In the long term, reverse remodelling of the LV takes place which leads to better condition for the patient. [68]

To predict the effect of the MitraClip patient specifically, a reliable and valid measurement of the EOA and EROA is necessary. The EROA after placement of the MitraClip can't be measured in a correct way, because of the small residual flow jets caused by the clip. The reliability of the measurement of EOA with echocardiography is very low. This has to be improved for the use of

EOA in patient specific simulation.

In case the contour plot is validated with actual patient data, the effect of a certain therapy on the  $CO_{max}$  can be predicted for a single patient whose EOA and EROA are known before treatment.

As previously stated, a homogeneous study population is recommended for further research. Figure 12 shows that for lower EROAs, EOA has more influence on  $CO_{max}$  than for higher EROAs. When investigating the influence of a certain parameter on  $CO_{max}$ , especially for a subgroup with small EROAs, the patient population should be homogeneous for EOA to diminish its effect on  $CO_{max}$ .

#### 4.7 Simulation 6

Both the RVEDV and LVEDV increase during exercise. In order to provide the necessary stroke volume to raise the CO the LVEDV has to increase. The LVEDV in rest is higher for a larger EROA because the extra regurgitant volume of the previous systole enters the LV during the next diastole, raising the LVEDV.

With a larger EROA, the maximum pulmonary pressure is reached at a lower CO. The higher the pulmonary pressure, the higher the RV afterload will be. To provide the LV with the required volume to achieve a certain CO, the RV has to overcome this increased resistance by increasing the RVEDV. Because of that, the RVEDV at a certain CO is higher for patients with a higher EROA.

To realise an increase in CO, the venous return increases, which leads to a bigger RVEDV. Because healthy subjects can reach a higher CO, the maximum RVEDV that is reached is higher for patients with a smaller EROA. RVEDV during exercise, with respect to different grades of MI, increases more steeply for larger EROAs.

The heart is surrounded by the pericardium, which prevents the heart from infinitely increasing its volume. The RV in CircAdapt is modelled like a bag within the LV. [69] When exercise is simulated, both LV and RV will increase its EDV, to meet the needed CO for the effort. At a certain point the pericardium starts to resist the increase in volume of the ventricles, making the amount of expandable volume finite. Since the RV can be seen as a limiting factor during exercise, it dilates sooner than the LV. [63] Fighting for the same finite amount of space, the expanding RV

pushes away the LV as the septal wall bulges to the left. The volume of the LV can't increase any further which means that the LVEDV will reach a plateau. Any further exercise beyond this point is deemed unrealistic as the LVEDV plunges down because of the increasing volume of the RV for increasing CO.

The LVEDV plateaus at lower CO levels for increased MI severity. This seems to indicate that the RV starts to push the LV away at a lower CO when EROA is increased. Apparently the RV becomes more of a limiting factor during exercise for bigger sizes of EROA.

Cut-off points for CO are used to show physiological values of RVEDV and LVEDV. CircAdapt can continue to simulate, even though the response will be supraphysiological. The validity of the model decreases when more extreme values of parameters are simulated.

These graphs give more insight in the importance of the RV during exercise. RV mechanics during exercise are important to consider in further studies and in clinical decision making.

## 4.8 Simulation 7

Increasing the maximum dependency of EROA on CO does indeed have a negative effect on the  $CO_{max}$  for any given EROA at rest. This is however not the most interesting result as this is the direct consequence of the imposed fictive relationship. More importantly, it has shown that some form of dependency does indeed have an effect on the result which is in line with the liter-

ature. It is of clinical importance to add such a relationship between EROA and CO intrinsically to the model.

The relationship between exercise and EROA is still unknown. However, research shows that the EROA in rest does not correlate with the exercise-induced changes in EROA. [70] The relationship that was imposed did depend from the EROA in rest, so the simulation results will not perfectly match reality.

Another shortcoming of the imposed relationship is that the increasing dependency on CO was ascending from a CO of 5 L/min to a CO of 25 L/min. The  $CO_{max}$  the virtual patient could deliver was somewhere in between those two values. This means that a virtual patient who reaches a lower  $CO_{max}$ , reaches a lower dependence of EROA on CO. Perhaps, the dependence should be the highest on the  $CO_{max}$  that a certain patient can reach, regardless of the value of CO at that moment. The exact relationship between EROA and CO has to be investigated to make substantiated statements.

To make accurate simulations with the model for dynamic behaviour of the heart, EOA and EROA have to be dynamic during every heartbeat, by making them based on a fluid-structure interaction. In such a model, the fluid domain of the blood is coupled with the structural domain of the valve. The fluid domains has influence on the structural domain and vice versa. [71, 47] Those accurate simulations could also contribute to more patient specific simulations.



## 5 Conclusion & Recommendations

Assessment of the validity of the CircAdapt model for patients with MI, is not possible with restricted data. Simulation results are however in line with expectations based on known physiology and pathology.

It is recommended to do a prospective study to create a homogeneous group for further validation. To test the influence of different parameters, homogeneous subgroups will contribute to the validation of the CircAdapt model. For creating homogeneous patient groups, inclusion and exclusion criteria have to be clearly stated, so the influence of comorbidities will be as low as possible.

The measurement and handling of the necessary data also has to be improved. Data should be acquired through operator independent methods with low bias and high accuracy. Especially, when this data are to be used for patient specific simulation. Furthermore, parameters like ventricle volumes, LVEF, EROA and EOA, have to be

evaluated critically. Alternative parameters also need to be addressed, such as VCA, if they can give more accurate results.

To eventually make specific simulations for patients with MI, further research on a few aspects is necessary. At first, the RV has shown to be one of the limiting factor in maximum exercise, making it a promising predictor for the condition of a MI patient. Therefore the function and mechanics of the RV need to be further examined. Also, the relationship between  $CO_{max}$  and EROA has to be further determined. EROA, EOA and  $CO_{max}$  are clinically relevant data for patient specific simulations.

With patient specific simulations, predictions could be made on what the prognosis for one patient will be and what therapy to treat MI should be the best and what parameters should be targeted. Those results will contribute to more efficient treatment of patients with MI. More research is needed before the CircAdapt model can be clinically applied to treat patients with MI. Future investigations can contribute to formulate a more substantiated answer to the main question.

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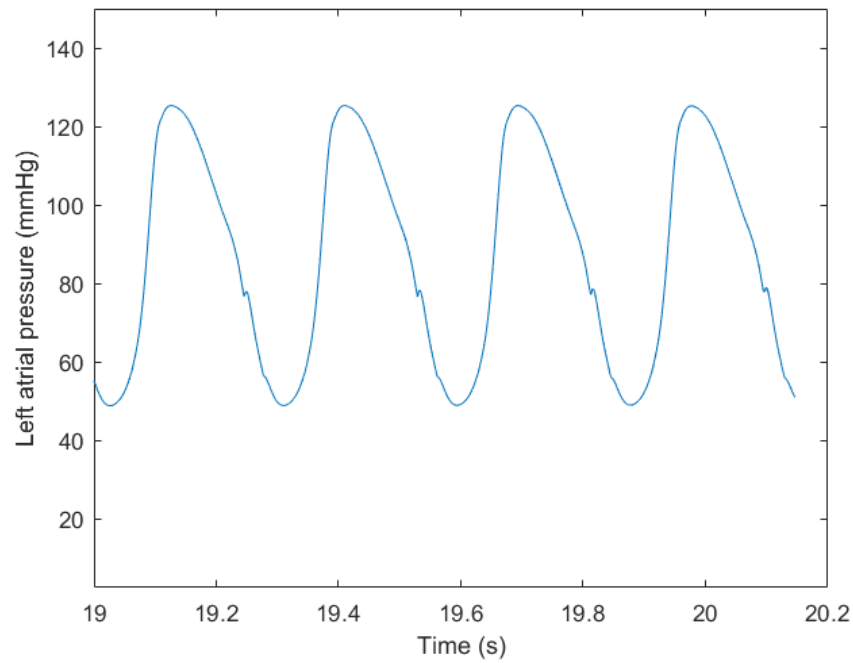
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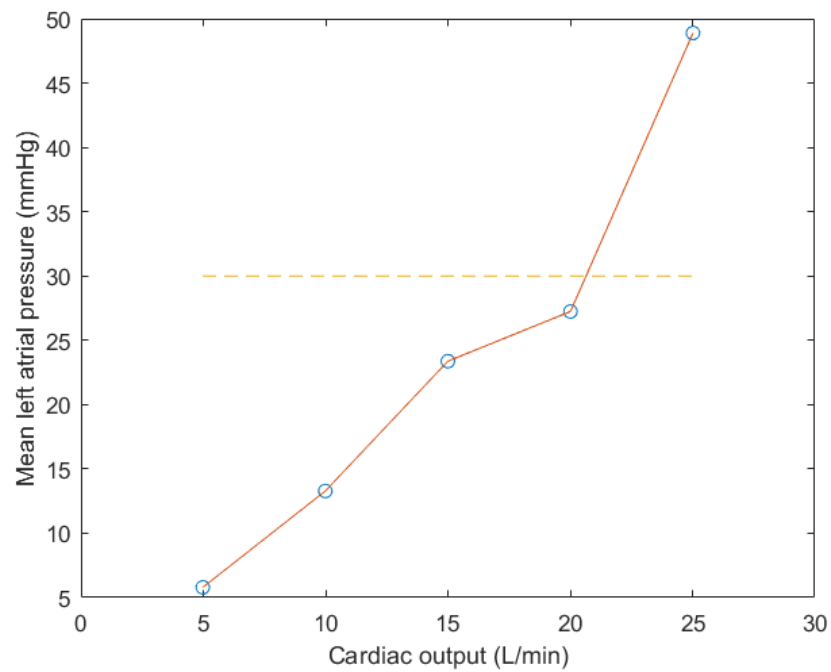
## 7 Appendix

### A

#### Simulation 1



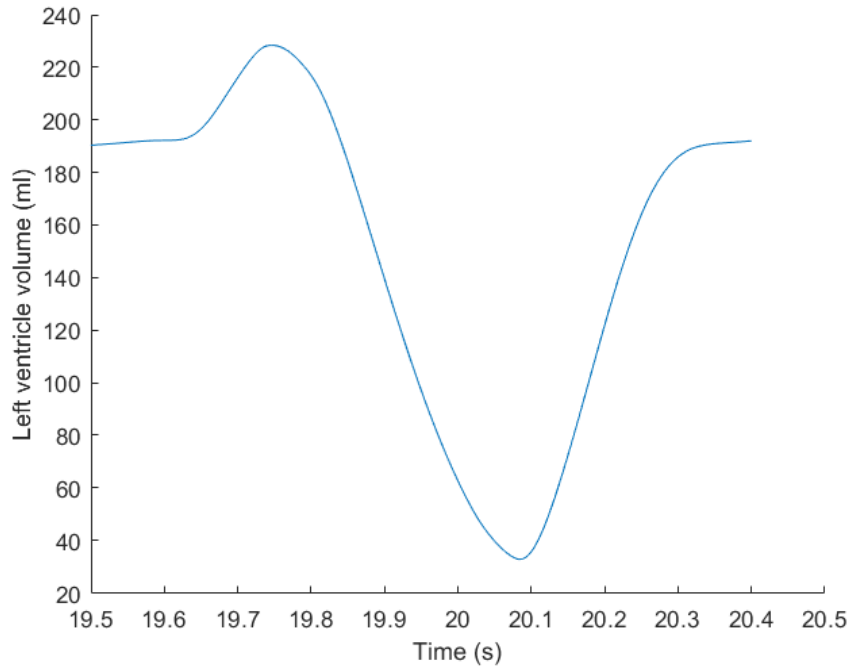
**Figure 16:** Left atrial pressure with respect to time for a single EROA. The mean left atrial pressure is determined from this plot and for all other EROA.



**Figure 17:** Cardiac output with respect to mean left atrial pressure. Maximum cardiac output determined at 30 mmHg line for a single EROA. This graph is plotted for multiple EROAs.

## B

### Simulation 2



**Figure 18:** Left ventricular volume with respect to time for a single EROA. The maximum and minimum left ventricular volume correspond to the end diastolic and end systolic volume respectively. This graph is plotted for multiple EROAs

## C

### Simulation 3

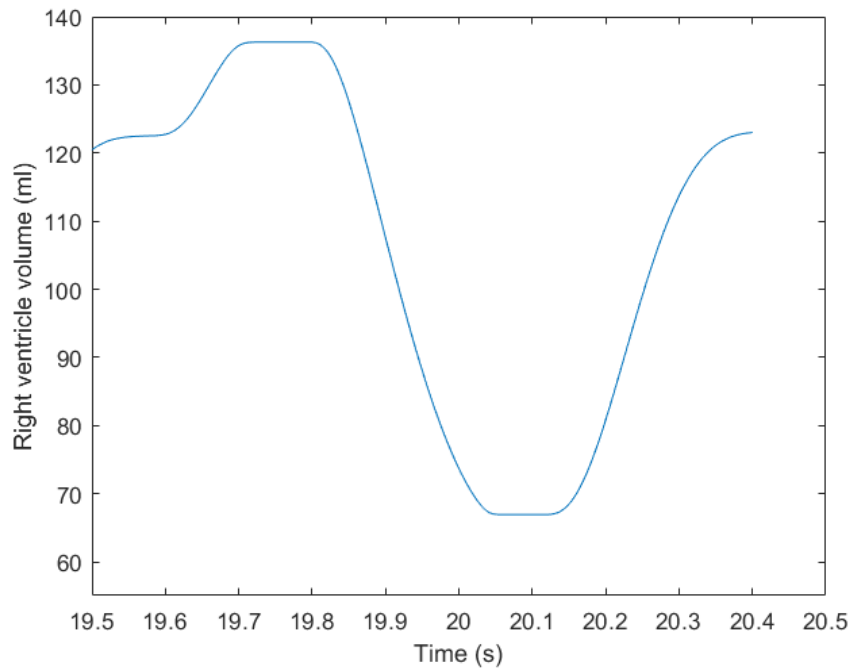
**Table 4:** Determination of  $Sf_{Act}$  in kPa for LV, RV, LA and RA at different grades of wall contractility. In CircAdapt the walls of the ventricle consist of the free cavity wall and the septal wall. The walls of the atria solely consist of the free cavity wall.

|           | 50% contractility                                              | 75% contractility                                              | Reference contractility                                          |
|-----------|----------------------------------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------|
| <b>LV</b> | $SfAct(Lv1) = 50 \text{ kPa}$<br>$SfAct(Sv1) = 50 \text{ kPa}$ | $SfAct(Lv1) = 75 \text{ kPa}$<br>$SfAct(Sv1) = 75 \text{ kPa}$ | $SfAct(Lv1) = 100 \text{ kPa}$<br>$SfAct(Sv1) = 100 \text{ kPa}$ |
| <b>RV</b> | $SfAct(Rv1) = 50 \text{ kPa}$<br>$SfAct(Sv1) = 50 \text{ kPa}$ | $SfAct(Rv1) = 75 \text{ kPa}$<br>$SfAct(Sv1) = 75 \text{ kPa}$ | $SfAct(Rv1) = 100 \text{ kPa}$<br>$SfAct(Sv1) = 100 \text{ kPa}$ |
| <b>LA</b> | $SfAct(La1) = 30 \text{ kPa}$                                  | $SfAct(La1) = 45 \text{ kPa}$                                  | $SfAct(La1) = 60 \text{ kPa}$                                    |
| <b>RA</b> | $SfAct(Ra1) = 30 \text{ kPa}$                                  | $SfAct(Ra1) = 45 \text{ kPa}$                                  | $SfAct(Ra1) = 60 \text{ kPa}$                                    |



D

#### Simulation 6



**Figure 19:** Right ventricular volume with respect to time at a single EROA. The maximum of this plot corresponds to the end diastolic volume. This graph is plotted for multiple EROAs.

E

**Table 5:** EVEREST eligibility requirements for a MitraClip procedure, based on valve morphology. [31]

| Ideal valve morphology for a MitraClip procedure                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Unsuitable valve morphology for a MitraClip procedure                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mitral regurgitation originating from the mid portion of the valve (degenerative or functional aetiology)<br>Lack of calcification in the grasping area<br>Total mitral valve area $> 4 \text{ cm}^2$<br>Length of posterior leaflet $\geq 10 \text{ mm}$<br>Non-rheumatic or endocarditic valve disease<br>Flail-width $< 15 \text{ mm}$ , flail-gap $< 10 \text{ mm}$<br>Sufficient leaflet tissue for mechanical coaptation: coaptation depth $< 11 \text{ mm}$ , coaptation length $> 2 \text{ mm}$ | Perforated mitral leaflets or clefts, lack of primary and secondary chordal support<br>Severe calcification in the grasping area<br>Haemodynamically relevant mitral stenosis<br>Length of posterior leaflet $< 7 \text{ mm}$<br>Rheumatic valve disease with restriction in systole and diastole or endocarditic valve disease<br>Gap between the leaflets $> 2 \text{ mm}$ |

F

**Table 6:** Cardiac output and heart rate relationship during exercise. [15]

| Exercise level | 1  | 2   | 3   | 4    | 5   | 6    | 7   | 8    | 9   |
|----------------|----|-----|-----|------|-----|------|-----|------|-----|
| CO [L/min]     | 5  | 7.5 | 10  | 12.5 | 15  | 17.5 | 20  | 22.5 | 25  |
| HR [bpm]       | 71 | 89  | 106 | 124  | 141 | 159  | 176 | 194  | 211 |