Development of a balloon catheter for fetal aortic valvuloplasty

Master Thesis

E.E.M. Gigengack

TU Delft

LUMC Leids Universitair Medisch Centrum

Development of a balloon catheter for fetal aortic valvuloplasty

by Eline Gigengack

in partial fulfillment of the requirements for the degree of

Master of Science
in Biomedical Engineering

at the Delft University of Technology
to be defended on Tuesday June 29, 2021

Thesis committee

dr. J.J. van den Dobbelsteen	TU Delft
Mw. Dr. M.C. Haak	LUMC
dr. T. Horeman	TU Delft

Preface

As my high school time was ending, the moment arrived that I had to decide what I wanted to study. As I am not always great with making choices, this was a very difficult one. Multiple options arose from Medicine to Clinical Technology to Industrial Design Engineering. Eventually, Industrial Design Engineering was the winner and I am still happy with that choice. Whereas it was difficult to choose my bachelor program, it was very easy to choose the master program that would follow, since Biomedical Engineering had the best of all three considered bachelors. Applying design knowledge to solve medical problems is what I love to do, and therefore I am happy to have worked on this project to end my university education where it all comes together. For this, I want to thank John and Monique, since they provided me with this very exciting project.
John, thank you for your guidance throughout the project and providing feedback when needed. Monique, thank you for always making time for me in your busy schedule and introducing me to other experts on this subject. Your enthusiasm for this project and knowledge about the subject helped me to make the best of it. Even though the majority of our meetings had to be online, I have really enjoyed these meetings and our collaboration.

The help of the following people also contributed greatly to the successful completion of this project:

Medical specialists

- Mw. Dr. M.C. Haak, *gynaecologist & fetal therapist (LUMC)*
- Prof. Dr. N.A. Blom, *pediatric cardiologist (LUMC)*
- Mw. Dr. R. Bökenkamp, *pediatric cardiologist (LUMC)*
- Dr. A.J. Moon-Grady, *pediatric cardiologist & director of UCSF Fetal Cardivascular Program (USCF Benioff Children's Hospital)*
- Dr. L.E. Wilkins-Haug, *gynaecologist & clinical lead at the Maternal Fetal Care Center (Boston Children's Hospital)*
- Dr. G.A.P. de Kort, *(neuro)interventional radiologist (UMC Utrecht)*

Your input from the clinical perspective was extremely relevant and provided me with insights that were required to design a new medical device.

Prototyping

- Jan van Frankenhuyzen *(TU Delft)*

It was helpful to be able to brainstorm with you about my ideas and discuss the possibilities regarding prototyping, and thank you for helping me with the production of some needed parts.

- Jurgen and Gerrit Jan at *Medical Production Technology Europe*

Thank you for inviting me to Leek and taking the time to share your knowledge regarding the balloon production process with me, and helping me to produce several prototypes of my design. It was above my expectations to be able to make a working prototype on this scale and you made that possible.

I also want to thank my parents, for making it possible to study in Delft. Your interest and enthusiasm for the things I did led to many good conversations that I value greatly. And thank you for not only supporting me to enjoy studying, but also to have fun and make the best of my student time in Delft.
Lastly I want to thank Nick, who contributed a lot to making the best of my student time. I feel lucky that I have been able to discuss my struggles and celebrate milestones with you during (almost) my entire life as a student.

Eline Gigengack
June 2021

Executive summary

This thesis describes the design process of a new instrument that can be used to perform a fetal aortic valvuloplasty procedure. Congenital heart defects occur in 8 to 12 out of every 1000 live births. Aortic stenosis (AS) is one of the most common congenital heart defects. When AS occurs, the opening and closing of the aortic valve does not work well. This is often caused by two leaflets being fused together. If left untreated, aortic stenosis could have severe consequences such as the development of hypoplastic left heart syndrome (HLHS). To prevent this, the fetal aortic valvuloplasty (FAV) procedure is performed. In this procedure, a balloon catheter is advanced percutaneously into the fetal heart at ± 26 weeks of gestation. The problem with this procedure is that still many complications occur, of which some can be attributed to the used instruments. The currently used instruments are designed for an angioplasty procedure in adults, and therefore quite large. This led to the need for the design of a dedicated device for FAV, which was the goal of this thesis.

The thesis started off with a literature study and clinical interviews to determine the design focus, requirements and wishes. It was found that reduction of cannula diameter reduces the risk of complications, which therefore became the aim of this project. Currently an 18G cannula is used, which has an outer diameter of 1.27 mm. It would however be preferable to use a 20G cannula, which has an outer diameter of 0.91 mm. The 18G cannula is now required due to the crossing profile of the balloon that is used, which does not fit through a smaller needle. The crossing profile of a balloon refers to the maximum diameter found between the proximal and distal end of the balloon catheter, while it is still folded. To be able to use a smaller needle, this crossing profile needs to be reduced. Therefore, it was determined that the design focus should be on reducing the crossing profile of the balloon catheter, while still being able to reach the required diameter at inflation.

After exploring multiple ideas and concepts, the final concept was generated. This concept is based on the fact that the FAV procedure requires other balloon properties than an angioplasty procedure. Less pressure is required, the procedure is performed under ultrasound instead of x-ray guidance and the guidewire does not have to be changed and used for complex steering. Based on these differences, several design choices were made that lead to a smaller crossing profile and enhance the performance of the FAV procedure. Amongst others, this new design contains a fixed guidewire, longer cones and a low wall thickness.

Multiple prototypes were developed for testing and validation, which was done on both clinical and mechanical level. The clinical tests gave insights regarding preferred shape and configuration, and established that there was enough control and steerability provided with the fixed guidewire. The mechanical tests provided information regarding the force exerted by the balloon, (burst) pressure and diameter of the balloon. The prototypes had crossing profiles of around 0.6 mm, which is a significant reduction compared to the crossing profile of 0.8 mm of the current balloon. This allows for the use of a 20G cannula instead of an 18G cannula, which has an outer diameter that is almost 0.4 mm smaller.

The final design fulfilled all requirements and wishes, and therefore a proof of principle for a suitable alternative instrument for the FAV procedure was provided. Further research is recommended concerning the production of a more accurate prototype and elaborate clinical testing to optimize the design and gain more insights in the behaviour of this balloon.

Table of contents

6. Concept validation

7. Final concept design

8. Discussion

10. Future recommendations

References

Glossary

Appendix

1 Introduction

1.1 Fetal Aortic Valvuloplasty

Congenital heart defects occur in 8 to 12 out of every 1000 live births. One of these congenital heart defects is aortic stenosis (Hoffman, 2013). If aortic stenosis (AS) occurs, the aortic valve does not function properly which will have an influence on the development of the fetal heart. Due to a narrowing of the aortic valve, the left ventricle is not able to pump its blood into the body through the aorta. Instead, the development of the left ventricle will be abnormal and possibly cause the development of hypoplastic left heart syndrome (which will be elaborated in section 2.1). Fetal aortic valvuloplasty (FAV), or balloon valvuloplasty is a procedure that is performed in utero on the fetal heart to prevent this. The goal of FAV is to deliver a baby with biventricular circulation, meaning both ventricles are functioning.

The mean gestational age at which this procedure is performed is around 26 weeks, since it is said that around that age the heart is large enough to be able to perform the procedure, but it is still early enough in the fetal heart development to prevent permanent anomaly's to the heart (Yuan et al., 2016). Figure 1.1 illustrates the steps of the FAV procedure.

First, the mother is put under anaesthesia (both local and general anaesthesia is possible). After that, it is essential to get the fetus into the right position. This is necessary because otherwise it is not possible to access the fetal heart percutaneously. After the fetus is in the right position, it receives an anaesthetic to stay in this position. This is done by intramuscular injection. Now a hollow needle (cannula) with sharp obturator is advanced through the maternal abdomen into the fetal chest wall where the fetal heart is punctured at the apex into the left ventricle (LV). After the cannula has entered the LV, the sharp obturator is retracted, and a 0.014" guidewire with dilatation balloon is introduced. When the balloon is positioned across the valve, it is inflated until the diameter is between 10 to 20% larger than the valve diameter. Depending on the situation, inflation and deflation is repeated 2 to 5 times. Often there are two surgeons involved in this procedure. An obstetrician handles the placement of the needle and ultrasound transducer, and a cardiac surgeon handles the placement, inflation, deflation and retraction of the balloon catheter. Sometimes the ultrasond transducer is operated by a third person.
If all these actions are executed, all instruments are retracted. The procedure is defined as being technically successful when balloon inflation across the valve has succeeded, followed by improved flow across the aortic valve or new aortic regurgitation indicated by color Doppler (Pickard et al., 2020).

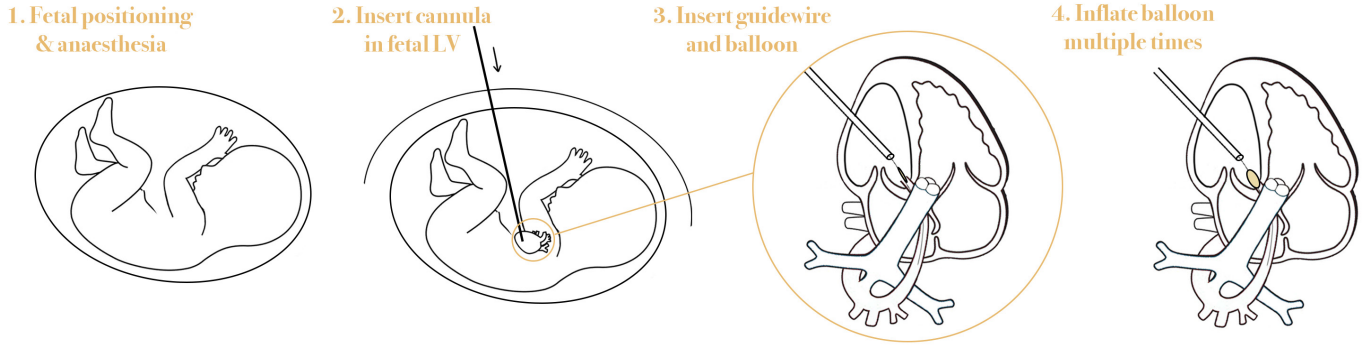


Figure 1.1: Illustration of the procedural steps for the fetal aortic valvuloplasty procedure.

1.2 Problem Definition

Prior to this thesis, a literature study was performed. Based on the results that are described in the current literature, it is clear that the FAV procedure improves the birth outcomes of fetuses with critically aortic stenosis. The technical success rate of the most recent high volume study (Patel et al., 2020) is as high as 83,3%. This study includes the data of different centers over the world and is therefore representative for the current status of FAV. Not all fetuses that underwent a successful FAV are born with biventricular outcome, however the most recent articles show that between 31% and 50% of the technical success cohort does achieve biventricular circulation (Patel et al., 2020; Pickard et al., 2020). These numbers and outcomes validate the value of this procedure, however there is still a risk of serious complications.

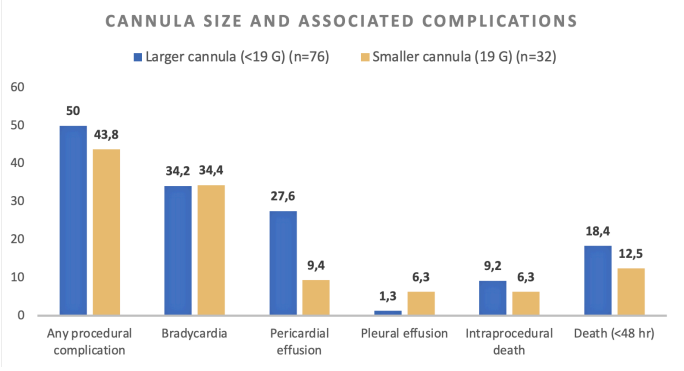


Figure 1.2: Bar graph showing occurance of complications in FAV (in percentages). Comparison between larger cannula (<19G) and smaller cannula (19G). Data retrieved from Patel et al., 2020.

The most common complication is bradycardia. Due to the puncture of the fetal heart with the cannula, a small hole in the heart allows blood to accumulate in the pericardial sac (pericardial effusion). This makes it harder for the heart to pump, eventually causing bradycardia. This complication is most likely to occur at withdrawal of the instruments. In the high volume study of Patel et al, it becomes clear that a larger cannula size increases the risk of pericardial effusion and in general any prodedural complications (see Figure 1.2).

This data shows that a smaller cannula is preferred, and implies that a cannula which is smaller than 19G would cause even less complications. It also shows that currently 19G cannulas are used much less frequently than larger cannulas. The three main components of the instruments used in FAV are illustrated in Figure 1.3. Section 2.2 elaborates more on these instruments. The currently used instruments are balloon catheters which are developed for adult or pediatric coronary angioplasty procedures, not for fetal cardiac interventions. This makes them quite large and therefore not the entirely suitable for the FAV procedure. This leads to the problem definition as stated below.

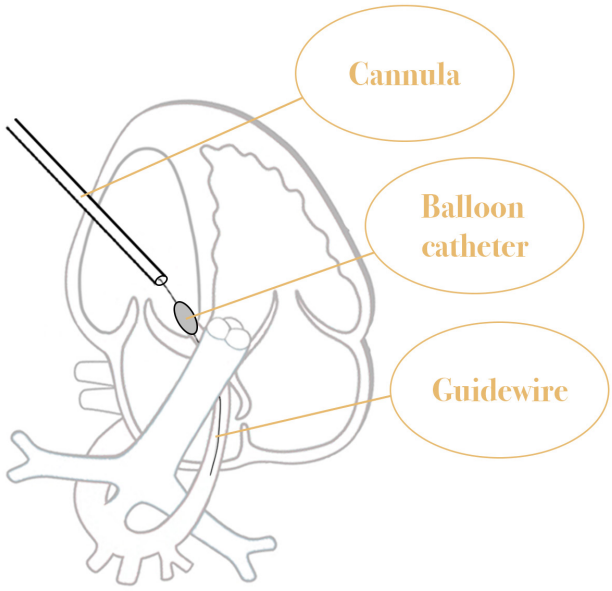


Figure 1.3: Illustration of the heart with three main components of instruments used for FAV: a cannula, balloon catheter and guidewire.

PROBLEM DEFINITION

The FAV procedure has a high risk for complications. The currently used instruments contribute to this, since there are no dedicated instruments that are developed for the purpose of performing the fetal aortic valvuloplasty procedure. This leads to the use of large instruments, which increases the risk for complications. The occurrence of these complications could be lowered by using smaller and more suitable instruments, however these instruments are not on the market.

1.3 Project Goal

The previous sections described the need for a new instrument to improve the FAV procedure. Many aspects contribute to the success of the procedure, but to make this thesis useful it is important to define clear boundaries. For this project it is decided that the procedural approach will not change. This means that the fetal aortic valve will still be accessed percutaneously through the left ventricle and subsequently will be opened by dilatation.

The goal of this thesis is to provide a proof of principle for a novel dedicated device to improve the FAV procedure by reducing the risk of complications.

The aim to achieve this is by enabling the use of smaller instruments.

1.4 Project approach & thesis outline

This thesis presents the design process of a novel instrument, and therefore follows a design cycle up until the goal is achieved; the development of a proof of principle. The course of this process is depicted by the double diamond model, which is often used to describe design processes. See figure 1.4.

The double diamond model is used to help designers with defining different phases throughout the process, and stimulates decision making at the right moments between these phases. On one hand it stimulates the designer to diverge by collecting information and researching different possibilities and ideas. On the other hand it also encourages the designer to converge at the right time by making choices and deciding on key aspects during the process. Throughout the report the four phases of the double diamond will function as a reading guide to show where in the design process you are.

Discover
The first section is the discover section. In this section the project context is defined and boundaries are set, but to be able to do that all relevant background information has to be collected first. This is done by collecting relevant information from the previously performed literature study, but also by listening to the clinical perspective. To gather information on this clinical perspective multiple interviews are performed. Next to that, some key aspects of balloon catheters are researched such as materials and mechanical behaviour. Finally, the variety of applications for balloon catheters that are currently on the market are evaluated and summarized.

Define
When enough information is acquired to feel comfortable in the field and the project context is clear, the discover phase shifts towards the define phase. Choices regarding focus points are made and eventually all information is converged into a list of requirements and wishes. At this point it is decided that the design focus should be on the dilatation instrument. This will be the starting point for the creative development process.

Develop
The develop section contains the creative ideation process which is divergent again. Many different ideas are generated regarding an instrument that has the goal of dilating an aortic valve. Eventually the most promising ones are developed into concepts. The most promising concepts are worked out further and evaluated based on relevant criteria. This leads to a weighed decision for the final concept, which is found to be an optimized version of a high pressure balloon developed specially for FAV.

Deliver
When all relevant aspects of the design are researched and defined, it is time to gain insight on the proof of principle of the concept. The validation of this concept is split into both clinical and technical validation. These categories are tested and evaluated by separate tests. Based on these outcomes a conclusion can be drawn on the proof of principle of this novel design for a balloon catheter.

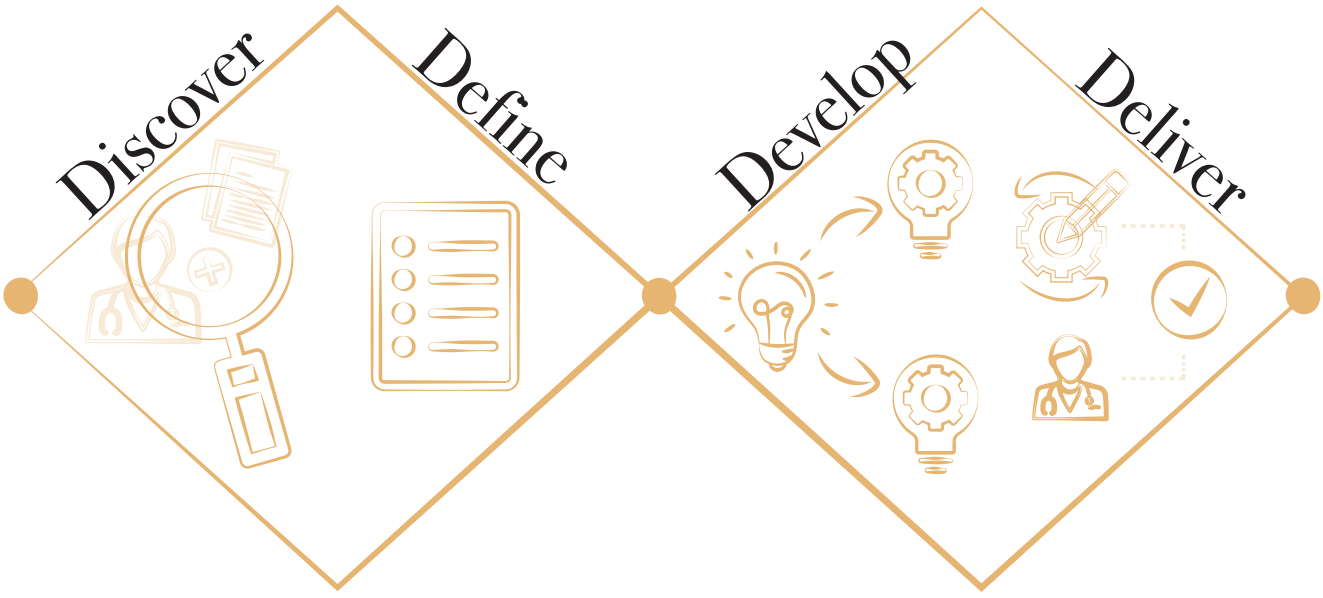


Figure 1.4: The double diamond model that describes the thesis approach with four main phases: discover, define, develop and deliver.

Througout the entire process the clinical perspective will be of great importance. The industry of medical devices and technology is rapidly evolving due to new techniques and innovations. Think about surgical robots and minimally invasive devices but also the use of artificial intelligence in hospital systems such as automated disease detection models. These new technologies provide useful possibilities to the improvement of healthcare and have the ability to reduce complications and provide more patient comfort. However, in the development of these new technologies often the clinical perspective is lost out of sight. This leads to the development of technologies and products which are not adapted to the needs and wishes of the end users; the clinicians.

The development of new products should be done using a more co-creative approach where the opinions and ideas of the clinicians are taken into account. This way, relevant problems will be solved and useful solutions are provided. When the end user is included in the design process the final product will have a higher chance of being accepted and fulfilling the clinical need.

Based on this idea, during the course of this thesis, the collaboration with clinicians is key. The demand for this project was based on the clinical need as defined by Mw. Dr. M.C. Haak from the LUMC. As she is an expert in the field of fetal surgery, throughout the process a close collaboration is pursued.

Discover

Chapter 2

Background

Aortic Stenosis & HLHS

FAV instruments

Balloon catheters

Mechanics & materials
Market overview

Interviews with experts

Background

2

The background chapter contains the most relevant information that was acquired by performing general literature research on FAV and more specific subjects such as the balloon catheter. Next to that the clinical need was established by performing interviews with experts on the topic. This information helps to discover the subject of this thesis and is necessary to understand and define the requirements and wishes for the new design.

2.1 Aortic stenosis & HLHS

As described earlier, Aortic Stenosis (AS) is a congenital heart defect. AS accounts for about 3-6% of the congenital heart defects (Singh, 2019) and refers to the narrowing of the aortic valve. A healthy aortic valve consists of three leaflets of tissue. These three leaflets can separate entirely, and thereby opening the valve. When AS occurs, the opening and closing of the valve does not work well. This can be caused by two leaflets being fused together, in which case we speak of a bicuspid aortic valve (see Figure 2.1).

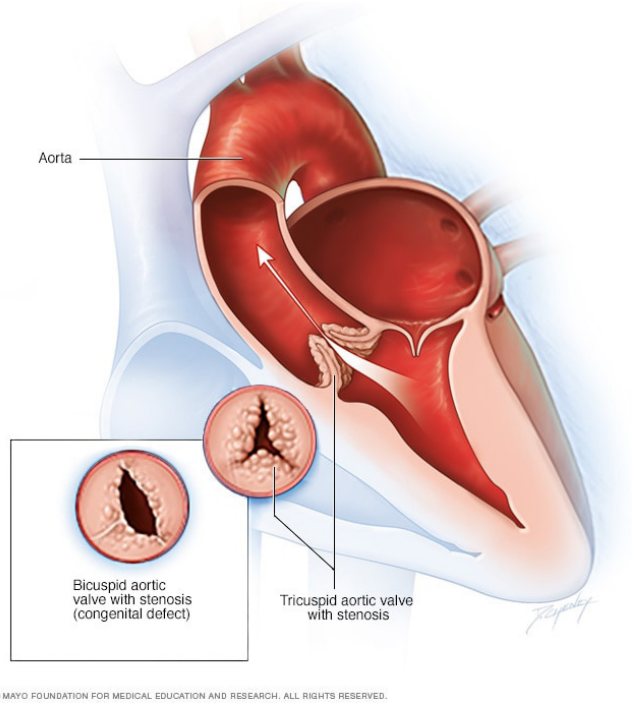


Figure 2.1: Heart with stenotic aortic valve. Healthy heart consists of three triangular 'cusps' that open and close, but bicuspid or tricuspid valves can not do this properly. Source: Mayo Foundation for Medical Education and Research, 2021

This is the most common cause for congenital aortic stenosis, and with that also the most common congenital heart defect (Michelena et al., 2011). Next to that another anomaly is seen in which there are three leaflets (tricuspid valve) but they are stiff and not able to move enough. Finally,, it is also possible that the valve develops into one leaflet (unicuspid) or four leaflets (quadricuspid) but this is quite rare (Singh, 2019). The cause of AS is believed to be genetic (Singh, 2019; Schidlow et al., 2014). The development of congenital AS is mostly completed by the first trimester, but can evolve throughout the pregnancy. The severity of AS can differ, ranging from mild to critical. When the valve does not function properly anymore, the condition is classified as being severe or even critical. Critical aortic stenosis requires immediate intervention at birth. However, when intervention is performed on a neonate, there is a chance that the fetal heart has already developed severe problems during gestation.

One problem that could be a consequence of critical aortic stenosis is the development of Hypoplastic Left Heart Syndrome (HLHS). Due to the narrowing of the valve the left ventricle (LV) experiences a lot of resistance when pumping the blood into the aorta and therefore into the body. This results in dilation of the LV due to an overload of blood volume, eventually causing dysfunction of the LV (Yuan, 2014). Myocardial perfusion diminishes, eventually resulting in the stop of growth in the LV. Since the blood that is coming into the LV can not all go to the aorta, it flows back into the left atrium (LA). This is called mitral regurgitation.

The dysfunction of the LV can lead to HLHS, which is defined by Cruz-Lemini et al. (2019) as "*underdevelopment of the left-sided structures of the heart, which renders them unable, because of an inadequate size, function, or a combination of both, to support the systemic circulation after birth*". In this definition it is stated that the systemic circulation is not supported after birth, because during the pregnancy HLHS can be compensated by the fetal heart structure. Figure 2.2 shows how this circulation goes.

As is illustrated, this circulation is dependent on an atrial septal defect (ASD), which is a hole between the left and right atrium. In fetuses the ASD is formed by the foramen ovale which is present in every healthy fetal heart during the pregnancy. Besides the foramen ovale the patent ductus arteriosus (PDA) is an important structural connection that is required for sufficient blood flow to the body. If AS has led to underdevelopment of the LV, oxygen rich blood flow will start to go in retrograde direction, meaning from left to right. This left-to-right flow can be observed in the foramen ovale (Yuan, 2014; Frommelt, 2014). In this case, the blood flows through the right atrium and right ventricle (RV) into the pulmonary artery, which is connected to the aorta through the PDA. This means that the RV is now responsible for pumping all blood throughout the body, which is usually done by the LV. After birth the PDA closes, which means that this pathway for oxygen rich blood into the body is no longer possible. Without intervention the prognosis of HLHS is always lethal (Graupner et al., 2019).

Due to the severe consequences of the development of HLHS it is important to diagnose this as early as possible. The left to right flow in the foramen ovale, severe LV dysfunction, retrograde flow in the transverse aortic arch (due to the blood supply from the PDA) and monophasic mitral flow are all features that indicate the development of HLHS (Yuan, 2014; Schidlow et al., 2014; Frommelt, 2014). Thanks to current technology these features can be detected in utero by echocardiography and Doppler flow measurements before there are structural changes in the heart which are difficult to reverse (Singh, 2019). Regarding the size of the LV it is observed that it first grows in size significantly, before it starts to become abnormally small. It is therefore key to diagnose the features that indicate HLHS development, and perform a fetal intervention before the LV starts shrinking, since by then the space for intervention is too small.

The ability to diagnose AS and the development of HLHS enables fetal intervention which can prevent irreversible changes to the heart structure. The goal of the FAV procedure is to do this. When the fetal heart has a stenotic aortic valve the anatomical dimensions are different from a healthy heart. These are of importance for the procedure and should be kept in mind when choosing or designing instruments for the FAV procedure. The most important difference is the aortic valve diameter, which is smaller than usual. At the moment of intervention it is often between 2.8 mm and 3.1 mm (Patel et al., 2020).

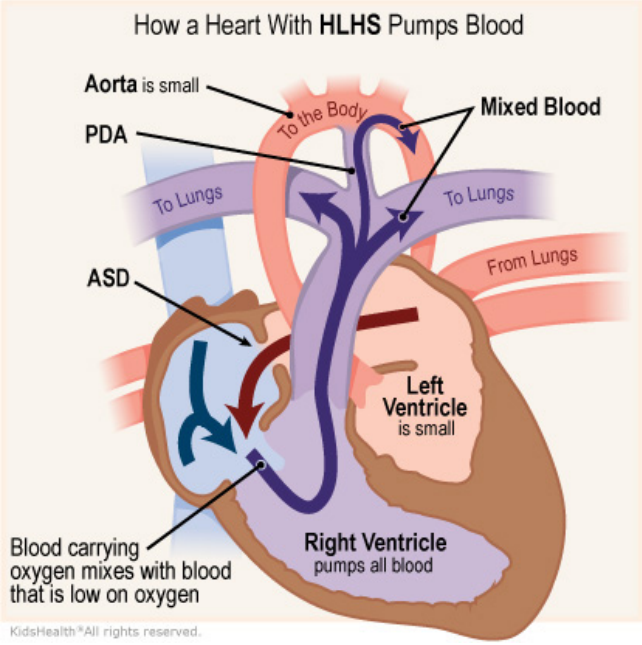


Figure 2.2: Blood circulation in a fetal heart with Hypoplastic Left Heart Syndrome (HLHS). PDA = patent ductus arteriosus, ASD = atrial septal defect. Source: Bingler, 2018.

2.2 FAV instruments

The three instruments that are always used for FAV are an introducer needle (cannula), guidewire and balloon catheter. This section discusses the purpose of the three different components and the problems that are experienced with the currently used instruments. Figure 2.3 shows an overview of these instruments.

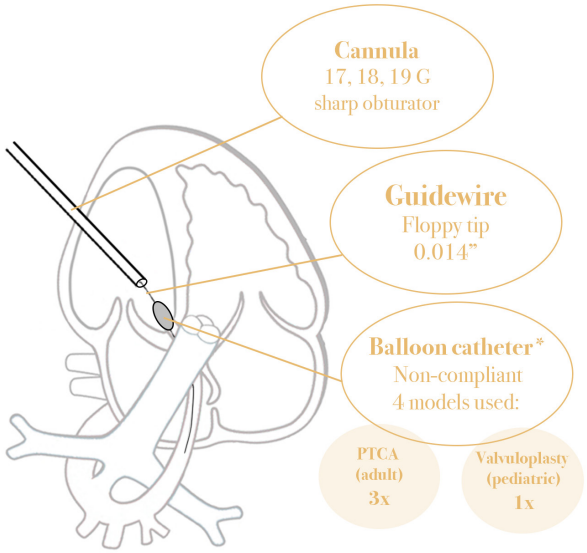


Figure 2.3: Heart with three main components used for FAV. Of each component details are provided regarding the instruments that are currently the most frequently used.

The introducer needle, or cannula has as main purpose to provide access to the left ventricle. This is done by puncturing the different tissues and therefore requires a sharp tip and enough stiffness. A cannula is a hollow tube allowing for the instruments (guidewire and balloon catheter) to pass through its lumen. During puncture the cannula is obturated with a sharp inner needle to provide stiffness and a sharp tip. This obturator is removed when the needle is in the correct position.

Cannula sizes are indicated in Gauges. Gauge sizes with corresponding diameters are shown in Table 2.1. Currently, for FAV the 18G needle is most often used. In some cases a 17G or 19G needle is used but smaller or larger sizes are rare. The inner diameter of the cannula has to allow for the balloon catheter to be advanced through it. This means that the choice of cannula is based on which balloon is required and how large its deflated diameter is. The key problem with the cannula is that it has to be large enough to allow for passage of the balloon, but it should also be as small as possible since it directly punctures the very small fetal heart. As discussed before, a larger cannula size means a bigger risk for procedure related complications.

The guidewire is used to accommodate the balloon catheter to the lesion site. To do this a 0.014" guidewire is currently used. The guidewire has a floppy tip which means that the tip is made of a different, more flexible material. This is convenient since the floppy tip prevents the guidewire from causing any damage during the navigation to the lesion site. No significant problems are experienced with the current guidewire in the FAV procedure. However, it would be of value if it's visibility on ultrasound is improved. This would allow for better knowledge about the position of the guidewire, and with that it would provide more confidence regarding the balloon placement.

The balloon catheter has an inner lumen which slides over the guidewire, and therefore it directly follows its path. The balloon catheter is used to dilate the valve. It follows the guidewire and is positioned across the aortic valve. When the balloon is in the right position it is inflated to a diameter which is 10 to 20% larger than the valve diameter. The inflation is done with a fluid which also enhances the visibility on ultrasound. A remarkable finding is that the currently used balloon catheter models are mainly designed for adult purposes. There is no balloon catheter on the market that is designed for fetal interventions. From the four models that are found in literature, 3 are primarily designed with the purpose of performing a percutaneous transluminal coronary angioplasty (PTCA). One of them is designed for pediatric valvuloplasty. Different requirements are important for every procedure, and even though the current balloons are able to perform the needed dilatation, they are not ideal. Since they are developed for a PTCA procedure in adults it is less important to make the crossing size as small as possible. This is however an extremely important feature for the FAV balloon. This is why a redesign of the balloon catheter could lead to big procedural improvements.

The general conclusion concerning the instruments for FAV is that the approach of using a cannula with balloon catheter works well, however the currently used instruments introduce an increased risk of complications. Therefore, ideally a new solution is designed to allow for the use of a smaller cannula with balloon catheter combination. The most promising way to achieve this is expected to lie within the design of the balloon catheter. To validate this a more comprehensive understanding of the balloon catheter is required. The following sections will elaborate on some key aspects of the balloon catheter.

Table 2.1
Gauge sizes and corresponding inner and outer diameters in mm.

Gauge nr.	Outer Diameter (mm)	Inner Diameter (mm)
12	2,77	2,16
13	2,41	1,80
14	2,11	1,60
15	1,83	1,37
16	1,65	1,19
17	1,47	1,07
18	1,27	0,84
19	1,07	0,69
20	0,91	0,60
21	0,82	0,51

Note: data retrieved from https://www.hamiltoncompany.com/laboratory-products/needles-knowledge/needle-gauge-chart

2.3 Balloon catheters

Balloon catheters are used for many different procedures. Every procedure asks for its own balloon properties. Therefore balloon catheters exist in many different shapes and sizes. The material of the balloon has a big influence on the properties of the final product, and also determines some possibilities regarding shape and size. Hence it is relevant to know the most common materials and key considerations when choosing a material. The balloon mechanics also play an important role when designing the shape and choosing a certain material. Besides that it is important to get an idea on what is currently on the market regarding balloon catheters, to find out what is possible.

2.3.1 Mechanics & materials

A key property for the balloon material is related to the compliance it provides. The compliance refers to the amount of pressure that is needed to change the shape of the balloon. Compliance is divided into three categories; compliant, semi-compliant and non-compliant. A balloon is designed and manufactured to have a certain diameter. This diameter is called the nominal diameter (Food and Drug Administration [FDA], 2010). Compliance refers to the amount of pressure that is needed to increase the diameter of the balloon above this nominal diameter. Non-compliant materials generally increase between 0 and 10 % above the nominal diameter before reaching the burst pressure. For semi-compliant materials this is between 10 and 30%. Compliant materials can expand much more and can even expand to several times the original volume (Jing et al., 2018). Non-compliant and semi-compliant balloons tend to shape into the designed dimensions with little deviation. Compliant balloons however have a much less controllable shape and tend to adjust their shape to their surrounding. This is preferred when the balloon catheter is used for the purpose of occluding a certain area, yet for the FAV purpose non-compliant and semi-compliant materials are required. The controllable shape of the balloon is relevant since non-compliant balloons often have the goal of dilatating a certain lesion. If the shape and diameter is not controlled there is a risk of damaging or rupturing the dilated area.

Two key mechanical properties for balloon catheter materials are the yield strength and tensile strength. The yield strength refers to the stress at which a material undergoes plastic deformation. The tensile strength refers to the stress at which the material will rupture. Both of these properties are relevant since they have influence on the failure behavior of the balloon.
The stresses that are present on the balloon wall can be described by the model of a thin-walled pressure vessel since the wall thickness (t) is less than a tenth of its diameter. See Figure 2.4 for an illustration of the stresses that act on the thin-walled pressure vessel.

The formula for the hoop stress (σ_H) within the vessel wall can be derived from this model, and is described in formula 1 below:

$$\sigma_H = \frac{Pr}{t} \quad (1)$$

Next to the hoop stress, also a longitudinal stress (σ_L) is present. This is described by formula 2:

$$\sigma_L = \frac{Pr}{2t} \quad (2)$$

Since the pressure (P) , radius (r) and thickness (t) of the vessel are equal in both formulas, the hoop stress is always twice the longitudinal stress. This means that if the balloon fails due to a stress exceeding the ultimate tensile strength it will always rupture in the longitudinal direction. This is beneficial, since a longitudinal rupture will allow for more easy retraction than a circumferential rupture. Figure 2.5 shows an example of a circumferential cut made into a PTCA balloon, illustrating the problem with retraction in this type of rupture.

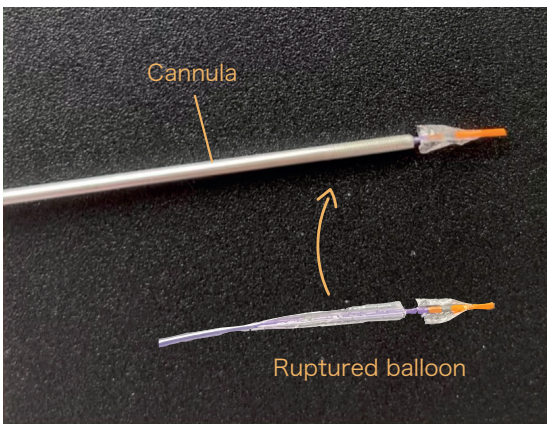
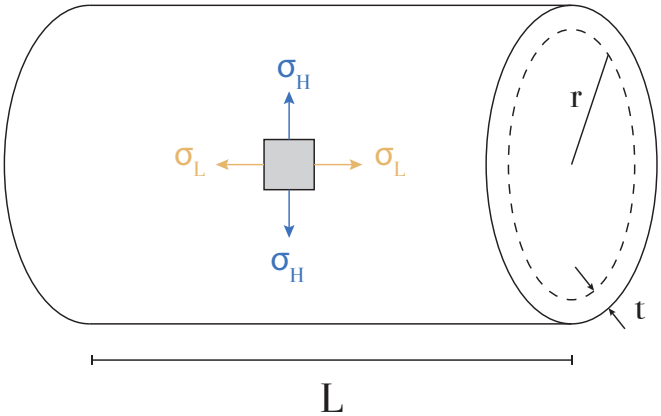


Figure 2.5: Circumferentially ruptured balloon inside cannula.



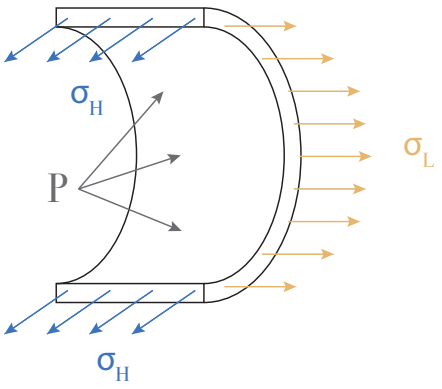


Figure 2.4: Free body diagram of a thin-walled pressure vessel that represents a high pressure balloon. σ_H = hoop stress, σ_L = longitudinal stress, r = radius, t = wall thickness, L = cylindrical length, P = pressure.

As stated before, when the hoop stress exceeds the tensile strength rupture will occur. Therefore it is useful to know the tensile strength of a material when selecting it as a base material for a balloon catheter. Besides that it is also useful to know the yield strength. If the yield strength is close to the tensile strength, the diameter of a balloon will increase very little with extra pressure before rupture (Abele, 1980). However, also the Young's modulus plays an important role in the material characteristics. If the Young's modulus is very low only little stress is needed to achieve strain. This means that materials will stretch a lot before high stress starts to accumulate. Table 2.2 shows the yield strength, tensile strength and Young's modulus of the most common medical balloon materials. It also shows at which level of compliance these materials are categorized. Note that these values are an approximation based on an average. Material properties of plastics are heavily influenced by manufacturing and processing parameters. This is due to the amount of crystallinity in the material which often increases upon extrusion, stretching and heating (Sauerteig & Giese, 1998). The plastic tubing, which is the base material for the balloon forming process, is produced by different manufacturers. This means that the properties of these tubings can also vary. Therefore it could be useful to perform a tensile test on different tubings to determine the most important properties and compare them to find the optimal material for the required application.

The hoop stress is also directly linked to the dilatation force that the balloon exerts. This relation is described in formula 3:

$$\sigma_H = \frac{F}{tL} \qquad (3)$$

In this formula σ_H refers to the hoop stress, F refers to the force exerted circumferentially on the cylindrical wall with thickness t and length L.
Besides that, circumferential force can also be described by formula 4:

$$F = T * L \qquad (4)$$

Where F is still the force exerted circumferentially, T is the wall tension and L is the cylindrical length.
Combining formula's 1, 3 and 4 leads to formula 5:

$$T = P * r \qquad (5)$$

This formula provides useful insight regarding the relation between balloon radius and dilating force. It shows that for the same pressure, a balloon with a smaller radius will provide less tension and therefore force. This indicates that balloons with small diameters require to withstand higher pressures and associated stresses to achieve the same dilation force.

To design the optimal balloon catheter it is relevant to keep these mechanics in mind, since balloon length, wall thickness, material properties and inflation pressures all relate to the dilating performance of the balloon.

Table 2.2
Categorized balloon materials and corresponding properties

		Youngs modulus (GPa)	Yield strength (MPa)	Tensile strength (MPa)
Non-compliant	**PET**	2,76 - 3,1	65 - 70	70 - 75
Semi-compliant	**PA12 (rigid)**	1,08 - 1,35	34,8 - 43,4	45 - 55
	Pebax® 65D	0,409 - 0,419	16,6 - 17,4	50,6 - 55,4
	Pebax® 55D	0,145 - 0,349	11,1 - 16,5	37,5 - 54,8
Compliant	**PE**	0,537	8,27 - 13,8	10,3 - 21,4
	TPU (55D)	0,148 - 0,152	14,6 - 15,4	47,3 - 53
	TPU (75D)	0,336 - 0,353	30,4 - 33,6	39 - 46
	TPU (80A)	0,0326 - 0,0334	36,9 - 42,9	36,9 - 42,9
	PVC	0,006 - 0,007	13 - 14	13 - 14

Note: data retrieved from CES EduPack 2019, ANSYS Granta© Granta Design.

2.3.2 Market overview

To determine the possibilities in balloon design it is useful to research the current market. To explore this market the different applications for the use of balloon catheters are reviewed. The different areas of intervention and some balloon properties are researched and summarized in Figure 2.6 and Table 2.3 below.

Note that this is an overview of the found information, and the entire balloon catheter market is certainly not covered by this table. Only relevant and interesting aspects with an eye on this research were presented.

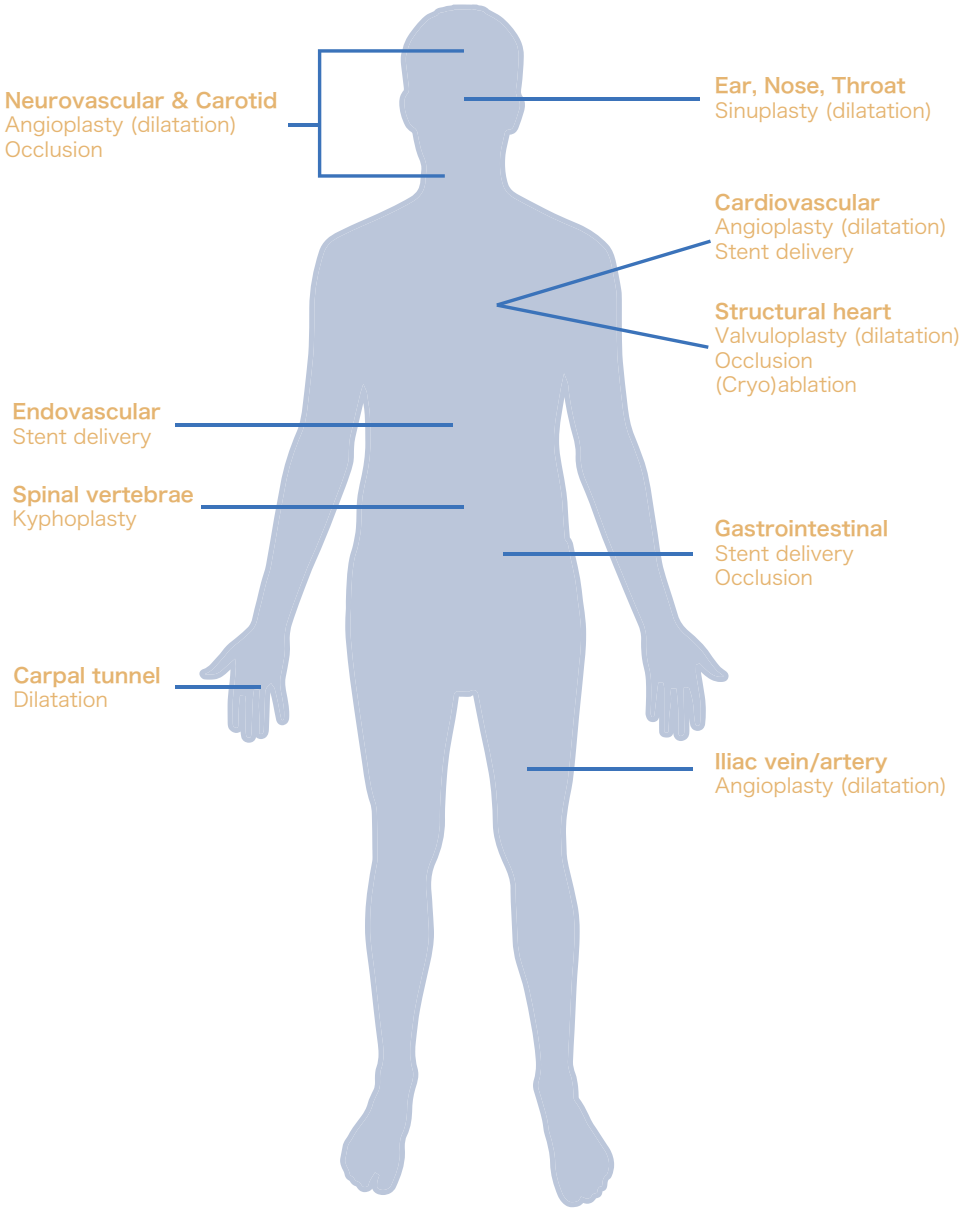


Figure 2.6: Overview of locations in the human body where balloon catheters are used for intervention.

Table 2.3
Overview of balloon catheter applications and relevant balloon properties

Intervention type	Dilatation			Kyphoplasty	Occlusion	Stent delivery	(Cryo)ablation	Atherectomy
	Angioplasty	Valvuloplasty	Sinuplasty					
Properties	High pressure	Almost same as angioplasty, but lower pressures	Pressure: 8 - 12 atm	Non-compliant	Compliant	Compliant or semi-compliant	Compliant	Purpose: extremely occluded lesions where angioplasty is not safe
	Non-compliant		Sizes ± 3 - 7 mm	Pressure: 8-9 atm	Elastomeric		Liquid refrigerant into balloon	
	Big range of sizes due to different purposes			Mostly 10G for access	Different sizes	Force required for opening stent		
	Thin-walled			Sizes between 10-20 mm			Balloon is for occlusion	
	Pressure: 2 - 20 atm							
Notable balloons	Artimes (BrosMed)	Tyshak Mini (NuMed)	RELIEVA Spinplus Sinuplasty System (Acclarent)	SYNFLATE system (Johnson & Johnson)	Occlusafe (Terumo)		Arctic Front (Medtronic)	AngioSculpt (Philips)
	Wedge (BrosMed)	TrueFlow (BD)		KYPHON IBT (Medtronic)				Chocolate XD (Teleflex)
	NC Emerge (Boston Scientific)	Advance Micro 12 (Cook Medical)						
	NSE Alpha (Braun)							

2.4 Interviews with experts

As stated before the clinical perspective is a very important factor in this project. Carrying out interviews with clinicians helps to define the clinical need and outlines a window of opportunities. Besides interviews clinical observations would be very useful to gain insight in the procedure, however due to the fact that FAV is not performed often and the current COVID-19 measures, this was not possible. The most important topics and findings of the performed interviews are summarized in this section. See Appendix A for a more elaborate summary of the interviews.

Prof. Dr. N.A. Blom, pediatric cardiologist (LUMC)

Topics: Currently used instruments for FAV

At the LUMC currently PTA balloon catheters (TREK Coronary Dilatation Catheter, Abott) are used for the performance of the FAV procedure. In most cases a 19G cannula is used. The guidewire that is used is a 0.014" balanced middle weight guidewire with a floppy tip, and is mainly required for atraumatic steering through the aortic valve. This could also be achieved with a smaller guidewire. A main improvement that could be achieved regarding the guidewire would be an increased visibility on ultrasound. Other than that, not much needs to be changed regarding the guidewire. The wish for dedicated instruments is confirmed, yet there are some key design considerations that need to be kept in mind that are required for the balloon catheter or a substitute device to work properly. Some of these considerations are that uniform pressure needs to be exerted, the diameter needs to be precisely controllable and feedback regarding the position needs to be provided. An important insight is that Dr. Blom expects that for the opening of the valve only 2 to 4 atmospheres pressure is required, whereas angioplasty procedures require around 14 atmospheres. A limitation that is currently experienced is that the limit of an operable valve diameter is around 3 mm, due to the available instruments. Yet lesions of larger diameters also occur and would also be useful to operate. Increasing the range of operable lesions would allow for more succesfull interventions. Other considerations can be found in Appendix A and are included into the list of requirements and wishes.

Dr. G.A.P. de Kort, (neuro)interventional radiologist (UMC Utrecht)

Topics: Different applications of balloon catheters and balloon properties

For neurological interventions, balloon catheters are mainly used for stent placement and coiling. Stent placement requires non-compliant or semi-compliant balloons. In neurological interventions a long distance needs to be covered to reach the lesion site. Therefore the catheter needs to be flexible enough to follow the path of the guidewire, yet also requires enough pushability. Balloons used for stent placement should provide enough force to open a stent, but this needs to be very controlled since otherwise there is a risk of rupturing the vessel. Compliant balloons are mainly used to support the coiling procedure. During this procedure an aneurysm is filled with coiling to prevent it from rupturing. This coiling should not enter the bloodstream, so a compliant balloon is used to close off the aneurysm. Balloon diameters between 2 to 4 mm are used in neurological interventions. It is important to keep in mind that the crossing profile of a balloon increases after inflation and deflation. Different materials result in different levels of re-folding.

Dr. A.J. Moon-Grady, pediatric cardiologist and director of USCF Fetal Cardiovascular Program (USCF Benioff Children's Hospital)

and

Dr. L.E. Wilkins-Haug, gynaecologist and clinical lead at the Maternal Fetal Care Center (Boston Children's Hospital)

and

Dr. M.C. Haak, gynaecologist and fetal therapist (LUMC)

Topics: Currently used instruments for FAV and resulting complications and limitations

The visibility is a big concern during the FAV procedure. Mostly in the interventions at an early gestation the visibility is difficult. This is due to the small LV and surrounding capillary muscle. It would be useful if there is any way to differentiate the wire or cannula from the surrounding. Often there is a seperate operator responsible for the ultrasound imaging. The poor visibility is mostly a problem since this means there is less feedback regarding the position of the guidewire and catheter. A pressure sensor at the tip of the guidewire could help determining this position, and this is something a research group in Michigan is working on. It is agreed upon that changing the instruments is a more useful improvement than changing imaging technique, since it would be a more generalizable change. Not all institutes have acces to advanced imaging techniques. Sometimes the balloon is inflated up to its burst pressure when the intended diameter is not reached otherwise. If this happens, the balloon catheter is not retracted through the needle, but needle and balloon catheter are retracted seperately. Not all institutes use this as a common approach. The reduction of size of the instruments is seen as a big improvement. It is discussed that in a research based on the IFCIR (International Fetal Cardiac Intervention Registry) database, of which Dr. Moon-Grady is founding member of the steering committee, the difference between 18G and 19G needles is determined. In this research it is established that using a 19G needle already reduces complications. Using a 20G needle will therefore reduce the complications even more, and therefore be a big step forward.

The conclusion that can be drawn based on the interviews would be that the need for dedicated instruments is confirmed. Improvement of visibility during the procedure is a big wish, yet the main focus point for redesign should be the reduction of size of the instruments. Based on previous research and experience this is assumed to cause a big reduction in complications. Unfortunately in other areas where catheters are used, no balloon catheters which are both non-compliant and this small in size are available yet. There are some design possibilities such as a reduced amount of pressure which is probably required. Requirements and wishes that were obtained based on these interviews are included in the list of requirements and wishes, discussed in the next chapter.

Chapter 3

Product context

Design focus

Requirements and wishes

Define

3 Product context

Based on all information that is acquired in the previous chapters, choices are made and design boundaries are set. This leads to a design focus allowing for more in depth research on this topic. From all information of the previous chapters key requirements and wishes are extracted and summarized into a list. The final product will have to fulfill all these requirements and preferrably the wishes are taken into account as well.

3.1 Design focus

As it became clear during the literature research, over the past 20 years merely the same instruments have been used. These instruments are not designed for the purpose of performing FAV but for performing angioplasty in adults. FAV is a procedure with a quite high complication rate of which a notable amount could be prevented by using the right instruments. Therefore the clinical need arose for the development of a dedicated device. The current equipment consists of three components; cannula, guidewire and balloon catheter. As illustrated in Figure 3.1, the design focus should be at redesigning the balloon catheter as this will reduce the size of the required instruments. A challenging yet realistic goal is to aim for the use of a 20G needle instead of an 18G needle. Table 3.1 shows the related dimensions.

Table 3.1
Cannula dimensions for different gauge sizes

Gauge size	Outer diameter (mm)	Inner diameter (mm)
18	1,27	0,84
20	0,91	0,60
Difference	0,36	0,24

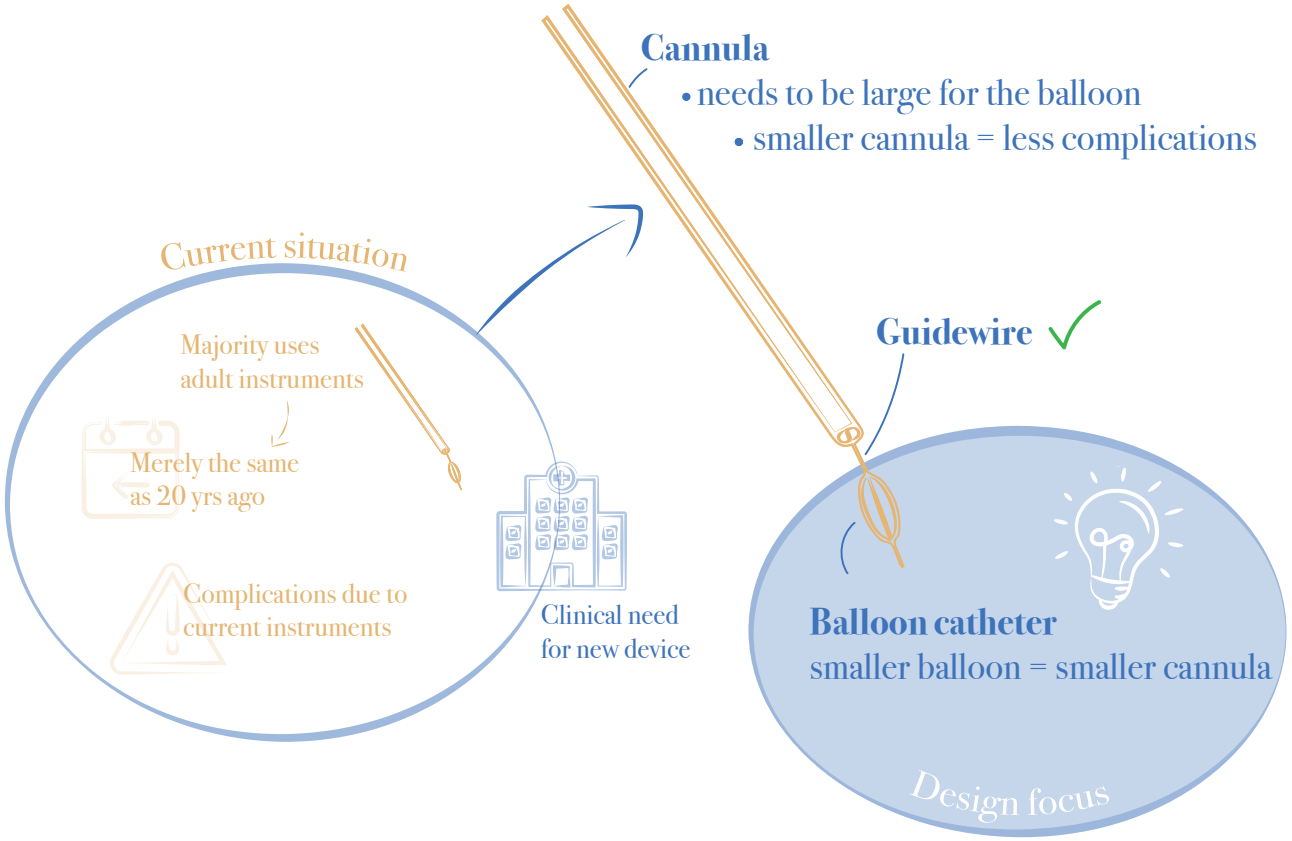


Figure 3.1: Design focus for this thesis based on previous research.

3.2 Requirements and wishes

The information of previous chapters is summarized into a list of requirements and wishes. This list will be used as a guideline when working out and evaluating the new concepts.

The list is divided into three categories:
- **FAV context**: in which context is the device used and which general requirements are defined by the FAV procedure
- **Intended use**: how and by whom is the device used
- **Structural**: structural demands for the device

FAV context

○ The general process of the procedure should not change:
  - The aortic valve of a fetus is dilated by the device
  - The fetal heart is accessed percutaneously
  - The fetal aortic valve is accessed through the left ventricle

○ The device should not introduce new complications or enlarge the occurrence of current complications
○ The device should not occlude the aortic valve longer than 15 seconds
  - After 15 seconds at least 50% of flow through the valve should be restored.

○ An 'average' fetal aortic valve on ± 26 weeks of gestation should be able to be dilated
  - Dilation is succesful when valve diameter is expanded by 120%
  - The diameter of a valve at this gestation is between 2,7 and 3,1 mm
  - Wish: dilatation of a valve with a diameter of 4mm is also possible

○ The device is used under ultrasound guidance:
  - The ultrasound (US) guidance provides enough visual feedback to determine location of the cannula
  - Wish: the guidewire tip is clearly visible on US

○ The device can be used in dim lighting in an OR

Intended use

○ One (fetal) surgeon controls needle placement
○ One (cardiac) surgeon controls catheter handling
○ Feedback on the position of the balloon and guidewire is integrated
  - It should be clear when the guidewire extends the cannula by 1,5 cm
  - It should be clear when the entire length of the balloon catheter has left the cannula

Structural

General
○ Wish: As many existing materials as possible should be used

Balloon
○ The balloon should not exceed the measurements of a 20G needle in deflated state
○ The balloon should be able to expand into 1,2 times of the operable aortic valve
○ The balloon should be able to provide enough force to open the valve
  - The material should be rated as non-compliant or semi-compliant

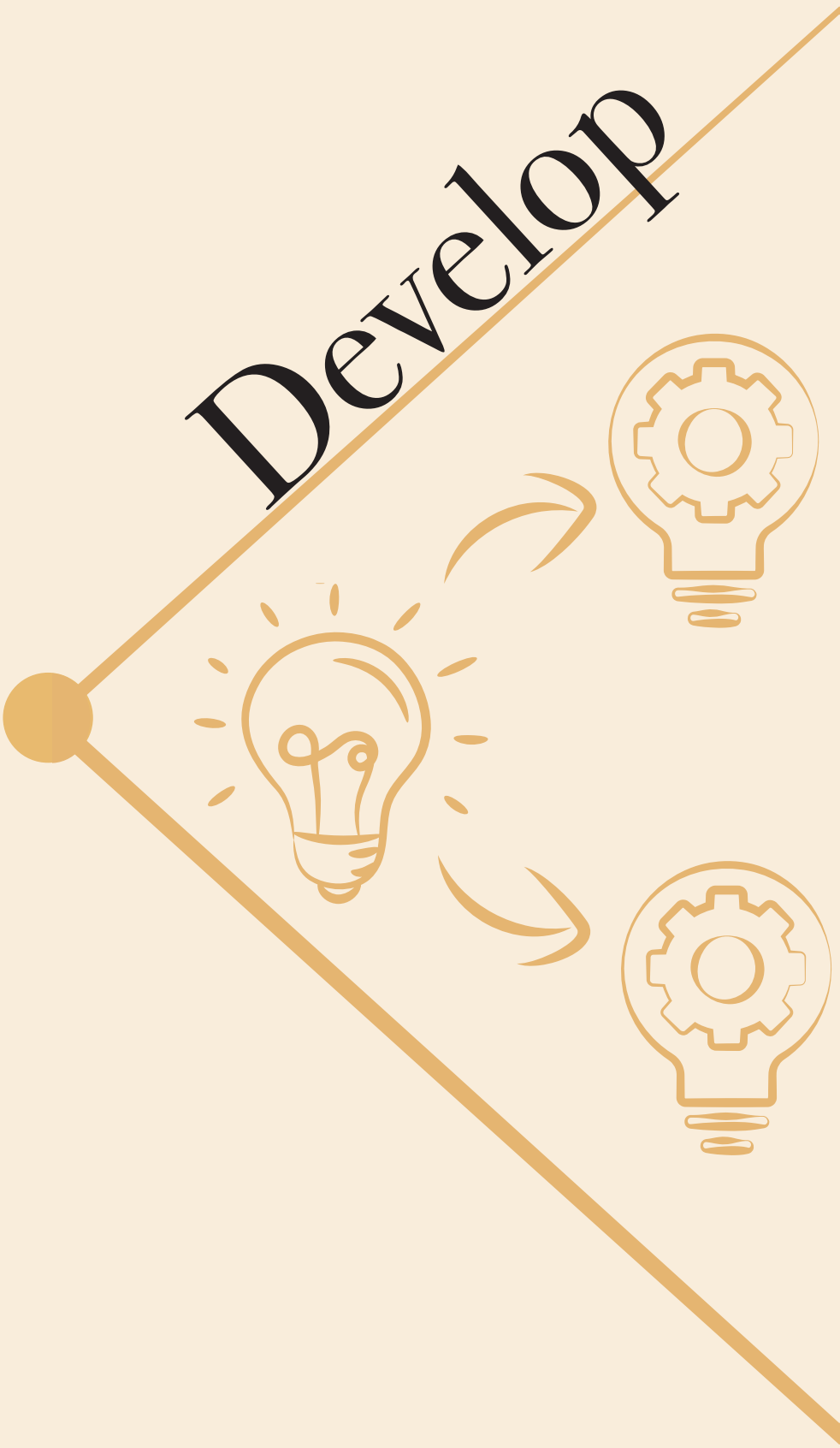
○ The length of the cylindrical body of the balloon should be between 10 and 15 mm
○ In the case of a catheter configuration
  - The length from distal to proximal is 40-60 cm

○ The diameter and shape of the balloon needs to be known at a certain pressure
○ The balloon needs to be able to be retracted through the cannula after inflation and deflation
○ The balloon needs to behave consistently after multiple inflations and deflations

Needle
○ The needle should not exclude the dimensions of a 20G needle
○ The needle is obturated during puncture and placement
○ The needle has a sharp tip for puncturing
○ The length of the needle is between 12-20 cm
○ The needle with obturator is able to puncture the maternal abdomen

Guidewire
○ The diameter of the guidewire should not exceed 0,014"
○ The guidewire has a floppy tip
○ The guidewire is able to cross the valve with ± 1,5 cm
  - The distance between balloon and guidewire tip is minimally 1,5cm

○ The guidewire is able to cross the stenotic valve lesion
  - There is always an opening of 1 mm in the valve


Develop

Chapter 4

Concept design

Ideation and concept selection

Concept embodiment

- Markers for visibility
- Fixed guidewire
- Balloon shape
- Folding and pleating
- Material selection
- Catheter assembly

Concept design

4

This section describes the diverging part of the second diamond. The develop phase consists of generating many ideas first, which are evaluated on their feasibility and improvements. Hereafter the most promising ideas are worked out further, resulting in three concepts. These concept are again evaluated and one final concept is developed into detail. This concept will then continue to the next phase; prototyping and testing.

4.1 Ideation and concept selection

To start the diverging phase, a brainstorm was conducted. In this brainstorm as many ideas as possible were thought of and written down, without directly thinking of the limitations and feasibility of each idea. The generated ideas can be found in Appendix B. After the brainstorm a c-box was generated to decide which ideas should be worked out further. On the horizontal axis of the c-box is the feasibility. This takes into account whether the idea would work, keeping in mind the procedural and production aspect. With regard to the procedure some ideas are just simply not possible or desirable (e.g. crossing the valve with the needle is not desired). With regard to production it is important to keep in mind that is has to be structurally possible to develop the concept, keeping in mind that production is in a millimeter scale. On the vertical axis of the c-box procedural improvements are measured. This refers to how much this new idea will improve the way the FAV procedure is performed. This includes the reduction of complications but also the ease of use. If the idea is feasible but does not bring enough procedural improvements it is still not really useful.

The upper right quadrant shows the most promising ideas since they are both feasible and will bring significant procedural improvements. At this stage the ideas are no more than just a basic principle. The three best ideas are then worked out into a real concept that can be rated on some key properties. These three ideas are the compression, double balloon and balloon optimization. The three concepts are summarized into Figures 4.2, 4.3 and 4.4, a more elaborate research on the concepts can be found in Appendix C.

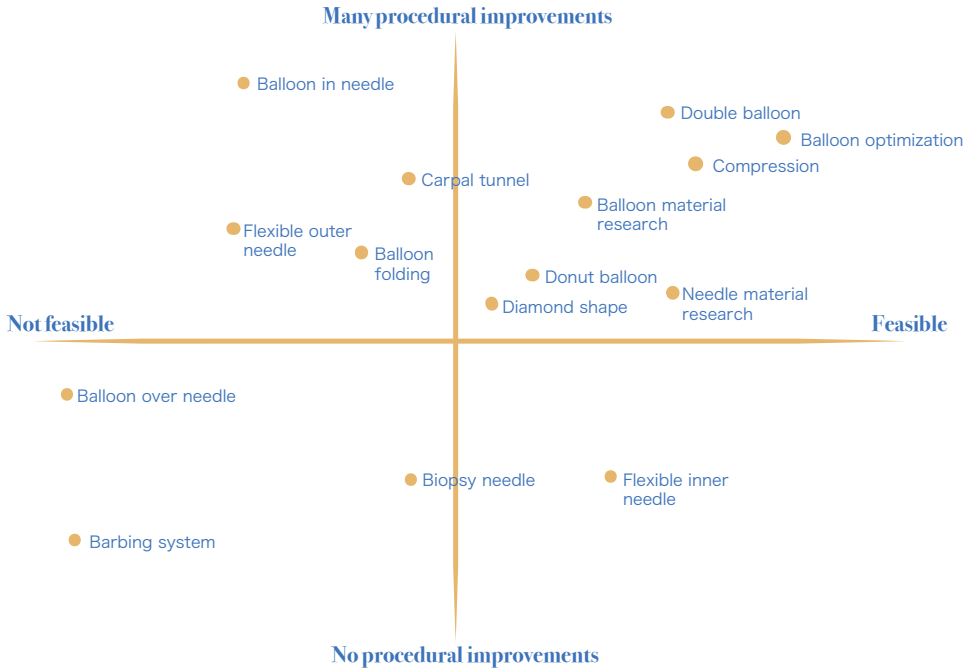


Figure 4.1: C-box which illustrates the generated ideas. Feasibility is measured on the x-axis, procedural improvements compared to current situation is measured on the y-axis

Concept 1

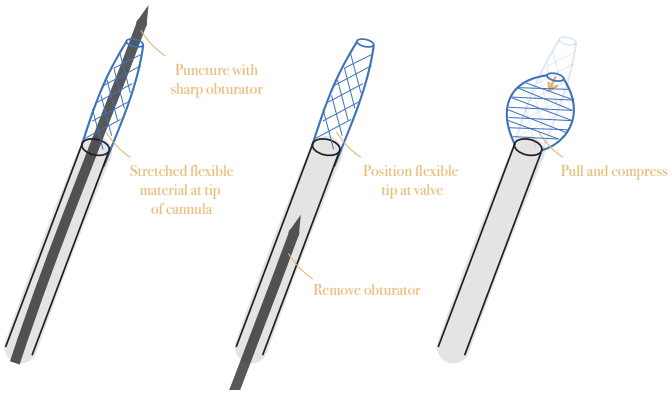


Figure 4.2: Illustration of concept 1: compression.

Concept 2

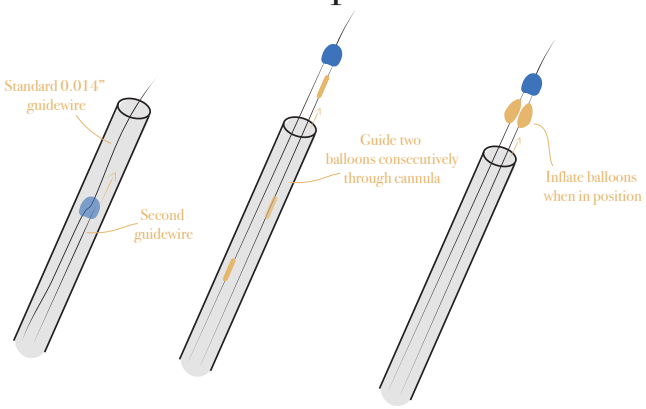


Figure 4.3: Illustration of concept 2: Double balloon.

Concept 3

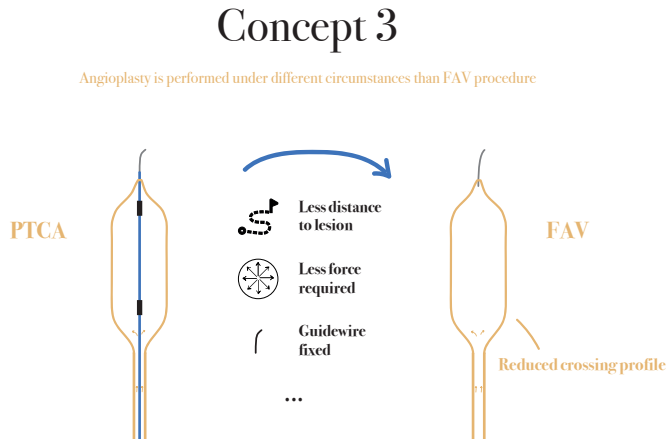


Figure 4.4: Illustration of concept 3: balloon optimization.

The 'compression' and 'double balloon' ideas led to Concept 1 and Concept 2 respectively. Both concepts are quite complex regarding handling and production, though simplicity is preferred in such small devices. The basic design of the balloon that is currently used is simple and effective. However, it is developed for the main purpose of performing a different procedure and therefore has some main disadvantages, the most important being that it is too large. Therefore Concept 3 focuses on optimizing a balloon catheter for the main purpose of performing FAV.

To determine which concept is a feasible solution and the biggest improvement compared to the current instruments 5 key properties are important. The final concept ofcourse has to fulfill all requirements, however it is hard to evaluate concepts on these requirements at this stage. Hence these 5 key properties are now used which are based on the requirements and will therefore indicate the feasibility of the design:

• **Manufacturability**: The dimensions of the final product will be very small, which complicates the manufacturing process. A complex product with mechanical systems and multiple parts icreases the complexity of this already challenging manufacturing process. Therefore simplicity of the product is preferred.

• **Procedural changes**: The goal of the new concept is that as little procedural changes as possible should be introduced. This means that the aortic valve is still dilated by expansion of some sort. If as many instruments and actions stay the same the new product is more likely to be adapted by the users.

• **Reduced complications**: The main goal of the project is to develop a product which reduces complications of the FAV procedure and one of the ways to do this is by minimizing the crossing profile.

• **Ease of use**: There is only limited space in the LV, so as little actions as possible should be performed in utero. Besides that there is also limited visibility asking for an intuitive and easy control of the device.

• **Predictable behavior**: The shape and dimensions of the dilating part of the device is necessary to guarantee the safety of the product. It is important to know outside of the body what is happening inside, also when there is bad or no visibility of the device. This means for example that the diameter of the balloon has to be directly related to a certain measured pressure. Besides that, the product must work in the same predictable way every time and in all conditions.

These properties are evaluated and scored for the three concepts. For each property each concept is rated -2, -1, +1 or +2 which is summarized in the so called Harris Profile (see Figure 4.5). This gives a visual indication on which concept is the most promising and determines which will be worked out further. The rating is done based on the performed research on the three different concepts.

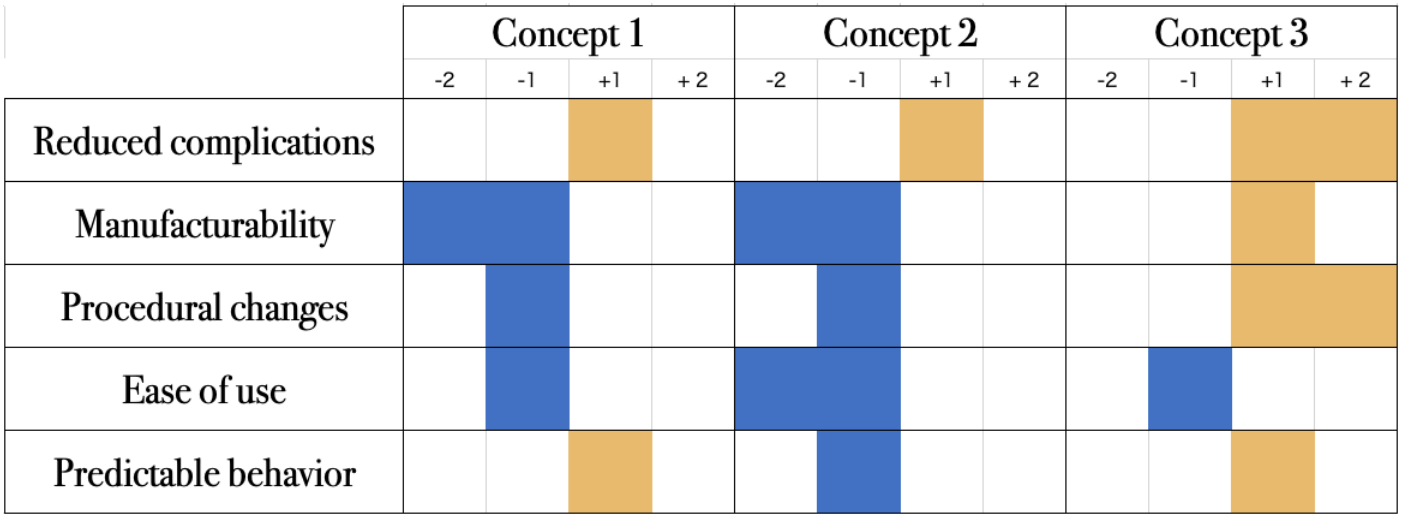


Figure 4.5: Harris Profiles for three most promising concepts. Concept 1: compression, concept 2: double balloon, concept 3: balloon optimization. Evaluation based on 5 key requirements. Scoring on a scale of -2 to +2.

Based on the Harris Profile it becomes clear that the third concept, the optimization of the balloon, is the most viable concept. Both concept 1 and 2 have the ability to reduce complications, however to achieve this the product would have to become very complex. This has a negative influence on the manufacturability since the production and assembly of mechanical structures and parts at this scale is very complicated. Concept 1 introduces procedural changes since the cannula now has a flexible tip which takes over the function of the balloon. This also has an influence on the ease of use of the product since compression of the material will require a pulling action at the proximal end while at the same time keeping everything in position. When the product is placed in the right position the material will behave predictable since it can be directly reasoned how the pulling distance results in dilatation. This will always be the same due to material properties. Concept 2 also introduces procedural changes due to the use of two balloons instead of one, which also complicates the actions to be performed since they have to be positioned very precisely in a very tight spot. The use of two balloons also introduces a risk of unpredictable behavior since they could slide away from each other, or be positioned incorrectly in the first place. Concept 3 shows the most promising properties since the basic principle of the balloon stays the same. Therefore the procedure does not have to change at all, but due to changes in the structure of the balloon it might become harder to maneuver it through the valve. Besides that the visibility and control of the balloon is currently experienced as a challenge and this will probably not change very much. Optimizing the balloon for the purpose of FAV is a concept which has high simplicity, and strips down the balloon leave only what is strictly needed for this procedure.

Out of many generated ideas a final concept is chosen. It was found that entirely new concepts quickly become too complex to be realistic at the required small scale. Concepts were rated based on 5 key properties that represent the list of requirements and wishes. The chosen concept is an optimization of the current balloon catheter, by looking at what is required for the performance of the FAV procedure. The power of this concept lies with its simplicity yet effectivity. The expectation is that this concept will be able to reduce the complications significantly, while still being well manufacturable. This concept is now developed further into detail during the concept embodiment

4.2 Concept embodiment

Based on research and conversations with medical experts as well as medical device manufacturers, the optimization of a balloon catheter for a FAV will lead to a significant decrease in complications due to the decreased size of equipment. Figure 4.6 shows some key differences in development requirements between a percutaneous transluminal coronary angioplasty (PTCA) balloon, which is currently used, and the ideal balloon for FAV. This shows that there are several aspects in the design of a new balloon catheter for the FAV procedure that could lead to a smaller crossing profile. Removing unnecessary parts and making different choices regarding structural and material properties contribute to this. The crossing profile of the balloon is a key aspect for the design, since this defines the cannula size that is required. The FDA defines the crossing profile (CP) of a balloon catheter as "*the maximum diameter found between the proximal end of the balloon and the distal tip of the catheter*" (Food and Drug Administration [FDA], 2010). The goal of the balloon catheter redesign is to minimize the crossing profile as much as possible, and the components in Figure 4.6 all contribute to this goal. The following subsections will elaborate on the changes of the design and their influence on the crossing profile.

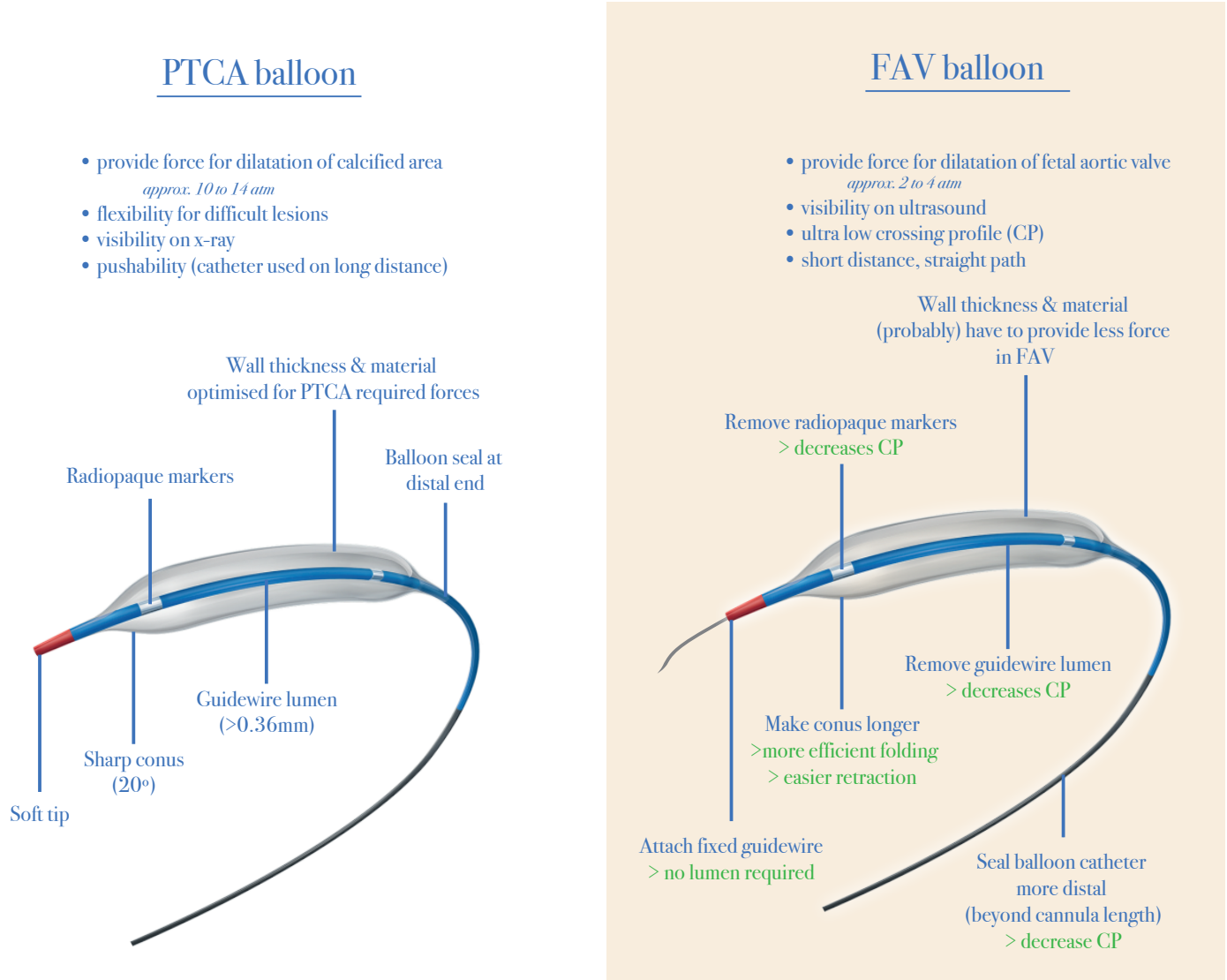


Figure 4.6: Comparison of balloon properties required for Percutaneous Transluminal Coronary Angioplasty (PTCA) and Fetal Aortic Valvuloplasty (FAV) and influence on balloon design (marked in green). Balloon render: EMERGE™ PTCA Dilatation Catheter, Boston Scientific 2021.

4.2.1 Markers for visibility

In most of the current balloon catheters one or two marker bands are placed on either the center or both ends of the balloon respectively. These markers are radiopaque and often made out of platinum-iridium, gold, or tantalum (Boyden, 2020). The markers provide visible feedback regarding the position of the balloon catheter under X-ray imaging. The basic principle of X-ray is that different tissues or materials absorb different amounts of electromagnetic radiation. Therefore the metal markers are clearly visible under x-ray guidance. However, the FAV procedure is performed under ultrasound, which decreases the functionality of these markers. Ultrasound works with the reflection of high frequency sound waves. Due to the small size and smooth surface the reflections are not clearly visible. If the markers do reflect the ultrasound waves there is also a risk of them causing too much reflection or scattering and with that ruining the imaging field. Besides the functionality of the markers the location is not optimal for FAV either. It would be more useful if there were markers at the tip of the balloon as well as at the tip of the guidewire. This provides more useful information regarding the positioning of the balloon (personal communication with experts).

Therefore the current marker bands can be removed from the inner lumen of the balloon and replaced for markers at the tip of the balloon and guidewire, made out of an echogenic material. Instead of using metal marker bands, other technologies such as coatings or sensors could also provide a useful alternative (Sahagian, 1999).

To find out what the possibilities are two manufacturers of ultrasound enhancing techniques were contacted. The first of which was B.Braun regarding the Onvision® technology. Figure 4.7 illustrates the key working principle of their technology. It allows for visibility of a selected point by means of a colored dot or circle. In this case, the tip of the needle is the selected point, which contains a sensor that allows for the positioning feedback. Currently this technology is not yet applicable for the FAV procedure since the needle that is integrated into this system only allows for the passage of fluids. Instruments such as the balloon catheter and guidewire can not pass through this needle. As for the development of this technology, allowing for passage of other instruments could be something that is featured later on, as well as applying this technology to balloon catheters or guidewire tips.

The second possibility that was explored was the Sono-Coat ™ technology developed by Encapson. This technology uses a coating that enhances ultrasound visibility. The coating uses microspheres, which enhance the reflections of ultrasound and therefore enhance visibility of the part that is coated (see Figure 4.8). This coating can be applied to many different materials amongst which are Nylon, Pebax, PVC but also steel, nitinol and titanium. Application is done by dipcoating, meaning that the product is dipped into the coating. Therefore it is possible to coat the two ends of a balloon, however the estimation is that at least a length of 5 mm would need to be coated. Further research would have to be done to figure out what would be preferred regarding these dimensions. It is believed that the coating does not have a significant influence on the mechanical behavior of balloon catheters, and would add approximately 0.03 to 0.04 mm of material to the surface. Since the product needs to be dipcoated application to a guidewire would be challenging. This is due to the coil of which a guidewire often consists, and if the coating would come between the coil, it loses its flexible property. Therefore application of the coating to a guidewire would only be possible if this consists of a soft tip.

Removing the markers inside the balloon will allow for a more tight folding since there will no longer be the risk of damaging or puncturing the balloon wall material with the metal bands. Besides that, the extra thickness caused by the markers is also removed. A suitable replacement for the current marker bands would be the application of a coating such as Sono-Coat ™ to both ends of the balloon.

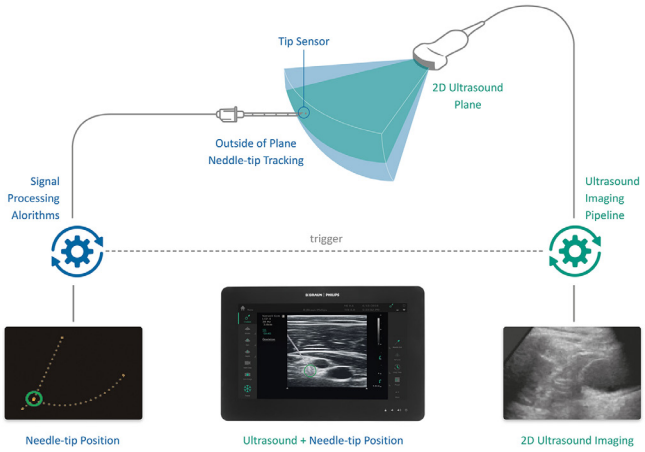


Figure 4.7: B:BRAUN OnVision® technology working principle. Source: https://www.bbraun.nl/nl/producten-en-therapieen/pijntherapie/onvision.html

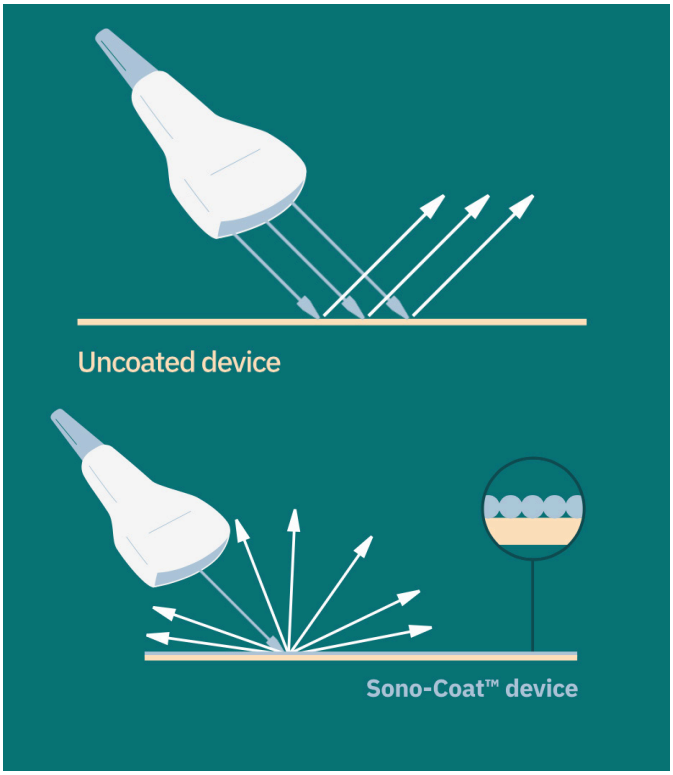


Figure 4.8: SonoCoat™ coating technology working principle developed by Encapson. Source: http://encapson.eu

4.2.2 Fixed guidewire

Most balloon catheters contain a lumen for a guidewire. The lumen has, depending on the configuration, an opening at the distal end of the catheter ("over the wire") or at around halfway the catheter shaft ("rapid exchange"). This lumen enables insertion of a guidewire through the catheter. The guidewire is often used to make sure the catheter follows a controlled path to the lesion site and helps crossing small lesions. Due to the guidewire lumen in each catheter exchanging a catheter can be done easily while keeping the guidewire in place. For the FAV procedure this feature is not needed. The main function of the guidewire in this procedure is to allow for atraumatic crossing of the valve without damaging any tissue. This is possible due to the floppy tip it contains. It also helps to steer the guidewire into position, since it can be moved and twisted at the proximal end. However, the guidewire only needs to be steered over a very small distance since the needle is positioned right in front of the aortic valve (see figure 4.9). Next to the short distance, the blood stream also makes positioning within the aortic valve easier. The direction of the blood flow goes from the mitral valve to the aortic valve, and this flow also guides the guidewire and balloon in the direction of the aortic valve instead of the mitral valve. This allows for a fixed guidewire at the tip of the balloon. The distance is set and defined by clinical testing. Due to the fixation of the guidewire, a lumen is no longer required. This adds simplicity to the balloon design and reduces the crossing profile. The influence of removing the guidewire lumen on the crossing profile is explained in section 4.2.4.

There are two possible configurations regarding the fixation of the guidewire, both shown in Figure 4.10. As is illustrated the first option is to let the guidewire start at the distal leg of the balloon, where it is sealed off at the end. In this configuration, both a 0.014" (0.36 mm) and 0.011" (0.25 mm) guidewire is possible. It would be dependent on clinical preference which would be used. In the second configuration the guidewire goes through the balloon, and ends at the distal catheter shaft. In this configuration it is assumed that only the 0.011" guidewire would be suitable since the 0.014" has a too large diameter. A suitable 0.011" guidewire would be the Terumo® Radifocus® guidewire. Based on clinical testing it is determined which configuration is preferential.

An important property to monitor during clinical testing is the ability to push and control in configuration 1, since the stiffness of the guidewire is gone. This introduces a risk of kinking, which is not desirable. Section 6.1 will discuss the clinical test and the corresponding results and choices.

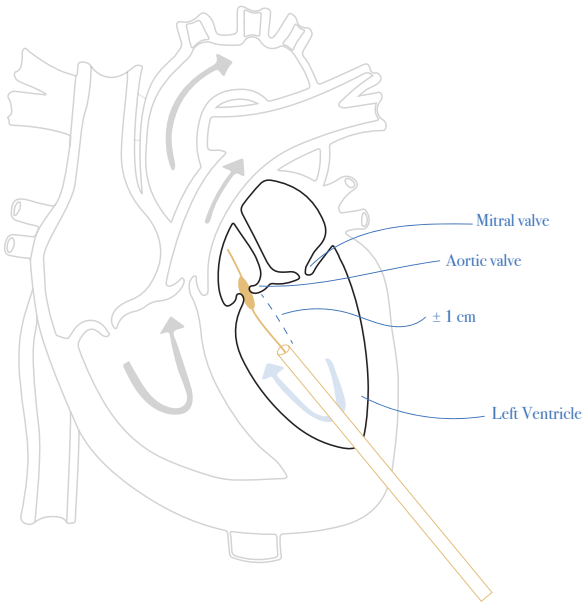


Figure 4.9: Heart with cannula position and distance to aortic valve during FAV procedure. Blood flow indicated by arrows.

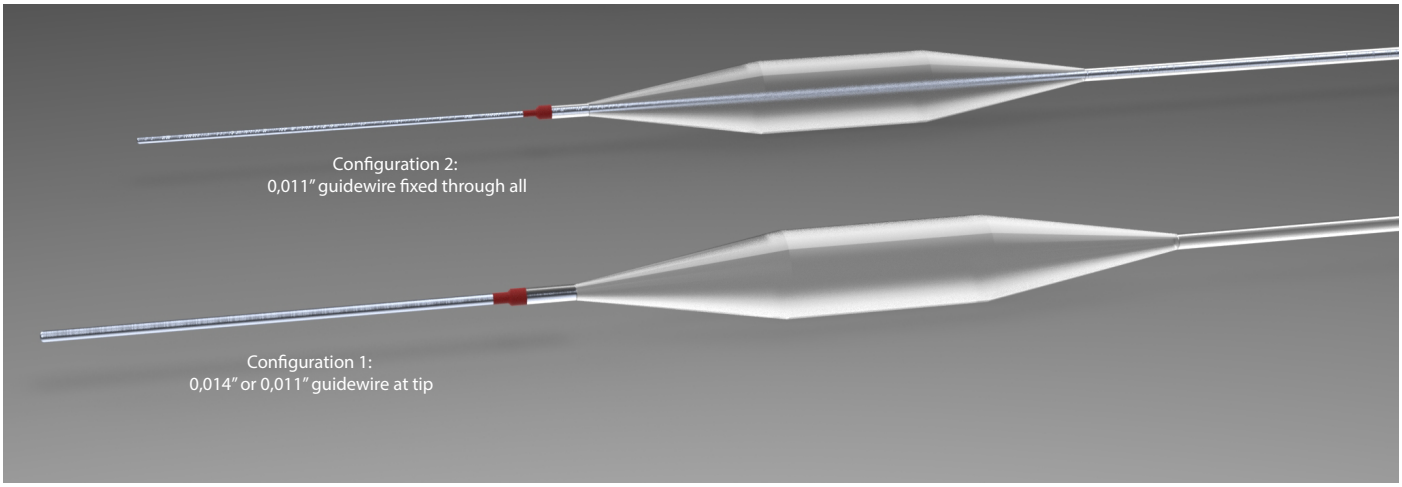


Figure 4.10: Two configurations for guidewire fixation in new balloon design. Configuration 1 fixates guidewire at distal tip and does not advance through balloon. Configuration 2 fixates guidewire through entire catheter but is still without guidewire lumen. Seal is indicated in red and closes off the balloon.

4.2.3 Balloon shape

Many different shapes and sizes are available for non-compliant and semi-compliant balloons. Since these shapes are very controllable many variations exist (Saab, 2000). For the FAV procedure a standard balloon is sufficient. Figure 4.11 shows the shape of a standard balloon. It contains a cylindrical body, two conical tapers (cones) and a proximal and distal neck.

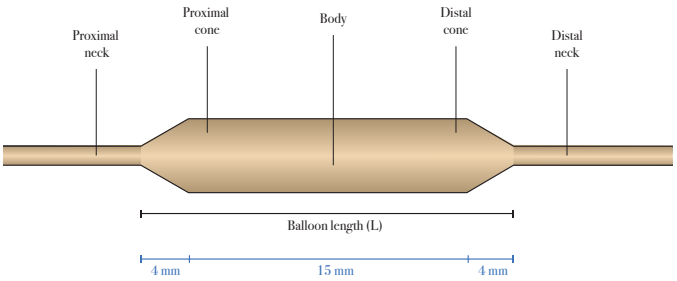


Figure 4.11: Standard balloon shape. Measurements of currently used balloon indicated in blue.

For the FAV procedure, the total length L of the balloon is preferred to be as small as possible. This is due to the limited space within the fetal LV. However, the cylindrical body needs to be long enough to enable positioning in the valve with some tolerance. Due to the poor visibility of the balloon it can be difficult to know the exact position of the balloon and if the cylindrical part is very short, the positioning would require too much precision. Only the cylindrical body of the balloon will reach the required diameter so if it is not positioned correctly, the procedure will not be technically successful. The right balance needs to be found between these considerations.
In Figure 4.11 dimensions of the current balloon are indicated in blue. The length of the new balloon design should not exceed the current length of 23mm. It is expected that the cylindrical body should not be shorter than 10 mm, yet this dimension is also tested and defined in the clinical test in section 6.1.

As can be seen, the cones are quite short in the current model. This has two disadvantageous consequences, the first of which has to do with the folding and will be elaborated in the next section (4.2.4). The second consequence is regarding the retraction of the balloon. A longer conus means that there is a more gradual transition towards the cylindrical part and therefore easier retraction is expected. All above mentioned considerations result in two proposed new balloon shapes which will both be tested on performance and functionality (Figure 4.12)

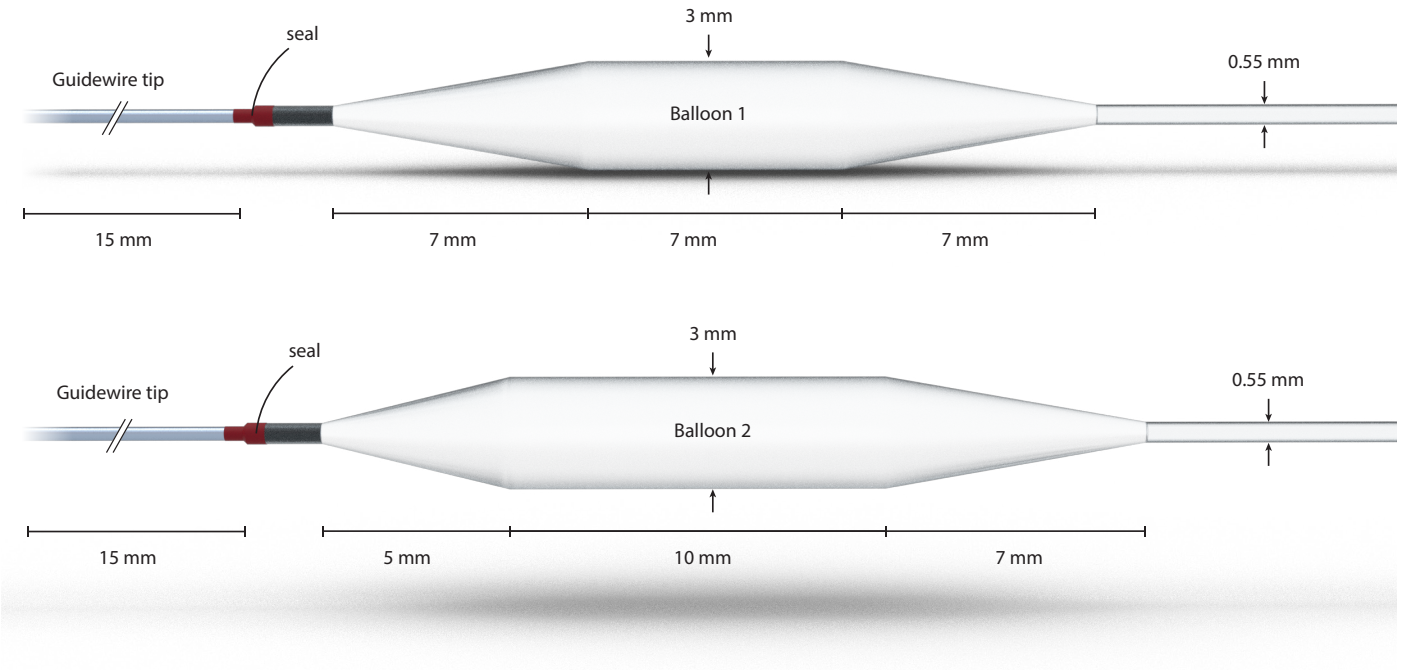


Figure 4.12: Proposed shapes for new balloon design. The upper balloon is a symmetrical balloon with a total length of 21 mm. The lower balloon is an asymmetrical balloon with a total length of 22 mm. Guidewire is fixated at distal end of the balloon.

4.2.4 Folding and pleating

The folding and pleating process of balloon catheters is an important determinant for the final crossing diameter. Efficient folding and pleating leads to the smallest crossing profile as possible. The folding and pleating process is depicted in Figure 4.13.
As the figure illustrates, the process starts with the so called folding. The most common are 3- or 5-fold balloons. Depending on balloon diameter and wall thickness it is decided which amount of folds is the most efficient. The crossing profile is at its lowest when the folds overlap each other minimally after pleating. However, the folds need to be long enough in order to be pleated correctly and stay pleated. The inner lumen also plays an important role in the amount of folding that can be done. As Figure 4.13 illustrates, if the lumen inside the balloon is smaller, the folds can be longer, eventually resulting in a smaller crossing profile. Currently a 0,014" guidewire is used which corresponds to a diameter of 0,36 mm. When keeping in mind that the goal is to make a balloon catheter with a crossing profile no larger than 0,6 mm in order for it to fit through a 20G needle, the diameter of the guidewire is quite large. To eliminate the lumen for the guidewire already decreases the crossing profile, but when the guidewire is also thinner or there is no guidewire inside the balloon at all (as discussed in section 4.2.2), this is effect is enhanced even more.

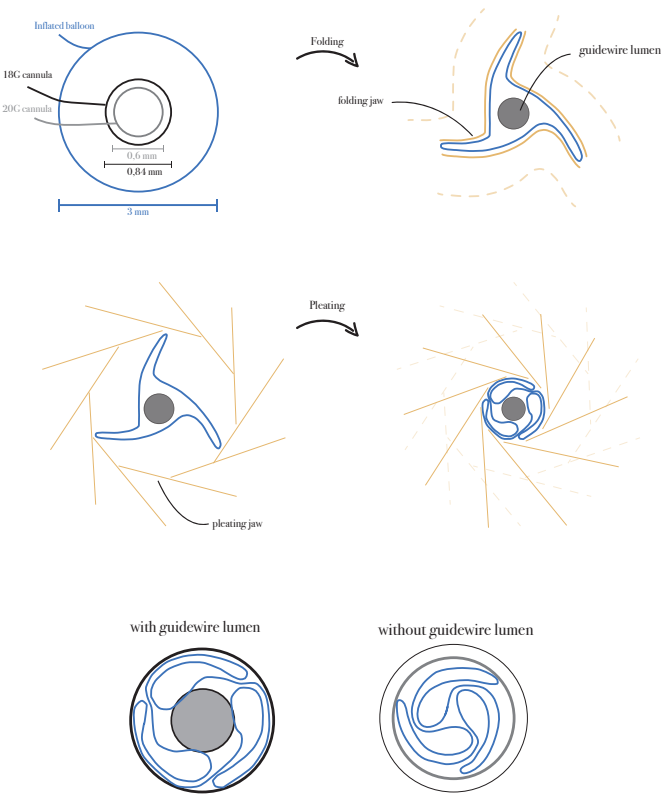


Figure 4.13: Cross-sectional view of balloon folding and pleating process. Balloon is indicated in blue, 18G cannula in black and 20G cannula in grey.

The elongation of the cones as discussed in section 4.2.3 enables more tight folding and pleating as well. As Figures 4.14 and 4.15 show, the cones are critical points when it comes to folding. If the cone angle is sharp, material adds up during folding, kinking occurs and the stresses become high (Geith et al., 2019). If the cone angle is more indistinct and the diameter increases gradually, this phenomenon occurs less. However, the cones will always be the least efficient folding area of the balloon. The crossing profile will be the largest at the conical areas, which are therefore also sometimes called the 'shoulders' of the balloon.

A quick search showed that most of the balloon catheters with a diameter of 3 mm are 3-fold (see Appendix D for an overview of the found data). This is however still with the configuration where a guidewire lumen is present. If this is removed a 5-fold configuration also has a potential of working. It is expected that a 5-fold configuration would result in an even lower crossing profile.

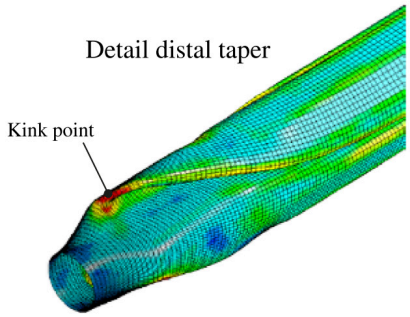


Figure 4.14: Detail of distal taper in simulated balloon folding process. Source: Geith et al., 2019

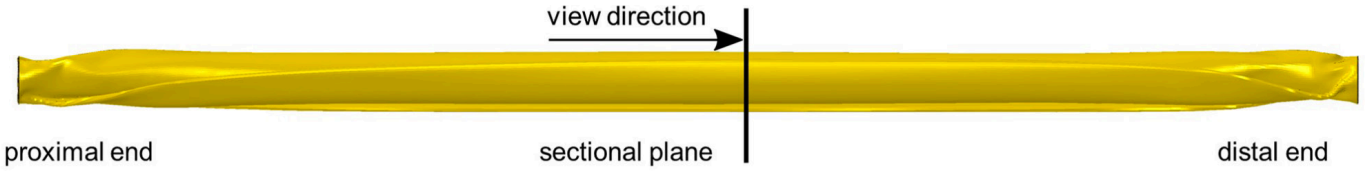


Figure 4.15: Side view of simulated balloon while being semi-folded. Source: Wiesent et al., 2019

4.2.5 Material selection

The balloon material has an important influence on its performance, as discussed in section 2.3.1. Some considerations regarding the FAV procedure also influence the balloon mechanics. First of all, it is assumed that the dilation of the fetal aortic valve requires less force than dilation of calcified vessels (see Appendix A). This would mean that the balloon wall thickness could be thinner or made of a more compliant material. Making the wall thickness as thin as possible would be beneficial for minimizing the crossing profile. Next to that, it would be ideal if one balloon has a wide range of diameters at which the required dilation force is achieved. To achieve this, a material would preferably have a moderate to high Young's modulus since it needs to be compliant enough to have a significant force and controllable shape. Besides that, the tensile strength is preferably a little bit higher than the yield strength. This allows for a slight change in diameter yet still providing enough force.
Due to the procedural approach where the balloon is retracted through the cannula, the balloon must have the ability to form back into its original shape. This makes retraction after deflation easier and introduces less risk of balloon rupture at retraction.
Based on these requirements and wishes, the available information on different materials and the knowledge of experts Nylon (PA12) and Pebax® with a high durometer (70D/72D) would seem to be the most promising materials for the FAV balloon. Both materials are categorized as being semi-compliant. The non-compliant material PET would be less suitable. This material has a higher stiffness, and is therefore more difficult to refold which makes it harder to retract the balloon (Saab, 2000). Materials that are softer and more compliant would require higher wall thickness and allow less control over the shape of the balloon.

4.2.6 Catheter assembly

Finally, some optimizations do not have to do with the balloon itself, yet refer to the entire assembly of the balloon catheter instead. The first of which is the seal where the balloon is shrunk onto the catheter tube. Currently, this is done directly at the end of the proximal cone after a short proximal neck. This transition of balloon material onto the catheter shaft brings a slight thickening with it. By enlarging the proximal neck up to 20 cm, the length of the cannula, this thickening will not have to cross the cannula and is therefore less of a limitation. Figure 4.16 illustrates this.
The entire length of the catheter can also be reduced to 40 cm. This makes catheter handling easier for the attending cardiologist. The proximal catheter shaft can be constructed in the same way as current balloon catheters but without the guidewire lumen. Most proximal catheter shafts are made out of thin, flexible metal.

A second improvement regards the marking at the proximal end of the catheter. This marking serves as a positioning feedback mechanism outside the body. It allows the surgeons to know when the balloon is entirely emerged out of the cannula. However, this marking system is currently not integrated into the balloon catheter design, so it is added to the instruments manually. Pre-operatively the catheter is advanced through the cannula, and when the balloon is fully emerged out of the cannula, a tape that serves as marker is added to the proximal end (Marshall et al., 2005; Pedra et al., 2014; Galindo et al., 2017). It would be optimal if this marking system is already included in the catheter design. For this marker system it needs to be kept in mind that the procedure is performed in dim lighting, so the marker has to be visible in a dim environment as well. To integrate this marking system in the catheter design, laser marking can be used. This is an approved method for medical devices and is used for reusable instruments but also long-term internal medical products such as pacemakers and implants. Laser marking can be applied to all sorts of materials, among which metals and plastics (MECCO®, 2015; Trotec® , n.d.). This laser marking method would allow for an integrated marking system as is illustrated in Figure 4.16. Since the proximal shaft is often made out of metal, a black laser marking is likely to provide enough contrast.

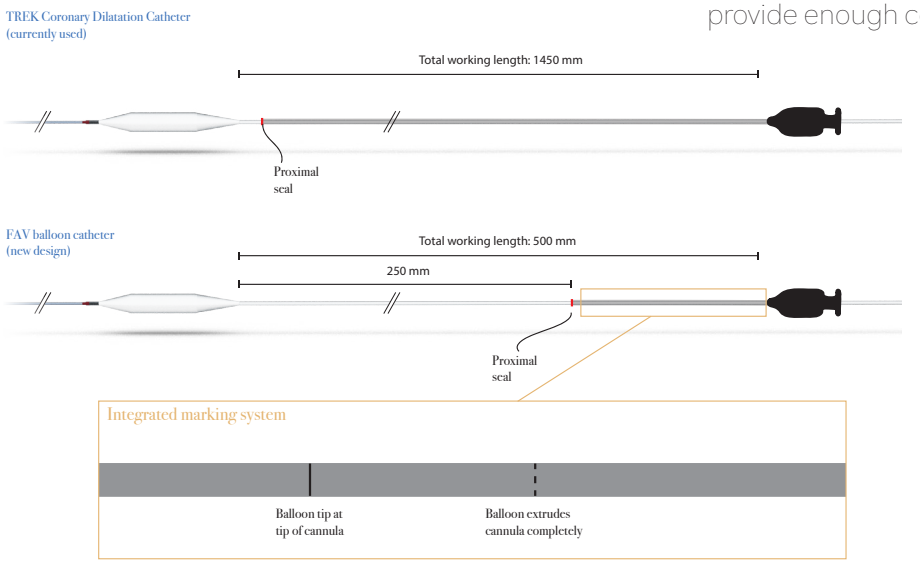


Figure 4.16: Overall assembly of balloon catheter with sizes and indication of integrated marking system.

Conclusion

Taking the FAV procedure as a starting point for the design instead of a coronary angioplasty allows for some key changes in the balloon catheter design. Different aspects in the design are believed to cause an improvement in functionality and decrease the crossing profile. Since the procedure is performed under ultrasound instead of x-ray, the radiopaque markers can be removed. Removing the radiopaque markers allows for more tight folding and eliminates scattering from the ultrasound image. These markers could be replaced with an echogenic coating applied to both ends of the balloon. The guidewire is only needed for atraumatic crossing of the valve, yet steering is required to a minimal extent. Therefore, the removable guidewire is not needed and it can be fixated. This allows for the removal of the guidewire lumen and guidewire through the balloon, again allowing for a more tight folding. By enlarging the cones, smooth retraction should be enhanced and the shoulders are reduced. The required forces and pressures are expected to be different for the FAV procedure compared to the PTCA procedure. Therefore, a different material with a lower wall thickness can be used. Lastly, by changing the position of seals to a more proximal part and integrating a marking system, the entire product will be more fit to perform a FAV procedure due to a reduced crossing profile and better-suited properties.

Chapter 5

Production and prototyping

Material selection

Final result

Chapter 6

Concept validation

Clinical validation

Mechanical validation

- Test 1: pressure vs force
- Test 2: pressure vs diameter
- Test 3: burst pressure

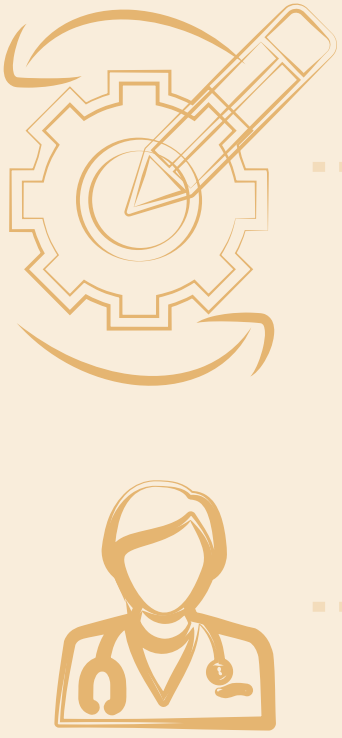
Chapter 7

Final concept design

Final concept choices

Requirements and wishes evaluation

Deliver



Production and prototyping

5

To validate the design, a prototype is produced. Development of the prototype of the FAV balloon catheter was done at Medical Production Technologies (MPT) in Leek, Groningen. They provided knowledge and equipment that made it possible to make a true scale prototype. This chapter elaborates on the production process of balloon catheters in general step by step. Parallel to that, the prototyping process is illustrated and differences and outcomes are discussed. During the process many different parameters determinant for the successful production of a balloon. Based on literature (Jackowski et al., 1991; Fu et al., 2017; Menary & Armstrong, 2006) and previous experience of the people at MPT, starting parameters were set. After that, based on the outcome, these parameters were tweaked. All parameters were documented and can be found in Appendix E.

5.1 Material selection

Based on the considerations as discussed in the material selection section (4.2.5), it was chosen to search for a high durometer Pebax® , or Nylon (PA12) extruded tube. Considering availability and dimensions, 12 possible tubes were selected. See Appendix F for an overview of the considered materials and their properties. On the website of the tubing supplier information regarding wall thickness, inner diameter and outer diameter is provided. Based on this information, calculations were done to estimate the resulting wall thickness for the balloon. These calculations can also be found in Appendix F. The four materials with the best outcomes were ordered, see Table 5.1. The materials will be referred to the names as described in column 1 from now on.

A simple stretch test was performed with the four materials. This was done to see the necking behavior of the different materials. Next to that, it was evaluated whether the materials were able to achieve the required diameter to fit into the mold (0.55 mm at the legs). All materials except for Nylon_1 could reach the required diameter. Both Pebax_1 and Pebax_2 were not suitable for cold stretching due to their improper necking behavior. Instead of necking, the entire tubing would stretch without a sharp transition to an unstretched area. This is required for the production process, as will be discussed in the following paragraphs. This led to the use of Nylon_2 for the production of the prototype.

Table 5.1
Materials considered for prototyping with properties

	Material	Inner Diameter	Outer Diameter	Wall thickness (tube)	Expected wall thickness (balloon)	Item number
Pebax_1	Pebax 72D	0,46	0,86	0,20	0,02	115-1366
Pebax_2	Pebax 72D	0,56	0,81	0,13	0,01	115-0821
Nylon_1	Nylon 12	0,74	0,99	0,13	0,02	115-2588
Nylon_2	Nylon 12	0,42	0,85	0,22	0,02	115-0526

Note: measurements provided in mm. Material properties and item numbers refer to data retrieved from Nordson Medical (https://www.nordsonmedical.com)

General production approach

The production of balloon catheters starts with extruded tubes of the chosen material. It depends on the manufacturer if this tube extrusion is done in house or externally. If it is done externally, it is important to be aware of the properties of the provided tubing, as discussed in section 2.3.1. The first step of balloon production is the generation of the so-called parison, which is done by stretching the material. The parison is generated by stretching the tube material so that necking occurs. Doing this mechanically and automated will allow for precise and repeatable outcomes. Therefore, the tubing is clamped and pulled on both sides through a die at a set temperature and speed until the parison has the desired length. During this process a part of the tube should not be pulled, this part is called the parison. The tubing becomes reinforced at the pulled area's due to realignment of the molecular chains that increases the crystallinity (Shrivastava, 2018). Due to this step, the parison is lower in crystallinity than the 'legs', and therefore the parison will eventually be the area which will expand during blow molding. Since the parison is the only part that will form the balloon, the length should be carefully determined. When it is too long there is a risk of material build up at the cones and a thicker wall thickness, but when it is too small there is a risk of rupture.

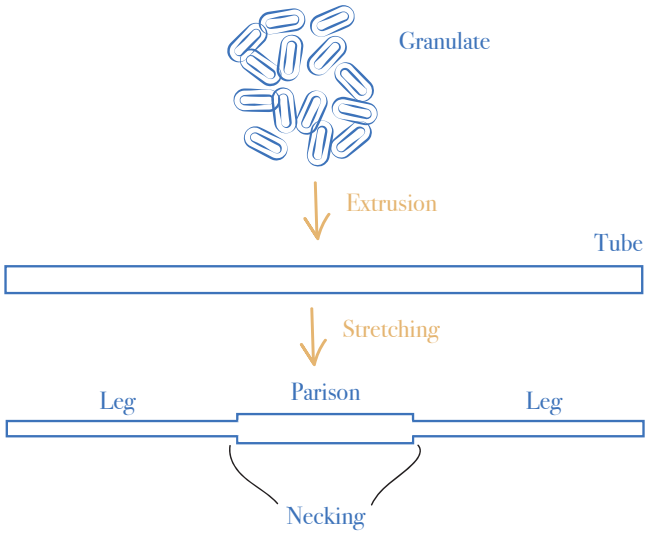


Figure 5.1: Production steps of the parison

Prototyping process

During the prototyping process, this first step was done manually due to the absence of the right equipment for this small tubing diameter. Therefore, the tube was clamped by a plier between two flexible silicone pads as shown in Figure 5.2. The silicone pads were added so the material would not be compressed. Both ends were then pulled with another plier to stretch the tube. By clamping the middle of the tube it was ensured that the parison would be formed in the middle. However, while clamping between the silicon pads, the precise length of the parison could not be seen and measured. Therefore the last part was free stretched above a caliper showing the correct length as shown in Figure 5.3. By trial and error the correct length of the parison was eventually set at 4,5 mm.

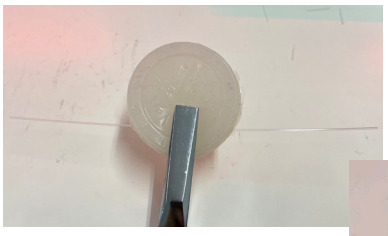


Figure 5.2 (above): clamped PA12 tube between silicon pads to create parison

Figure 5.3 (right): free-stretching setting with digital caliper indicating final parison size

Discussion

First of all, the tubing that was used has been delivered by an external party introducing the risk of certain unknown deviations in material properties amongst the delivered tubes. There is no guarantee on the quality and uniformity of each tube. Information regarding the material properties of the tubing was requested, yet not provided by the manufacturer. Next to that, stretching the parison manually adds another factor of inaccuracy. The speed and force at which the material is pulled can vary between each parison. This can result in small differences between each parison, introducing the possibility of each of them reacting differently to the subsequent production steps.

General production approach

The parison is inserted into the balloon molding machine. An illustrated cross section of the machine is shown in Figure 5.4. The parison is placed within the so-called center mold which is an insert for the heating block. The center mold is closed off by a conical taper mold on both sides. Figure 5.6 shows a blow molded balloon with the center mold on the left and the conical taper mold on the right. Both molds are ideally made of a beryllium copper alloy, since this has great heat conductivity (Lalli, 2006). The design of these molds determines the shape and diameter of the final balloon, and many variations are possible. When the parison is in place and the legs are clamped by the grippers, one of the legs is closed off at the end. The other leg is connected to a compressed air supply to enable the blow molding process. The first step is heating up the heating block. When this is at the right temperature, a timer is set to enable the mold and inner material to get to temperature. The set temperature and time are changeable parameters and depend on material, size and wall thickness amongst others. Next, the pressure valve is closed, meaning that the built up pressure is now applied on the balloon material. At the same time, a quick short pull is applied on both legs. This is done to enhance the blow molding of the parison. The applied pressure, pull speed and distance are again changeable parameters that influence the outcome. By now a rough version of a balloon should be formed. A second, much slower pull is now initiated. The pressure, temperature and distance of this second pull can be set. This second pull ensures the material is well distributed providing an uniform wall thickness, and should remove any material build up at the cones. After the balloon is fully shaped, the balloon is heated up once again to ensure it will keep its shape. This is called heat setting. This is done at a set temperature for a defined amount of time. After this the balloon can be removed from the mold and inspected.

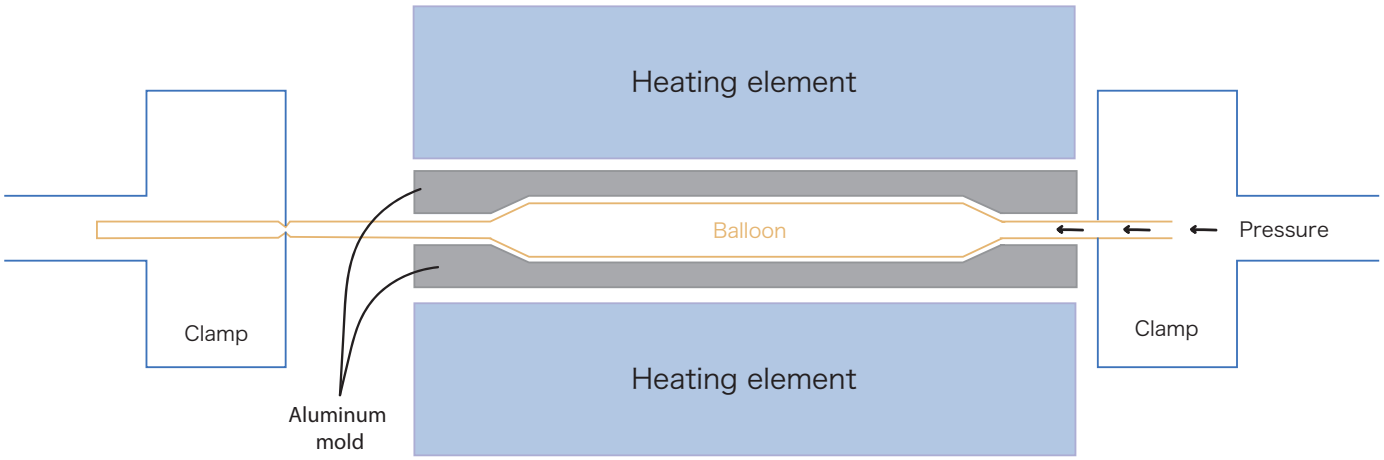


Figure 5.4: Illustrated cross section of the blow molding machine.

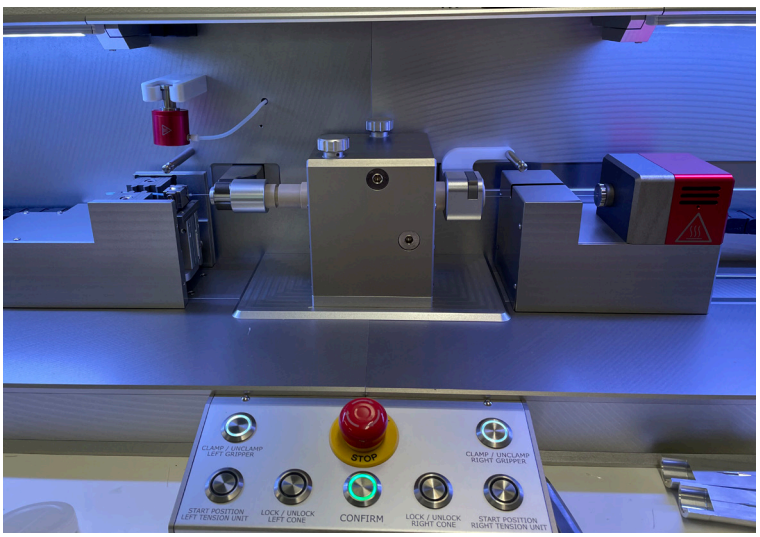


Figure 5.5: Image of the used blow molding machine (BFM-500-S2 by MPT Europe)

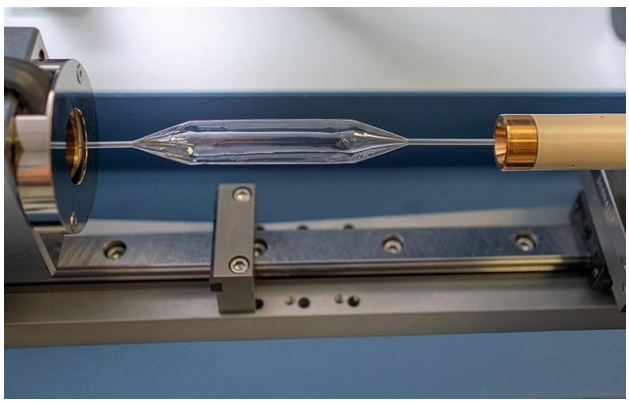
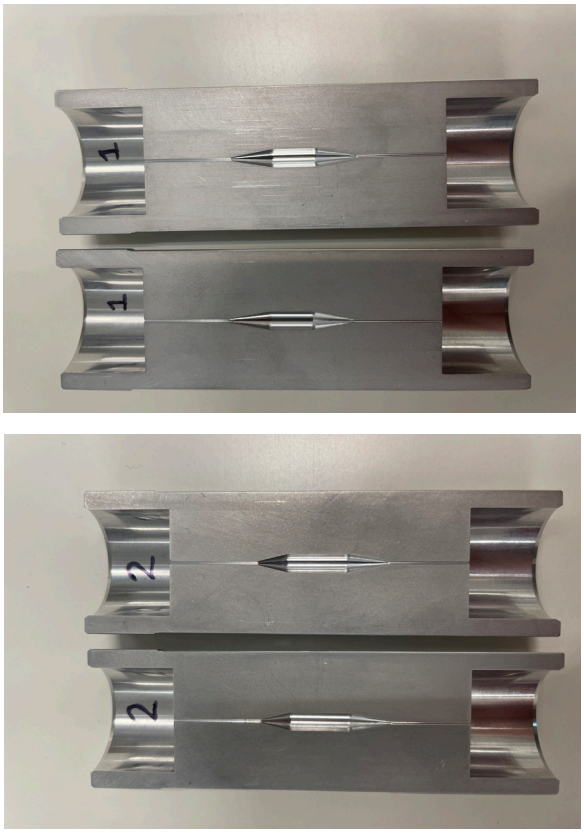


Figure 5.6: A blow molded balloon with cylindrical center mold (left) and conical taper mold (right) in the blow molding machine. Source: Bahmer, 2020.

Prototyping process

For the prototyping the BFM-500-S2 balloon forming machine of MPT was used. Instead of a center mold and two taper molds, aluminum split-molds were used. This was done due to the small scale of the product and production costs and time. Two different shapes as described in section 4.2.3 were milled into the molds as shown in Figure 5.7. The parison was placed in the middle of the mold and the two halves were placed onto each other. This cylinder was then put into the balloon forming machine the way the center mold would be placed. The process of determining the right pressure, temperature, heating time and pulling speed was a process of trial and error as discussed before. See Appendix E for the datasheet with the different parameters. Figure 5.8 shows a well-formed balloon just after it got out of the blow-molding machine. After the first balloon was successfully blow molded the process optimization started. This means that gradually the second pull and later on the heat setting steps were added. This way, not too many parameters were changed at once.



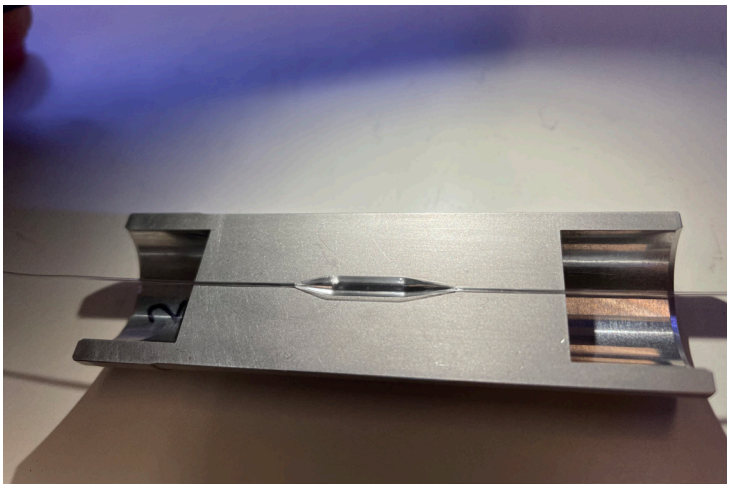


Figure 5.7 (left): Aluminum mold 1 for symmetrical balloon shape and aluminum mold 2 for the assymetrical balloon shape.

Figure 5.8 (right): Blow molded balloon in the aluminum mold just out of the machine.

Discussion

The optimization of this process can take a very long time since there are so many parameters to be tweaked, and they all influence each other. It is therefore difficult to know which parameter to change in order to get the perfect balloon. Since the goal of the prototypes is to deliver a proof of principle, the shape should be formed and the balloon needs to be sealed and watertight. This way tests can be performed and the new crossing profile can be measured, yet balloon mechanics and behavior could still be suboptimal. Next to that, the use of an aluminum split-mold instead of a beryllium-copper center mold introduces insecurities. There is a risk that a parting line forms due to the use of two halves, which could influence the stress distribution in the balloon. Besides that, the set temperature is measures at the heating block. Due to the thick aluminum mold it is difficult to say at which temperature the parison is at the time of blow molding. Aluminum generally is also a good conductor, yet not as good as the beryllium-copper alloy.

General production approach

Depending on the final application of the balloon it will be assembled. There are many different applications and configurations for balloon catheters. Next to that manufacturers do not prefer sharing detailed information regarding the production specifics. Therefore it is difficult to specify one general approach for the assembly of the balloon catheter. An essential assembling step that needs to be fulfilled in all cases however is sealing the balloon onto a catheter and ensuring it is leak-free. One way to do this is by welding it using heat shrink material. At this moment also the guidewire lumen (if present) is inserted and fixated.

Prototyping process

For the purpose of testing different concepts with the fixed guidewire, two configurations were made during assembly: one where a wire was advanced through the balloon and ends at the proximal neck, and a second configuration where the wire was welded onto the distal neck of the balloon and ends before the distal cone starts. Since the small guidewire that is integrated into the design was not available, it is now substituted for a 0,25 mm copper wire. The main goal of making the two different configurations is to outline the steerability and pushability of the balloon. To assemble and seal the balloon, the wire was advanced through the balloon as far as needed, and heat shrinking material was advanced over the wire/balloon combination at the distal neck (see Figure 5.9). This assembly was then fixated in the welding machine as shown in Figure 5.10. The temperature of the welding heat was set to 70˚C for 20 seconds. This caused the heat shrink material to shrink, and the nylon material to melt onto the copper wire.

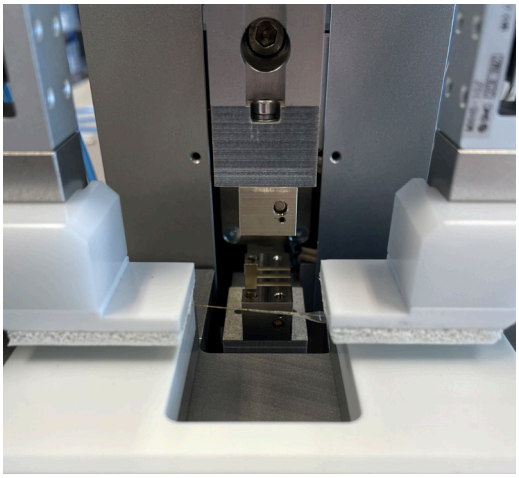


Figure 5.9: Welding machine with clamped balloon prototype.

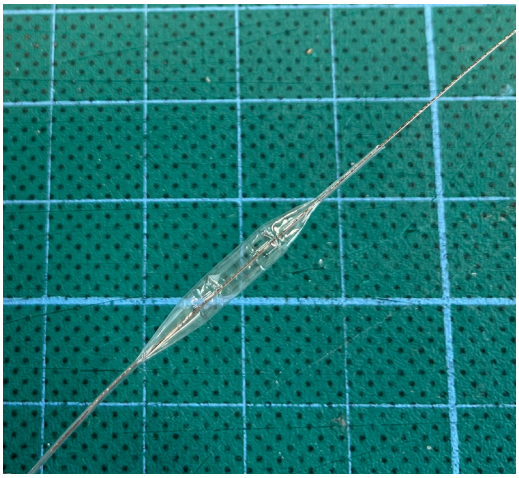


Figure 5.10: Balloon prototype with welded copper wire through balloon.

Discussion

During the welding of the guidewire onto the balloon, some heat is also applied onto the distal cone. This caused the first balloon to deform as can be seen in Figure 5.11. After this, the distance between cone and seal was increased which resolved the problem. However, it is possible that it had influence on material structural level which is not visible by microscope. Besides that, this caused the distal tip to be longer than designed. This will need to be taken into account during the user performance test.

Figure 5.11: Microscope image of welded balloon tip with slight deformation at distal cone of balloon.

General production approach

The general steps of the folding process have been discussed in section 4.2.4. A balloon catheter is inserted into the folding machine while being slightly inflated. A variable amount of blades will fold the balloon into a star shape. If the blades are at their maximum position, the balloon is drawn vacuum. When the balloon is still vacuum, it is inserted into the pleating machine which will shape the balloon into its final shape. The pleating blades move together to the smallest possible diameter. This is done under temperature guidance with a set maximum force. When the pleating blades can not move any further, the force is maintained for a set time to make sure the material stays in the demanded shape.

Prototyping process

Since a 5-folding machine was not available at this small diameter, a 3-folding machine was used. This was a manually controlled machine. When in the machine, the balloon was drawn vacuum by a syringe. The balloon forming machine and folded balloon are shown in Figure 5.12 and 5.13.

After this, the folded balloon was inserted into the pleating machine. Pleating was done at a temperature of 70°C, under a force of ± 140N. When the pleating blades could not move any further, they were kept in place for 30 seconds (see Figure 5.14). The result is shown in figure 5.15, which shows a folded balloon just out of the pleating machine.

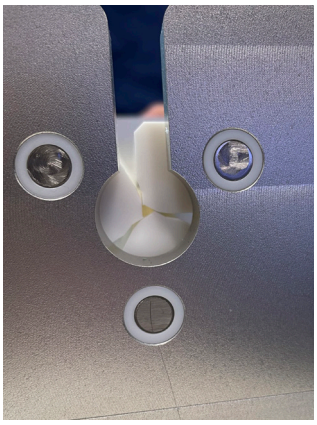
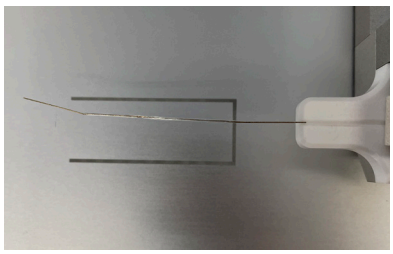


Figure 5,12 (top left): Front view of folding machine.

Figure 5.13 (top right): Front view of folded balloon.

Figure 5.15 (right): Top view of pleated balloon.



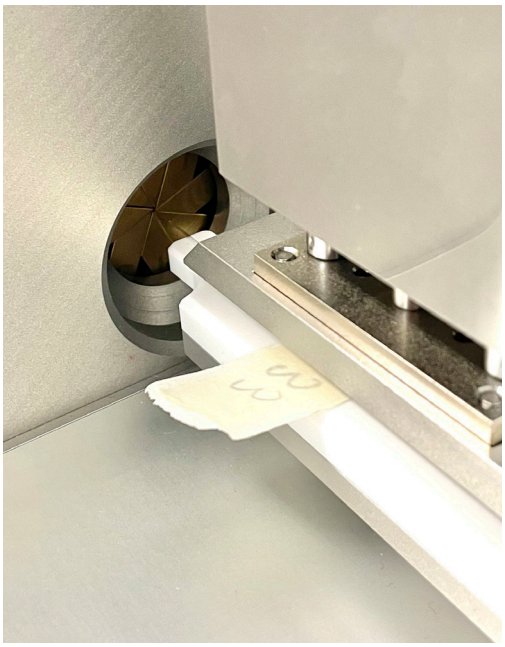


Figure 5.14: Balloon (33) inside pleating machine.

Discussion

Due to the absence of a suitable 5-fold machine, it was not possible to test if this would also be possible. However, based on the experience of the people at MPT, it is assumed that this would result in an even smaller crossing profile. Besides that, using a mechanically driven folding machine instead of manually would also provide more repeatable and accurate results.

5.2 Final result

During the prototyping process a total of 10 fully assembled prototypes were developed. Another 11 balloons were made, but those were not assembled due to time limitations. The assembled balloons will be used for both clinical as mechanical tests to determine the final design and evaluate the concept. Of these assembled balloons, 7 balloons were folded and pleated. This allows evaluation of the decrease of crossing profile. As the balloons were folded, they were measured and resulting crossing profiles are shown in table 5.2.

As the table shows, the crossing profiles are close to 0.6 mm. As the goal of the project is to make a balloon catheter that fits through a 20G cannula, which has an inner diameter of 0.6 mm, this is an important outcome. These prototypes prove that it is possible to make a balloon that has a higher nominal diameter (from 2.5 mm to 3 mm), combined with a smaller crossing profile (from 0.85 to ± 0.6 mm). Keeping in mind that the production process of these balloons is far from optimized, it is assumed that if this proces is optimized the crossing profile would not exceed the 0.6 mm.

Table 5.2
Balloon nrs of produced prototypes with corresponding measured crossing profiles

Balloon nr.	17	33	43	44	59	60	61
Crossing profile (mm)	0.62	0.69	0.61	0.59	0.61	0.62	0.66

The table also shows that one of the balloons, balloon nr. 44 has a smaller crossing profile than 0.6 mm. Therefore, this balloon does fit through the 20G cannula as can be seen in Figure 5.16. Figure 5.17 shows one of the fully assembled balloons as it is inflated.

Figure 5.16: Prototype balloon advanced through 20G cannula

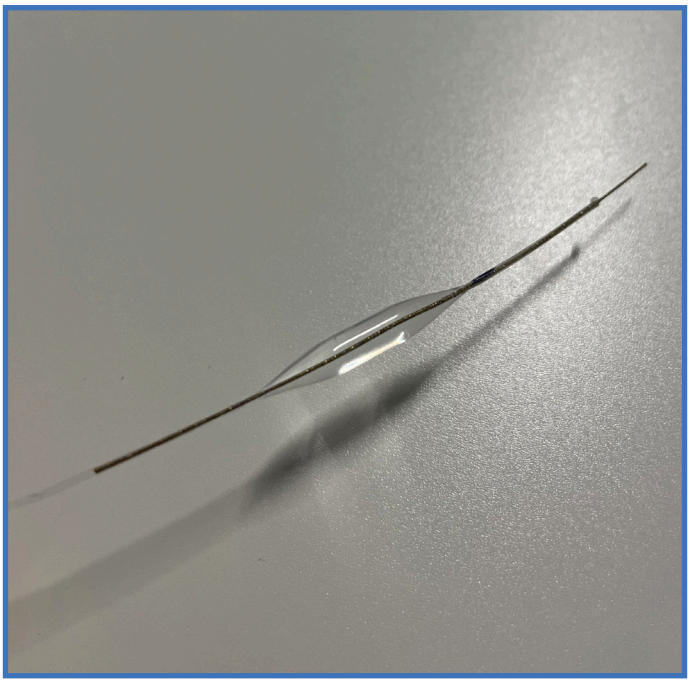


Figure 5.17: Inflated prototype balloon with copper wire through balloon and symmetrical shape

The final prototypes show promising outcomes for this new FAV design. The final crossing profiles of the assembled balloons are close to the 0.6 mm which is the eventual goal. Keeping in mind that the current production process was not yet optimized and many steps were done manually, it can be assumed that if this is optimized the crossing profile of 0.6 mm is achieved.

Concept validation

6

To validate if the changes in design do not influence the functioning of the balloon catheter tests are performed. This validation is split into two categories: clinical validation and mechanical validation. The clinical validation will mainly focus on the user interaction. Therefore the clinical validation will be done in collaboration with medical experts at the LUMC. The mechanical validation is more focused on the functionality of the balloon and will determine if the design choices will not decrease the ability of the balloon to perform a safe dilatation of the aortic valve. The following sections will discuss the goals, methods and results of the performed tests.

6.1 Clinical validation

To determine which model is preferred based on the clinical perspective a test is performed. This test mainly focuses on the steerability and control of the new catheter. To gain relevant insights regarding these aspects, four different configurations were produced as discussed in the concept embodiment section. In the datasheet in Appendix G, the balloons that were used for testing are highlighted. To acquire information about the user interaction and optimal design of the balloon, the following research questions need to be answered based on the test:

1. Is there enough control and steerability on the proximal end when there is no guidewire throughout the balloon?
• Is it possible to steer the balloon into the aortic valve instead of the mitral valve?

2. Does the folded balloon provide enough stiffness to reach and cross the aortic valve without a guidewire?
• If kinking occurs, there is not enough stiffness

3. Which balloon shape is preferred? Looking specifically at :
•Is a length of 7 mm too short for the cylindrical part?
•Is the total length of the balloon too long?
•Do the longer cones provide more easy retraction?

Materials and method

To get answers to these questions, a test setup as shown in Figure 6.1 was used. The test is performed on a simplified 3D printed model of a left ventricle in a fetal heart of ± 23 weeks gestation. See Appendix H for the measurements and production of the heart model. During the test a fetal surgeon and pediatric cardiologist performed the same test with the four different configurations. They were assigned to puncture the left ventricle, place the balloon catheter correctly and inflate and deflate it. Beforehand, marking was applied to both the distal and proximal end of the balloon. Also the proximal end of the catheter a marking was applied where the balloon has fully emerged the cannula. The four balloons were used in combination with an 18G cannula of 11,5 cm, together with an inflation device with a coupling piece to allow connecting the prototype balloons.

Before the test, it was discussed to which aspects attention should be paid. The test was recorded and notes were taken. See Appendix I for the notes.

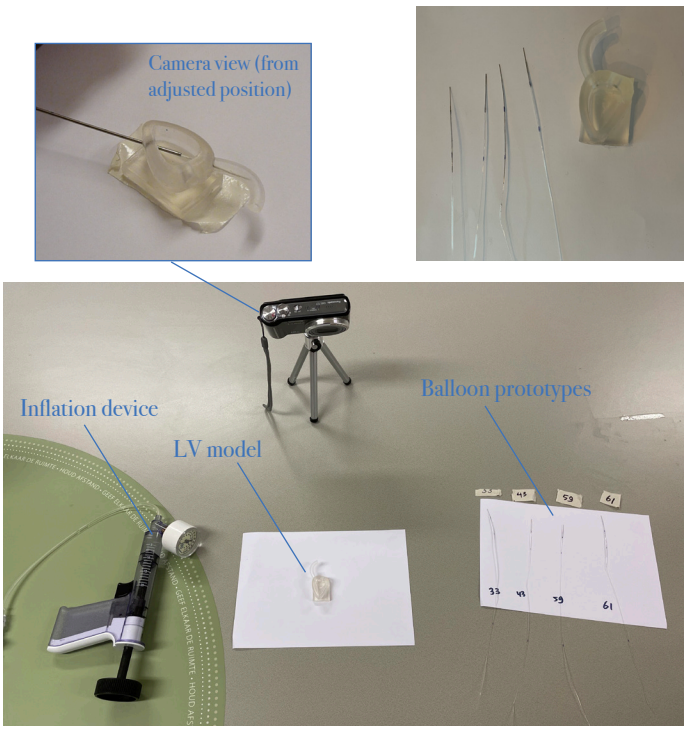


Figure 6.1: Clinical validation test setup with camera view (upper left), marked prototypes used for the test and heart model (upper right) and setup overview (bottom)

Results

All four configurations were easily placed within the aortic valve and inflated (see Figure 6.2). No kinking occurred, and none of the balloons were accidentally placed in the mitral valve. However, to be able to place the balloon correctly, the cannula had to be retracted a little bit. This was due to the limited space in the left ventricle in combination with the length of the balloon. The LV model was thought to be a bit smaller than in reality, and therefore the total length of the balloon was experienced as being quite long. Even though the length of the balloon is no longer than the currently used model. It was observed that the cannula is placed very close to the valve, and very little steering was required to achieve correct positioning. No difference was experienced between the configuration with guidewire at the tip or the guidewire through the balloon. One of the balloons had a longer guidewire tip than the others (20 mm instead of 15 mm). It became clear that this is not preferred, since a risk of entering the descending aorta or other branches of the aorta.

Figure 6.2: Model of left ventricle with balloon prototype inflated at aortic valve.

During the placement of the balloon the applied marking was proven useful. It would be optimal if these markers were also visible on ultrasound. However, using this type of marking makes it less convenient to use the asymmetrical configuration since it is more difficult to determine correct placement of the cylindrical part of the balloon. After the balloon was in the correct position, it was inflated. At around 1 bar of applied pressure the balloon deployed and at ±2,5 bar the balloon achieved the required diameter (3 mm). This was the same for all balloons.

Due to the coupling piece that was used it was not possible to pull the balloon entirely vacuum. Therefore retraction through the cannula was only possible in one of the four balloons. This will have to be tested in a separate test. It could be observed that the balloons reshaped into their original folded shape very well.

Limitations

Since this test setup was a simplified situation of the reality some conditions were neglected. The influence of these limitations is discussed in this section.

Blood flow

The direction and influence of the blood flow was not simulated, however this does have an influence on the ability to steer the balloon. In reality the blood is pumped from the mitral valve into the aortic valve, which is beneficial for the placement of the balloon. The blood flow steers the guidewire through the aortic valve, enhancing correct placement. Since it is likely that the blood flow does not have a negative influence on the steering and placement, the results regarding steerability are still useful. If it is possible without this factor, it is likely that it will work when this influence is present as well.

Visibility

In the real situation the left ventricle is only visible under ultrasound instead of directly visible and open. Next to that, the balloon and cannula are poorly visible, which is one of the challenges of this procedure. However, the behavior of the balloon and the ability to steer (which were the aspects to be tested) are not influenced by the visibility. The cannula is already sufficiently visible on ultrasound to allow for close positioning to the aortic valve. Since this can be achieved, the path to be traveled is short. The location of the markers could be evaluated in this test because the goal of these markers would be to ensure that they are well visible under ultrasound.

Copper wire

Due to the unavailability of the correct guidewire at production, a copper wire with the same diameter (0.25mm) was used instead. This copper wire does not have the same material properties of the proposed guidewire and is much less flexible. Therefore, during placement the wire sometimes got caught into the wall of the aorta model. This would not happen with the guidewire due to its flexibility and atraumatic tip. The copper wire did also introduce some extra stiffness to the balloons with the configuration where the guidewire goes through the balloon. However, since little difference was experienced between the two configurations, it can be assumed that this will not be of great influence. It is thought that using the flexible guidewire in combination with the movement of the blood flow will enhance positioning since the flexible guidewire will be easily caught in the blood flowand follow that direction.

LV size

As mentioned earlier, the size of the LV seemed to be a bit smaller than in reality. However, this is difficult to determine since this is variable for every procedure. The sizes of this model were based on literature, yet it is of course possible that in reality, these sizes are different. In general, the aim is to perform the procedure at the moment the LV is above average. It is possible that the data in the literature did not capture this moment since it requires very precise timing. Next to that, the setting and use of material could also influence the perception of size on the LV.

18G cannula

Due to the limitations in the prototyping process as discussed in chapter 5, the balloons that were used for testing did not fit through a 20G cannula. Therefore, an 18G cannula was used. With regard to puncturing, it is known that the 20G cannula also provides sufficient force due to data found in the literature (Debska et al., 2020; Guseh et al., 2020). Therefore, it is expected that the use of a 20G needle instead of an 18G needle will not influence user interaction and procedure performance.

Balloon retraction

Since the retraction test could not be performed during the clinical testing moment this was done separately. A few balloons were inserted into the needle at the distal tip and retracted from the proximal end. During this test, it became clear that the balloons that were not initially folded were not able to be retracted. Not all balloons could be tested due to the length of the balloon catheter (which was shorter than the length of the cannula). The influence of the extended cones on the ease of retraction is difficult to determine since the production process of the balloon was not optimized yet. Therefore the shape of the cones might not yet be representative. Besides that, there is no suitable balloon that would allow for comparative testing since cones with different lengths and angles should be tested to determine the optimal shape.

Conclusion

Key takeaways that should be kept in mind for the final concept design based on this test are as follows:

• An asymmetrical shape is not preferred since this makes it harder to determine whether the balloon is positioned correct. When the balloon is symmetrical it is easier to establish the middle of the balloon, which is relevant since this is the part that needs to cross the aortic valve.

• The guidewire should not exceed the balloon tip for more than 15 mm.

•The cylindrical part of the balloon should not be smaller than 7 mm, yet it would be preferred if the cones are shorter. However, if this means the crossing profile increases significantly, it should not be done.

• No significant difference in use is observed between assembling the guidewire at the tip or through the balloon.

• Cannula positioning is a significant determinant for the ease of performance of the procedure. When the cannula is positioned right before the valve, the guidewire and balloon require very little steering.

• Marking at both ends of the balloon would be useful. No other markings should be added since this would influence the ultrasound image too much.

6.2 Mechanical validation

To determine whether the new balloon configuration still fulfils the mechanical requirements to dilate the fetal aortic valve, some tests were performed. These tests aim to measure key properties, mainly related to the pressure within the balloon. The balloon pressure is a relevant property since it is related to both the dilatation force and the compliance of the balloon, as discussed in section 2.3.1. To determine if the balloon fulfills the requirements, the test was also performed with a PTA balloon that is currently on the market that has the same dimensions (Gateway™ 3.0 mm x 9.0 mm, Boston Scientific). Now that it is known which properties this balloon has the developed prototypes can be compared and it is known whether they function the same way. For the mechanical validation, the following research questions were set up:

1. Does the balloon provide enough force to open the aortic valve?

2. Which diameter corresponds to a certain pressure?
• At which pressure is the nominal diameter reached?

3. Is the burst pressure of the balloon above 14 bar?

By means of three separate tests, these questions are answered. These tests will be discussed separately in the following sections.

6.2.1 Test 1: force vs pressure

The aim of the first test is to answer the first research question. By measuring the force at a specific pressure for the prototype balloons, and compare this to the measured values of a reference balloon an answer to this question can be found. The reference balloon is known to be able to provide enough force since this is currently used in similar procedures.

Materials and method

For this test eight of the fully assembled and folded prototypes were used, as well as the GatewayTM for comparison. These balloons were inserted into the test setup, as shown in Figure 6.3.

The setup contains two sensors: a force sensor (LSB200 JR S-Beam Load Cell, FUTEK) and a pressure sensor (Compact Low Pressure OEM Pressure Transmitter, 3500 series, GemsTM). The force sensor was fixated at a set height, and connected to an amplifier, converter and laptop. The height of the force sensor was set at 3 mm above the trench to be able to measure at which pressure the balloon has reached its nominal diameter. The second sensor is the pressure sensor. To attach this sensor the analogue pressure gauge was replaced with the pressure sensor. This sensor was also attached to an amplifier, converter and laptop. The laptop recorded the measurements of both sensors simultaneously by using Labview and provided an .xls output file with the raw data (values in Voltage). This file also consisted of the converted data into Newton and Bar. The tested balloon is attached to the inflation device and positioned into a 3D printed bed with a trench of 3.2 mm. This ensures that the balloon will not move during inflation yet still allows for full circumferential expansion.

Protocol

Before inflation, the balloon number was noted and the crossing profile was measured with a digital caliper. The balloon numbers correspond to those in Appendix G. After the measurements, the balloon is attached to the inflation device. The inflation device is filled with water, and any air bubbles are removed. Next, the balloon is positioned into the 3D printed trench. When the balloon is in place, the Labview recording starts running and all data is measured. The balloon is inflated manually with the inflation device until a pressure of 14 bar is reached. This was chosen to be the end pressure since it is the burst pressure of comparable balloons. It was chosen not to inflate beyond this 14 bar since rupture of the balloons would make them useless after, and there would be a risk of water coming in contact with the electronics. After 14 bar was reached, the end diameter of the balloon was noted and it was then deflated. This protocol was repeated for eight prototype balloons and the GatewayTM balloon.

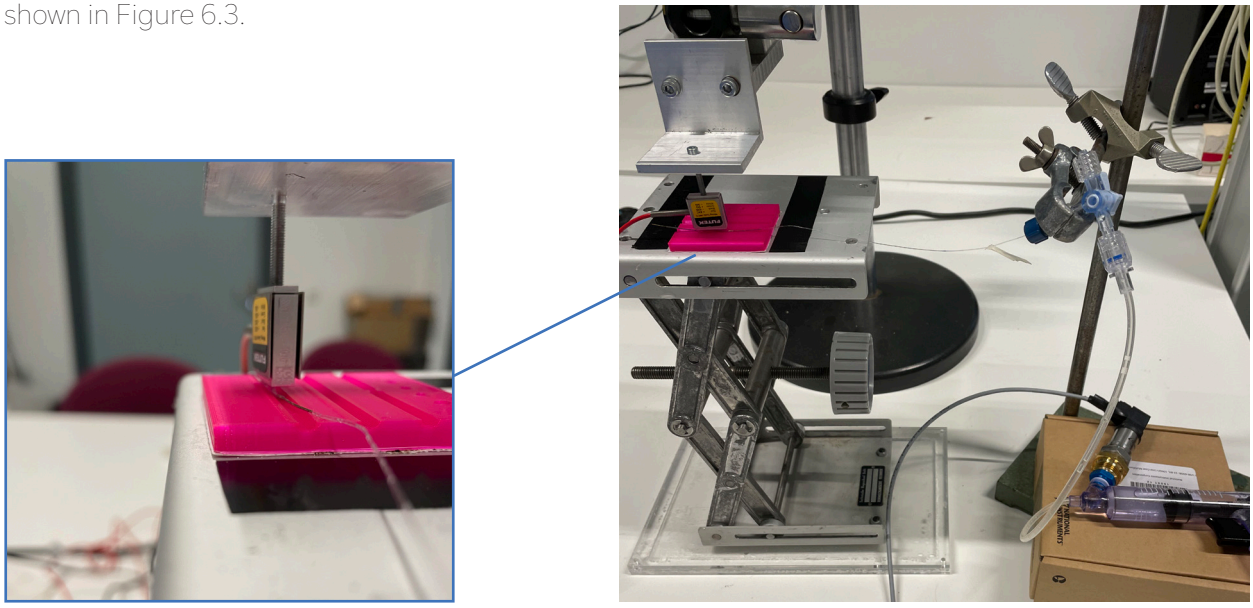


Figure 6.3: Test setup to measure pressure related to exerted force. Inflation device with attached pressure sensor at bottom right corner, force sensor with positioned balloon (in pink gutter) at the left.

Results

Figure 6.4 shows a plot of the pressure set out against the force. The data showed fluctuations due to the manual inflation and the accuracy of the sensors. Therefore, the polynomal trendline is shown in the plot. The corresponding raw data is plotted in the background. The R values are all very close to 1. The reference balloon (Gateway) is plotted in the red dotted line, the other lines all represent one of the other tested balloons. The data shows that all balloons except for two are able to exert the same force or higher for a given pressure. The balloons that did not reach these forces are balloon nr. 20 and 60. Both balloons start to exert force later and have a much lower force at the end pressure. Balloon 60 however does provide significant force up until 12 bar, yet does not increase enough after that. Balloon 20 never meets the required values. Next to that, balloons nr. 33 and 43 only provide data up to 9 bar, yet shows that up until then the balloons follow a path that exerts enough force. The remained 4 balloons all show a more gradual increase of measured force, and all exceed the values of the reference balloon.

Discussion

Interpretation of data

The R values of the trendlines are all close to one, meaning they are representative for the data. Therefore, these lines are used for the interpretation of the data. As is illustrated, during measurement two balloons seemed not to be able to exert the same forces as the reference balloon. The two balloons were balloon nr. 20 and 60. The cause of this is different for both balloons. For balloon nr. 20 the diameter was measured at 2.9 mm at the end pressure of 14 bar. Since the force sensor was set at a height of 3.0 mm it is understandable that this balloon was not able to exert enough force. Balloon 60 showed a very small leak at the distal seal after inflation. It is likely that the leak developed during inflation and pressure build up. This explains why up until a certain point the balloon functions properly, yet is not able to reach the end force. Balloons nr. 33 and 43 were measured with a pressure sensor that was limited at 9 bar, and therefore only information up until 9 bar is presented. Unfortunately, both balloons bursted during the use of this old pressure sensor, and therefore the measurements could not be repeated. Yet, this data up until 9 bar is useful regarding the predicted behavior. Based on the data, it can be said that the prototype balloons start to exert force earlier, indicating that for a certain pressure, these balloons provide more force. This could be due to a decreased wall thickness, see Section 2.3.1. It could also indicate that the reference balloon is slightly more compliant than the prototype balloons.

Limitations to the setup

Due to the availability of balloons, only eight different balloons could be tested. Next to that, only one reference balloon could be tested. Some of the prototype balloons had also been used for the clinical test, however that does not seem to have had any influence on the performance. The inflation device was handled manually. Therefore, the increase of pressure was not applied at the same speed for every balloon. This could have an influence on the measured force and stress build up in the balloon.
Lastly, the force was now measured at one point by the force sensor. However, in reality the force is exterted circumferentially on a lesion. Measuring the force at one point and restricting the balloon in all other directions could provide unrepresentative values for the force exerted on the aortic valve. Yet assuming both balloons are non-compliant, the shape should not be influenced

Conclusion

By means of a comparative test the goal was to determine whether the balloon prototypes are able to perform sufficiently. This means that the values could be unrepresentative for the forces that are exerted on the aortic valve. However it can be determined that the prototype balloons are able to exert the same amount or even more force than the reference balloon. Since the reference balloon is known to be able to open lesions, it can be assumed that the prototype balloons contain of the right properties regarding dilatation force.

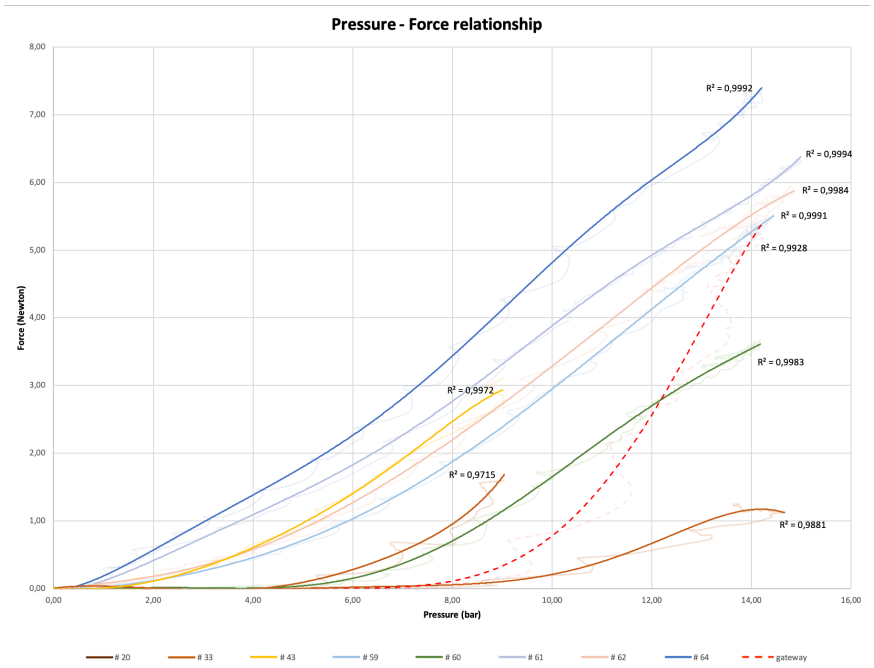


Figure 6.4: Graph showing the pressure - force relationship of 8 prototype balloons and one reference balloon. Polynomal trendline plotted and corresponding R values indicated at end of the line. Numbers in legend refer to balloon number.

6.2.2 Test 2: pressure vs diameter

The aim of the second test is to answer the second research question. The relationship between the inflated pressure and balloon diameter is relevant to know since this must be constant and predictable. Next to that, it provides insight regarding the level of compliance the material has.

Materials and method

The setup for this second test is comparable to the one used in test 1, yet the force sensor is not used in this test. In this test, the goal is to find out the relationship between pressure and balloon diameter. To measure the pressure, the pressure sensor is still connected to the inflation device. To measure the diameter, a digital caliper with an accuracy of 0.01 mm is used (Hogetex, 0-150mm). Even though the diameters for a specific pressure in the reference balloon are provided on the packaging, this balloon was also measured. This is done to ensure the comparison can be made. The measurement method of the manufacturer is probably different from this method and therefore by doing it all the same it will be more representative to make a comparison. This test was performed with ten produced balloons.

Protocol

The balloon is measured and then attached to the inflation device. The balloon is inflated with steps of 1 bar, and at each interval the diameter is measured with the digital caliper and noted. Again, the pressure limit was set as 14 bar.

Results

Figure 6.5 shows an overview of the retrieved data. Again, the reference balloon is plotted with the red dotted line. Two balloons, nr. 14 and 16, show the lowest values. Both of these balloons do not reach the aimed nominal diameter of 3 mm. All other balloons easily reach 3 mm. The maximum diameter of these balloons lies between 3.1 and 3.2 mm. The pressure to diameter ratio is comparable for all of these balloons. It can be observed that as the diameter increases, more pressure is required to cause a further increase in diameter. Therefore the plot starts to flatten more the higher the pressure and corresponding diameter gets. The reference balloon increases more gradually than the prototype balloons and is able to reach a higher final diameter.

Discussion

Interpretation of data

The two balloons that do not reach the aimed diameter were the first two balloons that were successfully blow molded. At this time in the prototyping process, the process was not yet optimized. These two balloons were not heat set (see chapter 5) and therefore it is likely that they did not hold on to their initially blown diameter. The flattening of the plot curve at a certain diameter is attributed to the compliance of the balloon. Non -compliant balloons generally do not expand far above their nominal diameter. The more a balloon increases above this nominal diameter, the more compliant it is. Therefore it can be assumed that the reference balloon is more compliant than the prototype balloons, since that curve increases more gradually and reaches a higher diameter.

Limitations to the setup

The measurement of the balloon diameter at each interval was done manually with the digital caliper. This approach is quite sensitive to errors, since the caliper can also compress the balloon a little bit during measurement. Each balloon was measured the same way by choosing the value at which the balloon could still move back and forth between the caliper with the same resistance. Doing this the same for every balloon, this risk was minimized.

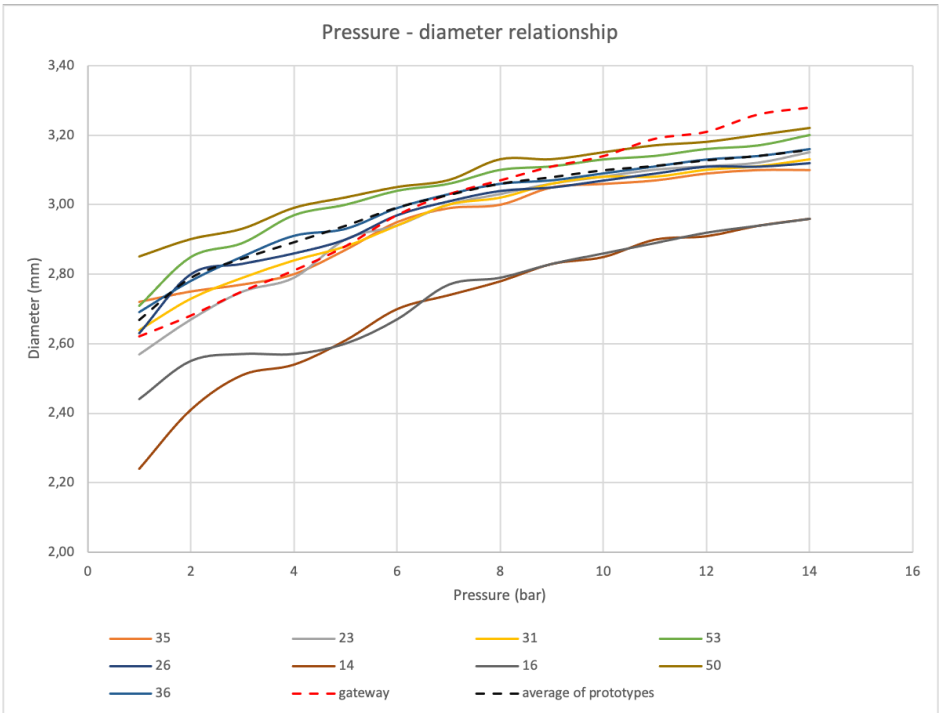


Figure 6.5: Graph showing the pressure - diameter relationship of 8 prototype balloons and one reference balloon. Average of prototypes indicated in blue dotted line. Numbers in legend refer to balloon numbers.

Conclusion

The maximum diameter that the balloon prototypes could achieve lies between 3.1 and 3.2 mm. This means that an aortic valve of 2.7 mm can be dilated with 120%, and therefore fulfills the requirements as set in section 3.2. Since the balloons do not exceed its nominal diameter with more than 10%, these balloons would be categorized as being non-compliant.

6.2.3 Test 3: Burst pressure

To answer the third and last research question this test is performed. If the burst pressure is unknown, there is a risk of the balloon bursting inside the patient, which could lead to complications. In this test it is tried to determine whether the balloon prototypes can at least reach the rated burst pressure of the currently used balloons.

Materials and method

For this test only the pressure sensor was used for measurements. Next to that, the inflation and burst of the balloon were recorded with a slow-motion camera. This test was performed with four balloons.

Protocol

Prior to attachment to the inflation device the double wall thickness of each balloon is measured with the digital caliper. The balloon is then inflated until it bursts while the pressure is measured.

Results

Table 6.1 shows the values of the four measured pressures at which the balloons ruptured. It shows that the values vary between 16 and 26 bar. It is relevant to keep in mind that for both test 1 and 2, all balloons (n=18) were inflated to a pressure of 14 bar, and none of them ruptured before reaching this pressure. Another relevant result is that all of the balloons ruptured into the longitudinal as expected. Figure 6.6 shows images of the ruptured balloons.

Table 6.1
Balloon numbers with related burst pressures in bar

Balloon nr	23	53	50	35
Burst pressure (bar)	22.9	19.5	16.5	26.4

Discussion

Interpretation of data

All balloons (including those of the previous tests) were able to handle pressures up to 14 bar. This indicates that the material is strong enough to withstand comparable forces to the balloon that is currently used, as this has a rated burst pressure of 14 bar. Balloon nr. 35 reaches the highest pressure of 26.4 bar. This could be explained by the fact that the wall thickness of this balloon was also measured to be the highest. However, the measurement of this wall thickness is more of an estimate since this could not be done very accurately.

Limitations to the setup

The key limitation to this setup is the number of samples that is used. Only four balloons could be measured. Next to that, due to availability, these balloons had already been used for test 2 and were therefore already inflated and deflated before. This should however not influence the performance of the balloon in a negative way, since in reality it also occurs that balloons are also inflated and deflated multiple times.

Conclusion

The currently used material can withstand at least 14 bar of pressure before rupturing with the produced wall thickness and shape. The measured balloons ruptured at pressure between 16 and 26 bar, yet no exclusive conclusion can be drawn regarding the rated burst pressure of the balloons due to the small data set. The fact that the balloons all ruptured into the longitudinal direction indicates that the material is well distributed, and the stresses on the balloon are present as expected.

Figure 6.6 a,b,c: Pictures of three longitudinally ruptured balloons.

7 Final concept design

The clinical and mechanical tests provided the proof of principle for the designed concept. Based on the outcomes of these tests, the last design choices were made and the final concept is developed. Figure 7.1 shows the final concept design of the fetal aortic valvuloplasty balloon catheter.

7.1 Final concept choices

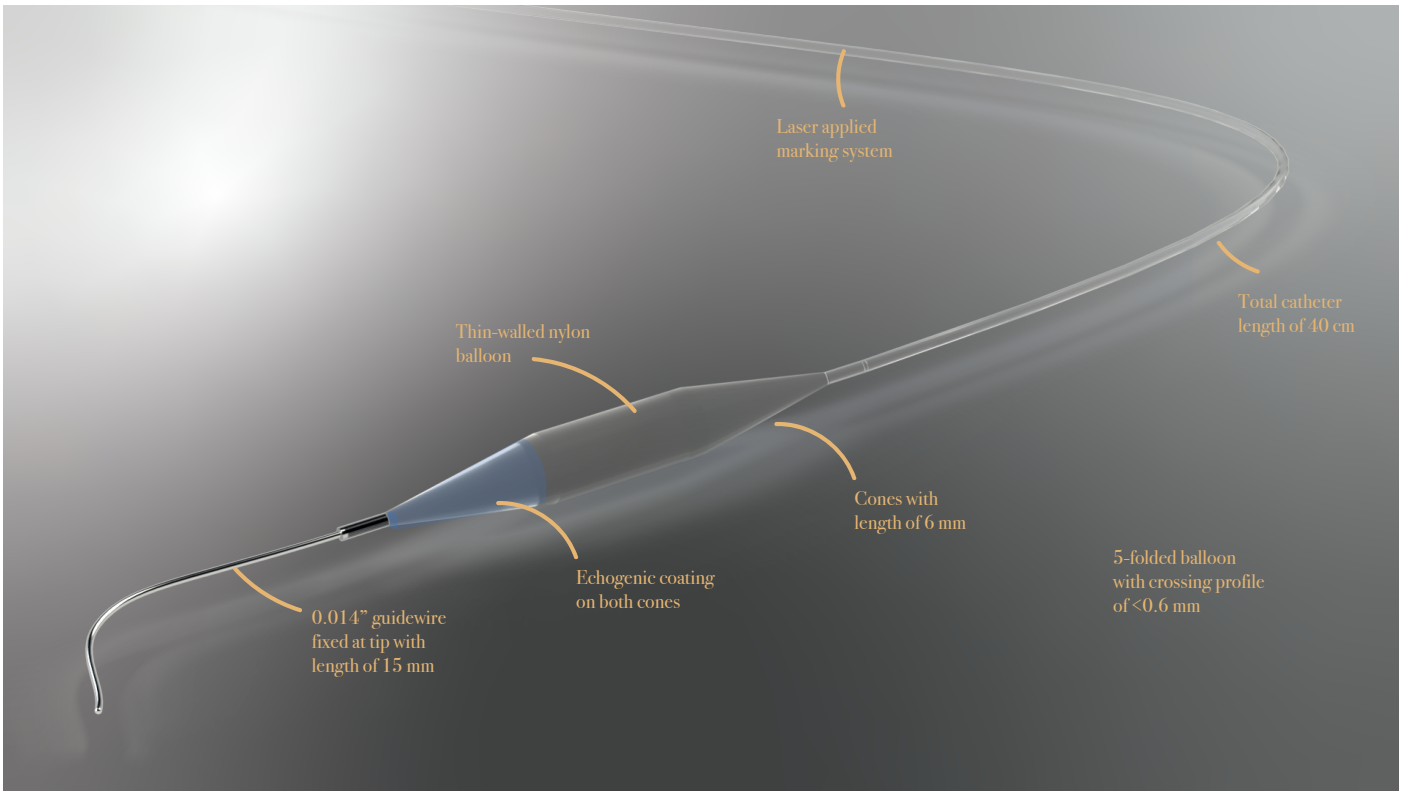


Figure 7.1: Render of final balloon design with key design choices indicated.

Balloon shape

For the final design, it was decided to use the balloon model that has two equal cones and a cylindrical length of 7 mm. During the clinical test, it was determined that a symmetrical model has the preference over an asymmetrical model due to ease of placement. The optimal length of the cones should be further investigated. However, it would be preferable if this was shorter than 7 mm. In the asymmetrical model one of the cones was 5 mm. Due to the fact that those cones were also able to be folded into the low crossing profiles it is assumed that decreasing the length of the cones to 5 mm would not increase the crossing profile significantly. The cones were not only made longer for folding but also for retraction. Therefore, the final value of the cones is now set at 6 mm. However, as stated before, to optimize this value, further research is recommended.

Guidewire

Since no significant differences were noticed between the use of both guidewire configurations it is chosen to include the guidewire into the tip and not let it extend through the balloon. In this configuration the currently used guidewire size (0.014") can still be used. Since this is a more conventional guidewire size, this will lower the costs and it is known that this works well with the conditions of the FAV procedure. During the clinical test, it was noted that most of the steering and positioning is determined by cannula placement. Therefore the fixation of the guidewire is thought to be possible. In the mechanical test, it became clear that some balloons showed leaking at the distal seal point. This has to be taken into account for the final assembly process.

Material
By testing the prototype balloons, nylon has proven to be a suitable material for the development of the balloon. This material is able to withstand the required pressures and provide enough force and shows non-compliant behavior. Next to that, the material is suited for tight folding, which provides strength during the placement of the balloon. Based on the outcomes of the mechanical tests it is assumed that the wall thickness could be reduced even further, possibly resulting in an even lower crossing profile.

Visibility
To improve the visibility it is recommended to apply an ultrasound enhancing coating to both cones of the balloon. The radiopaque markers are removed to prevent scattering from occurring and allow for a more tight folding.

Folding and assembly
The current prototypes have been 3-fold. However, based on expert knowledge, it is assumed that a 5-fold configuration would also be possible. Therefore in the final design, a 5-fold configuration is included to minimize the crossing profile. If this turns out to be less beneficial, the fallback option of a 3-fold balloon is always possible and already proven to be useful.

7.2 Requirements and wishes evaluation

In section 3.2, the requirements and wishes for the new device have been determined. In this section it is evaluated whether the new concept design meets these requirements. Some requirements are met and do not clarification, and are therefore only marked green. For requirements that need clarification, the explanation is added below in blue.

FAV context
- The general process of the procedure should not change:
  - The aortic valve of a fetus is dilated by the device
  - The fetal heart is accessed percutaneously
  - The fetal aortic valve is accessed through the left ventricle
- The device should not introduce new complications or enlarge the occurrence of current complications
- The device should not occlude the aortic valve longer than 15 seconds
  - After 15 seconds, at least 50% of flow through the valve should be restored.

During the clinical and mechanical tests, it has been observed that the balloon shows the ability to inflate and deflate rapidly. Even though the final balloon catheter will have an increased length, it is not likely that the inflation and deflation time will increase so significantly that the aortic valve will be occluded for longer than 15 seconds.

- An 'average' fetal aortic valve on ± 26 weeks of gestation should be able to be dilated
  - Dilation is successful when valve diameter is expanded by 120%
  - The diameter of a valve at this gestation is between 2,7 and 3,1 mm

The new balloon has a nominal diameter which has the ability to expand to 3.2 mm. With these dimensions, a valve of 2.7 mm can be expanded by 120%.

  - Wish: dilatation of a valve with a diameter of 4mm is also possible
- The device is used under ultrasound guidance:
  - The ultrasound guidance provides enough visual feedback to determine the location of the cannula

The cannula has not changed, yet the visibility of the cannula on ultrasound is already sufficient in most cases

  - Wish: the guidewire tip is clearly visible on US

Guidewire tip visibility is not increased, yet a coating should provide increased visibility on the balloon, which allows for more precise positioning.

- The device can be used in dim lighting in an OR

Intended use

- One (fetal) surgeon controls needle placement
- One (cardiac) surgeon controls catheter handling
- Feedback on the position of the balloon and guidewire is integrated
  - It should be clear when the guidewire extends the cannula by 1,5 cm
  - It should be clear when the entire length of the balloon catheter has left the cannula

For this purpose, a marking system is included at the proximal end of the catheter.

Structural

General

- Wish: As many existing materials as possible should be used

The cannula that is used stays the same (except for a smaller size). The tip of the currently used guidewire is included in the final design, and the balloon is new. However, the basic principle of a dilatation balloon has stayed the same.

Balloon

- The balloon should not exceed the measurements of a 20G needle in deflated state
- The balloon should be able to expand into 1,2 times of the operable aortic valve
- The balloon should be able to provide enough force to open the valve
  - The material should be rated as non-compliant or semi-compliant
- The length of the cylindrical body of the balloon should be between 10 and 15 mm

The length of the cylindrical body is decreased to 7 mm. Based on the clinical test, it was noted that this should also work.

- In the case of a catheter configuration
  - The length from distal to proximal is 40-60 cm
- The diameter and shape of the balloon needs to be known at a specific pressure
- The balloon needs to be able to be retracted through the cannula after inflation and deflation
- The balloon needs to behave consistently after multiple inflations and deflations

This is not tested, however, it is assumed that the balloon functions as other balloons that are currently on the market that are also made out of this material. Therefore, it is assumed that the new balloon will behave consistently.

Needle

No changes were made to the needle; it is known that the 20G needle is able to puncture the maternal wall since this is already used.

- The needle should not exclude the dimensions of a 20G needle
- The needle is obturated during puncture and placement
- The needle has a sharp tip for puncturing
- The length of the needle is between 12-20 cm
- The needle with obturator is able to puncture the maternal abdomen

Guidewire

- The diameter of the guidewire should not exceed 0,014”
- The guidewire has a floppy tip
- The guidewire is able to cross the valve with ± 1,5 cm
  - The distance between balloon and guidewire tip is minimally 1,5 cm

It was found that the distance between balloon and guidewire tip should be maximally 1,5 cm instead of minimally.

- The guidewire is able to cross the stenotic valve lesion
  - There is always an opening of 1 mm in the valve

As can be seen, the new design fulfils all requirements and some of the wishes. Therefore, the concept should function properly in the aimed context. The new instrument is expected to properly replace the current instrument and improve the procedure by reducing complications.

Discussion

8

Aortic stenosis is a congenital heart defect which refers to the narrowing of the aortic valve. This is often caused by the fusion of two valvular leaflets (Michelena et al., 2011). Aortic stenosis could lead to severe consequences and to prevent these, fetal aortic valvuloplasty (FAV) is performed. The FAV procedure is performed percutaneously with the instruments as described in section 2.2. This method was first described by Maxwell et al. in 1991 and has not changed much ever since. Due to the fact that there is still no dedicated instrument, the used instruments that are described in literature are often PTCA balloon catheters in combination with an 18G cannula. These instruments are not developed for the purpose of performing fetal intervention, and are quite large. A larger cannula increases the risk of complications (Patel et al., 2020). Therefore the goal of this thesis was to design a dedicated instrument for the FAV procedure with the aim of reducing complications by decreasing the cannula size. This aim assumes that the procedural approach and other factors remain unchanged. To be able to reduce the cannula size, the crossing profile of the balloon catheter needs to be reduced, since this needs to be advanced through the cannula.

The solution presented in this thesis was based on the theory that the PTCA procedure requires other balloon properties than FAV. By comparing these properties and eliminating the components that are not required for FAV, it should be possible to make the crossing profile of the balloon smaller. The balloon catheter that is currently used by the LUMC is the TREK 2.5 mm Coronary Dilatation catheter (Abbott). This balloon has a nominal diameter of 2.5 mm and a crossing profile of 0.81 mm. Changes in the design such as removing the guidewire lumen and elongating the cones as described in section 7.1 have reduced this crossing profile to ± 0.6 mm while allowing a nominal diameter of 3.0 mm. This new balloon design enables the use of a 20G cannula which is significantly smaller than the currently used 18G cannula, and therefore complication risks are decreased. Next to that, this design contributes to enhanced visibility and balloon retraction. Compared to the currently used balloons, this design provides a more suitable instrument since the key problems that are currently experienced are mainly associated with bad visibility and complications due to a large cannula (bradycardia). The changes in design also decreased the complexity of the product, and therefore it is assumed that this balloon would be cheaper to produce. Since the demand for this very specialized balloon is low, this is an important improvement.

To validate the design multiple prototypes were developed. There were a number of limitations to the production process as discussed in chapter 5, resulting in a prototype that does not have the same accuracy as those available on the market. However, this balloon was only required to provide a proof of principle and for this purpose the accuracy was sufficient. Clinical tests provided insights regarding the user experience and showed that the adjusted design still allows for enough steering and control. Mechanical tests showed that the developed balloons have the same or even improved properties related to force exertion and (burst) pressures. This validation provided a proof of principle for this new design. The crossing profile of the new balloon design is significantly smaller than the original balloon which proves that the optimization of the balloon is useful.
This thesis underlines the importance of carefully researching possibilities regarding medical instruments. Over 20 years the same instruments have been used, even though it is possible to develop an instrument that reduces complications and enhances the performance of the procedure. If the needs for performing a successful procedure are carefully researched and subsequently transformed into a product, complications can be reduced. However, this would require precision engineering in very specialized markets which is not always possible. In those cases it is important to constantly stay informed on the available products and evaluate whether the products that are currently used are still the most suitable for this application.

8.1 Limitations of the study

Even though the results of the different tests that are performed show promising outcomes, it is important to keep in mind the limitations and assumptions that were made during this process. This section discusses several limitations to the process that could have influenced the outcomes.

Literature research

The thesis contained several decisions based on information retrieved out of literature research. This literature research functioned as a starting point and, based on the retrieved information, the problem was defined. It is possible that some relevant literature or information was not included or data was not published at the moment of searching. Research was also done to explore the current balloon catheter market. However, getting to know all balloons that are currently on the market is extremely time consuming and requires many resources, and only little information is provided

on the specifics of medical devices by manufacturers. Consequently, it is possible that there are products on the market that already provide the solution for the stated problem but they are just not used yet. However, all research was performed in a structured way to minimize the risk of excluding relevant information.

Clinical perspective

As stated frequently throughout the report, the clinical perspective has been relevant and useful. It could be debated whether the opinion of one or two surgeons represents the clinical perspective properly. A limitation within the research to the subject of fetal cardiac interventions is the fact that it is a very specialized area, in which only a few people in the Netherlands are involved. To reduce this effect, key decisions such as the problem definition and requirements and wishes were also discussed with experts from Boston and San Francisco, which are both leading institutes in this field.

Design choices

At certain points in the design process, choices were made to be able to get further. This starts with defining the scope of the design and determining that nothing about the procedural approach should change. It continues throughout defining the design focus and choosing the final design concept. Choices were always made based on all available information at that moment. By making these choices, it is possible that other areas of interest were excluded from the research. However, without these choices at certain key moments, the research area would have been kept to broad and no concrete results could have been produced within the given time.

Production and prototyping

During the development of the prototypes, only one material turned out to be suitable for the production process. Due to delivering time and costs, it was not possible to make a comparison between materials with regard to optimal performance for this concept. The material that was used in the final prototype is currently also used for the production of many medical balloons. Therefore, it is known that this is a suitable material which has the potential of being implemented in the final product.

Mechanical testing

Mechanical functionality of the balloon prototypes were determined by three different mechanical tests. The amount of produced prototypes was limited, so some samples had to be used for multiple tests and the total amount of performed tests was not enough to make conclusive assumptions regarding the properties. However, that was also not the goal of the mechanical tests. The goal was to show that this design and material provides a promising starting point for the development of a new product. For this purpose, a comparative research suffices since it is known that the reference balloon is able to perform as required.

Conclusion

The goal of this thesis was to provide a proof of principle for a new medical device that reduces the complications for the fetal aortic valvuloplasty procedure. It was determined that one way to reduce these complications is by allowing the use of a 20G cannula, instead of the currently most often used 18G cannula. To achieve this while still performing the procedure similarly and safe, the balloon catheter was optimized. This optimization had to reduce the crossing profile of the balloon from 0.85 mm to <0.6 mm, since that is the inner diameter of the preferred cannula. A new balloon design is provided, which is able to withstand pressures up to at least 14 bar, is able to expand up to 3.2 mm and shows non-compliant behavior. The crossing profiles of the produced prototypes are close to 0.6 mm (0.59 – 0.67 mm). This is an indication that with an optimized production process the new balloon design reduces the crossing profile significantly allowing it to fit through the 20G cannula. This means that the research goal of this thesis was achieved and the new balloon concept provides a valuable solution for the defined problem.

Future recommendations

9

Now that the proof of principle for this concept is provided, the next steps are to be determined. Recommendations regarding what should or could be done in the future are provided in this section.

Optimize production process

To acquire more accurate data regarding the performance of the new design, the production process needs to be optimized. Therefore, more research needs to be done to the production parameters and their influence on the final result. This way, a product which is more representative for the final product can be made. An optimized production process also means that it is possible to produce balloons of higher quality, which allows for more data acquisition.

Clinical testing

When a prototype is produced that is more representative for the final product, more clinical tests should be performed. A test setup that imitates the real situation more accurately should be used eventually working towards in vivo tests. This will give more insights on the functionality and use of the product and allows for design iterations. Conditions that should be included in these tests are for example human body temperature, blood flow direction, cardiac contractions and visibility of the operable site.

Mechanical testing

For the mechanical tests also applies that a more accurate prototype will provide more relevant data. The FDA suggest several tests which a new balloon catheter design should undergo (Food and Drug Administration [FDA], 2010). These include, but are not limited to:

- Define the rated burst pressure and nominal pressure
- Test the balloon fatigue (will the behavior of the balloon change after multiple inflations?)
- Define the inflation and deflation time
- Test the reaction to approved sterilization methods

Since the current balloon is an adjustment to existing balloon catheters, these tests are likely to provide comparable results. However, to get a new product on the market FDA and/or CE approval needs to be granted. This will only be done when detailed information is provided regarding the performance and properties of the device.

Design optimization

As stated before, some aspects of the design are researched to a basic level. However, to eventually produce the best product possible, more research is required. Mainly the following topics should be researched:

- Material and wall thickness

More non-compliant and semi-compliant materials should be tested to see which performs optimally for this purpose. The key focus of the following material research should be which material is able to provide the lowest wall-thickness while still providing enough force.

- Required force

The wall thickness and material should be optimized while providing 'enough' force, however it is not known how much force exactly is enough force for this procedure. Therefore, during the performance of future procedures it would be useful to gain insight regarding the forces that are required to open the aortic valve. If this is not possible, computational simulation would be an alternative. However, simulations will not be able to provide as much certainty regarding the accuracy of data.

- Visibility

For now the use of an echogenic coating is recommended. However, the usability of echogenic coatings should be tested. Therefore, a prototype should be made in collaboration with one of the coating manufacturers. The possibilities and limitations of this technology should then be pointed out. Besides that, it is also relevant to research whether there are better alternatives for the improvement of ultrasound visibility. Clear ultrasound visibility is a problem that does not only occur for this procedure, which makes this a relevant research to perform with many stakeholders.

Cost estimation

The area of application for this device is very specialized. This makes the market demand for the product quite low. Therefore it would be very useful to make an accurate cost estimation and define whether some design choices could be made that reduce the costs. Since the concept is rather a simplification of the currently marketed balloons instead of introducing extra complications, this is already taken into account. Choices regarding materials for example should also include the associated costs.

Scope of intervention

As discussed in the previous paragraph, currently the design is developed for the purpose of one single procedure. Therefore it is not yet likely that manufacturers would be interested in investing in further development. However, if research shows that this balloon (albeit with some modifications) could be useful in more (fetal) interventions this chance would be increased.

References

B.Braun Interventional Systems Inc. (2020). MULTI-TRACK Angiographic Catheter. B.Braun Interventional Systems. Retrieved from: http://www.bisusa.org/sites/bbraunInterventionalsystems.com/files/documents/CV-1010%20-%20Multi-Track%20Rev.%206.20.pdf

Bahmer, M. (2020, 1 september). Confluent Medical opens catheter development center. Today's Medical Developments. Retrieved from: https://www.todaysmedicaldevelopments.com/article/confluent-medical-catheter-development-center-austin-texas/

Bingler, M. A. (2018, november). Hypoplastic Left Heart Syndrome (HLHS). KidsHealth. Retrieved from: https://kidshealth.org/en/parents/hypoplastic-heart.html

Boyden, A. (2020, 1 juni). The Benefits of Embedding Marker Bands vs. Swaging. Medical Design Briefs. Retrieved from: https://www.medicaldesignbriefs.com/component/content/article/mdb/tech-briefs/37126#

Cruz-Lemini, M., Alvarado-Guaman, M., Nieto-Castro, B., Luna-Garcia, J., Martínez-Rodríguez, M., Juarez-Martínez, I., Palacios-Macedo, A., & Cruz-Martínez, R. (2019). Outcomes of hypoplastic left heart syndrome and fetal aortic valvuloplasty in a country with suboptimal postnatal management. Prenatal Diagnosis, 39(7), pd.5470. https://doi.org/10.1002/pd.5470

Debska, M., Kolesnik, A., Rebizant, B., Sekowska, A., Grzyb, A., Chaberek, K., Witwicki, J., Debski, R., & Dangel, J. (2020). Fetal Cardiac Interventions—Polish Experience from "Zero" to the Third World Largest Program. Journal of Clinical Medicine, 9(9), 2888. https://doi.org/10.3390/jcm9092888

Food and Drug Administration. (2010). Guidance for Industry and FDA Staff Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters. In Federal Register.

Frommelt, M. A. (2014). Challenges and Controversies in Fetal Diagnosis and Treatment. Clinics in Perinatology, 41(4), 787–798. https://doi.org/10.1016/j.clp.2014.08.004

Fu, X., He, H., & Wang, W. (2017). Numerical simulation of forming process conditions and wall thickness for balloon. Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics), 10464 LNAI, 808–818. https://doi.org/10.1007/978-3-319-65298-6_72

Galindo, A., Gómez-Montes, E., Gómez, O., Bennasar, M., Crispi, F., Herraiz, I., Mendoza, A., Escribano, D., García-Torres, E., Carretero, J. M., Gratacós, E., & Martínez, J. M. (2017). Fetal Aortic Valvuloplasty: Experience and Results of Two Tertiary Centers in Spain. Fetal Diagnosis and Therapy, 42(4), 262–270. https://doi.org/10.1159/000460247

Geith, M. A., Swidergal, K., Hochholdinger, B., Schratzenstaller, T. G., Wagner, M., & Holzapfel, G. A. (2019). On the importance of modeling balloon folding, pleating, and stent crimping: An FE study comparing experimental inflation tests. International Journal for Numerical Methods in Biomedical Engineering, 35(11), 1–19. https://doi.org/10.1002/cnm.3249

Graupner, O., Enzensberger, C., & Axt-Fliedner, R. (2019). New Aspects in the Diagnosis and Therapy of Fetal Hypoplastic Left Heart Syndrome. Geburtshilfe Und Frauenheilkunde, 79(8), 863–872. https://doi.org/10.1055/a-0828-7968

Guseh, S. H., Friedman, K. G., & Wilkins-Haug, L. E. (2020). Fetal cardiac intervention—Perspectives from a single center. Prenatal Diagnosis, 40(4), 415–423. https://doi.org/10.1002/pd.5631

Hoffman, J. I. E. (2013). The global burden of congenital heart disease. Cardiovascular Journal of Africa, 24(4), 141–145. https://doi.org/10.5830/CVJA-2013-028

Jackowski, S., & Pinchuk, L. (1991). Stretch-blow molding method for manufacturing balloons for medical devices (Patent No. 5,017,325).

Jing, Z., Mao, H., & Dai, W. (2018). Endovascular Surgery and Devices. In Endovascular Surgery and Devices. https://doi.org/10.1007/978-981-10-8270-2

Lalli, D. (2006). Cycle-to-Cycle Control of the Angioplasty Balloon Fabrication Process (Issue May).

Luewan, S., Yanase, Y., Tongprasert, F., Srisupundit, K., & Tongsong, T. (2011). Fetal cardiac dimensions at 14-40 weeks' gestation obtained using cardio-STIC-M. Ultrasound in Obstetrics and Gynecology, 37(4), 416–422. https://doi.org/10.1002/uog.8961

Marshall, A. C., Tworetzky, W., Bergersen, L., McElhinney, D. B., Benson, C. B., Jennings, R. W., Wilkins-Haug, L. E., Marx, G. R., & Lock, J. E. (2005). Aortic valvuloplasty in the fetus: Technical characteristics of successful balloon dilation. The Journal of Pediatrics, 147(4), 535–539. https://doi.org/10.1016/j.jpeds.2005.04.055

Maxwell, D., Allan, L., & Tynan, M. (1991). Balloon dilatation of the aortic valve in the fetus: a report of two cases. 22(SUPPL. 1), 19–24.

Mayo Foundation for Medical Education and Research. (2021, 26 februari). Aortic valve stenosis - Symptoms and causes. Mayo Clinic. Retrieved from: https://www.mayoclinic.org/diseases-conditions/aortic-stenosis/symptoms-causes/syc-20353139

McElhinney, D. B., Marshall, A. C., Wilkins-Haug, L. E., Brown, D. W., Benson, C. B., Silva, V., Marx, G. R., Mizrahi-Arnaud, A., Lock, J. E., & Tworetzky, W. (2009). Predictors of technical success and postnatal biventricular outcome after in utero aortic valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome. Circulation, 120(15), 1482–1490. https://doi.org/10.1161/CIRCULATIONAHA.109.848994

MECCO. (2015). Right Part , Right Mark (Vol. 2). Retrieved from: https://pages.mecco.com/error-proofing-traceability.html#top

Menary, G. H., & Armstrong, C. G. (2006). Experimental study and numerical modelling of injection stretch blow moulding of angioplasty balloons. Plastics, Rubber and Composites, 35(8), 348–354. https://doi.org/10.1179/174328906X143877

Michelena, H. I., Khanna, A. D., Mahoney, D., Margaryan, E., Topilsky, Y., Suri, R. M., Eidem, B., Edwards, W. D., Sundt, T. M., & Enriquez-Sarano, M. (2011). Incidence of aortic complications in patients with bicuspid aortic valves. JAMA - Journal of the American Medical Association, 306(10), 1104–1112. https://doi.org/10.1001/jama.2011.1286

Patel, N. D., Nageotte, S., Ing, F. F., Armstrong, A. K., Chmait, R., Detterich, J. A., Galindo, A., Gardiner, H., Grinenco, S., Herberg, U., Jaeggi, E., Morris, S. A., Oepkes, D., Simpson, J. M., Moon-Grady, A., & Pruetz, J. D. (2020). Procedural, pregnancy, and short - term outcomes after fetal aortic valvuloplasty. Catheterization and Cardiovascular Interventions, 96(3), 626–632. https://doi.org/10.1002/ccd.28846

Pedra, S. R. F. F., Peralta, C. F. A., Crema, L., Jatene, I. B., da Costa, R. N., & Pedra, C. A. C. (2014). Fetal Interventions for Congenital Heart Disease in Brazil. Pediatric Cardiology, 35(3), 399–405. https://doi.org/10.1007/s00246-013-0792-3

Pickard, S. S., Wong, J. B., Bucholz, E. M., Newburger, J. W., Tworetzky, W., Lafranchi, T., Benson, C. B., Wilkins-Haug, L. E., Porras, D., Callahan, R., & Friedman, K. G. (2020). Fetal Aortic Valvuloplasty for Evolving Hypoplastic Left Heart Syndrome. Circulation: Cardiovascular Quality and Outcomes, 13(4). https://doi.org/10.1161/CIRCOUTCOMES.119.006127

Saab, M. A. (2000). Applications of high-pressure balloons in the medical device industry. Medical Device and Diagnostic Industry, 22(9), 86–97.

Sahagian, R. (1999, 1 mei). Critical Insight: Marking Devices with Radiopaque Coatings. Mddionline.Com. Retrieved from: https://www.mddionline.com/news/critical-insight-marking-devices-radiopaque-coatings

Sauerteig, K., & Giese, M. (1998). The Effect of Extrusion and Blow Molding Parameters on Angioplasty Balloon Production. 1–7.

Schidlow, D., Tworetzky, W., & Wilkins-Haug, L. (2014). Percutaneous Fetal Cardiac Interventions for Structural Heart Disease. American Journal of Perinatology, 31(07), 629–636. https://doi.org/10.1055/s-0034-1383884

Shrivastava, A. (2018). 1 Introduction to Plastics Engineering. In Introduction to Plastics Engineering. https://doi.org/10.1016/b978-0-323-39500-7.00001-0

Singh, G. K. (2019). Congenital Aortic Valve Stenosis. Children, 6(5), 69. https://doi.org/10.3390/children6050069

Trotec Laser Automation GmbH. (n.d.). Integrated laser marking in the UDI era. Retrieved May 13, 2020, from https://www.troteclaser.com/fileadmin/content/images/Laser_Applications/Medical_Technology/Trotec-UDI-medical-industry-Atricle.PDF

Wiesent, L., Schultheiß, U., Schmid, C., Schratzenstaller, T., & Nonn, A. (2019). Experimentally validated simulation of coronary stents considering different dogboning ratios and asymmetric stent positioning. PLoS ONE, 14(10). https://doi.org/10.1371/journal.pone.0224026

Yuan, S. M., & Humuruola, G. (2016). Fetal cardiac interventions: Clinical and experimental research. In Postepy w Kardiologii Interwencyjnej (Vol. 12, Issue 2, pp. 99–107). Termedia Publishing House Ltd. https://doi.org/10.5114/aic.2016.59359

Yuan, S.-M. (2014). Fetal cardiac interventions: an update of therapeutic options. Revista Brasileira de Cirurgia Cardiovascular, 29(3), 388–395. https://doi.org/10.5935/1678-9741.20140099

Glossary

Apex	The blunt extremity of the heart formed by the left ventricle
Anaesthesia	State of controlled, temporary loss of sensation or awareness that is induced for medical purposes
Angioplasty	A minimally invasive endovascular procedure used to widen narrowed or obstructed arteries or veins
Anomaly	Something that deviates from what is standard, normal, or expected
Aortic stenosis	A narrowing of the aortic valve opening
Balloon compliance	Balloon property related to the amount of pressure that is needed to increase the diameter of the balloon above its nominal diameter
Biventricular circulation	Blood circulation in the heart when both ventricles function properly
Bradycardia	A sustained fetal heart rate less than 110 beats per minute
Burst pressure (in balloon)	The pressure at which 99.9% of balloons can survive with 95% confidence
Congenital heart defect	A defect in the structure of the heart or great vessels that is present at birth
Crossing profile	The maximum diameter found between the proximal end of the balloon and the distal tip of the catheter
Crystallinity (of plastics)	The degree of structural order and regularity in molecular arrangements of a plastics material
Distal	The more (or most) distant of two (or more) ends
Doppler flow	A type of ultrasound that uses sound waves to measure the flow of blood through a blood vessel
Echocardiography	The use of ultrasound waves to investigate the action of the heart.
(Fetal) aortic valvuloplasty	The widening of a stenotic aortic valve using a balloon catheter inside the valve (in fetuses)
Gestational age	Length of time that a fetus grows inside the mother's uterus
Hypoplastic left heart syndrome	A congenital heart defect in which the left side of the heart is severely underdeveloped
In utero	In the uterus, before birth
Intramuscular	Within or into the muscle
Leaflets	The cusps or flaps of which a valve consists
Left ventricle	One of the four chambers of the heart
Lesion site	Site of damage or abnormal change in the tissue of an organism
Lethal	Sufficient to cause death
Nominal diameter (in balloon)	The diameter that the balloon is designed and manufactured to have
Obstetrician	A doctor with special training in how to care for pregnant women and help in the birth of babies
Percutaneously	Access provided through skin
Pericardial sac	A conical sac of fibrous tissue which surrounds the heart and the roots of the great blood vessels
Proximal	Toward the beginning, the nearer of two (or more) ends

Appendix

A. Clinical interviews

B. Generated ideas

C. Concept 1&2

D. Balloon folds

E. Production parameters

F. Prototyping materials

G. Tested balloons

H. Heart model

I. Clinical test - notes

Appendix A

Clinical interviews

Prof. Dr. N.A. Blom
Pediatric cardiologist at the LUMC
Topics: currently used instruments, especially the balloon catheter.

Findings:
General:
- Surrounding in operation room has dim lighting to enable ultrasound visibility
- At the LUMC PTA instruments are used, in combination with a 19G needle in most cases
- The balloon:annulus ratio that is used is between 1.1 and 1.2
- When the guidewire is positioned, the balloon is still in the needle.

Guidewire:
- The current guidewire is a 0.014" balanced middle weight guidewire.
- Guidewire with floppy tip is nice, 0.014" is the right size. Not much should change with regard to the guidewire
- It would be useful if the visibility of the tip of the guidewire is better, so you know exactly when the position is correct
- Currently an improvised marking system is used to know when the balloon is entirely out of the needle. This system works with small pieces of tape, but could be improved
- The guidewire goes up to ± 1,5 cm past the valve.

Balloon catheter:
- The balloon should be 10-15 mm long
- The total length of the catheter should be reduced to ± 40-60 cm. The cardiologist is standing next to the fetal surgeon, so it should be long enough for him/her to control the catheter, but when it's much longer its inconvenient
- Over the wire configuration is preferred
- ± 14 atm is needed to inflated a balloon in a PTA procedure, but perhaps an aortic valve is easier to dilate and requires less pressure
- Lesions up until ± 3 mm can be treated with the current materials. Sometimes lesions of ± 4 mm also occur, it would be nice if those were also treatable

---

Dr. G.A.P. de Kort
Interventional radiologist at UMC Utrecht
Topics: the different applications of balloon catheters and balloon properties

Findings:
- For brain interventions balloon diameters between 2 to 4 mm are used.
- The most common application of balloon catheters in the brain is for stent placement and coiling
- To reach the intended location a flexible catheter is often desired.
- PTA (dotteren) requires non-compliant balloons, otherwise they are not able to dilate the vessel enough
- Coiling requires compliant balloons. They are used to close off an aneurysm before coiling. This is done to prevent the coil from entering the bloodstream
- Stent placement requires semi-compliant or non-compliant balloons. They should provide enough force to push open the stent, but not too because then the vessel might rupture. Other than that, in interventionradiology semi-compliant balloons are not really used.

- If the tip of the guidewire is roughened, its visibility on ultrasound is improved

- The crossing profile of the balloon becomes larger after inflation and deflation. This is due to less optimal folding and some residue in the balloon. The recommended sheath diameter takes that into account and is found on the packaging

A.J. Moon-Grady, MD
Pediatric cardiologist and Director of UCSF Fetal Cardiovascular Program
Founding member of the steering committee for the International Fetal Cardiac Intervention Registry

And

L.E. Wilkins-Haug, MD, PhD
Clinical Lead, Maternal Fetal Care Center at Boston Children's Hospital

And

Dr. M.C. Haak
Gynaecologist and fetal surgeon at the LUMC

Findings:

General procedural:
- There is a seperate operator for the ultrasound imaging
- Two or three people are working on needle placement
- Interventional cardiologist threads the guidewire and balloon catheter through the needle
- Improving the instruments would be a more useful improvement than changing the imaging technique, since it would be a more generalizable change. Not all institutes have access to all imaging techniques.

Visibility:
- Visibility is concerned as a big concern during the FAV procedure
- Mostly in early gestation the visibility is difficult. This is due to the small LV and capillary muscle that is around
- If there is a way to differentiate the wire or trocar from surrounding it would be very useful. For example by applying a pattern which is visible on ultrasound
- The current echogenic tip of the trocar does not help enough
- Injecting saline contrast to enhance position visibility is not possible since you can not make as many the catheter changes
- A pressure wire could help defining the position of the guidewire, a research group in Michigan is working on that (refer to articles)
- MRI guidance for FAV has not been tried yet

Balloon catheter:
- In Boston, if the balloon is not able to reach the intended diameter by just inflating up to the rated burst pressure, they routinely burst it on purpose at the last inflation. In that case there is a theoretical risk of severing off a piece of material. At the LUMC and UCSF this is not common.
- It would be more convenient to decrease the length of the balloon catheter, and could perhaps mean that it is possible to reduce the personnel.

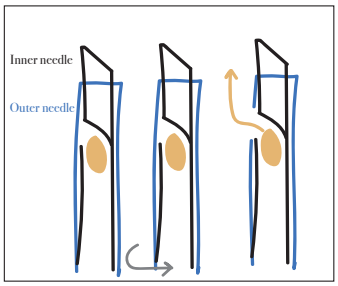
Fetal placement:
- It is more difficult to position the fetus correctly in mothers with a higher BMI

Needle:
- In the IFCIR registry it is shown that the complications are less with 19G needles than with 18G. Using a 20G needle will mean even less complications. This will be a real step forward.

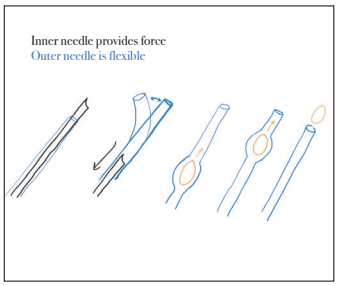
Appendix B

Generated ideas

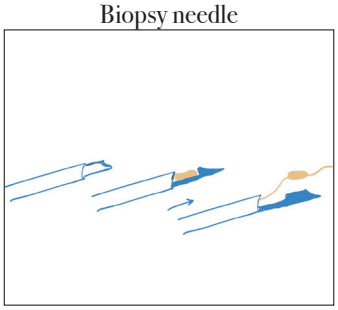
Balloon in needle



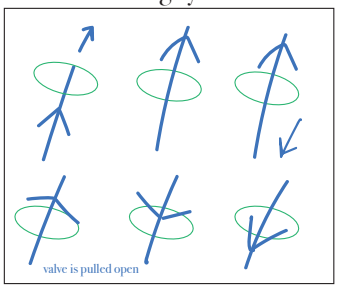
Flexible outer needle



Biopsy needle

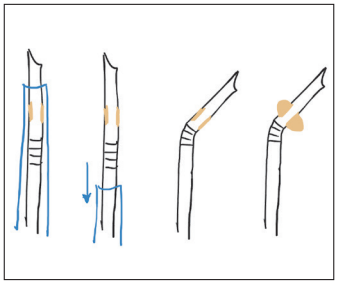


Barbing system

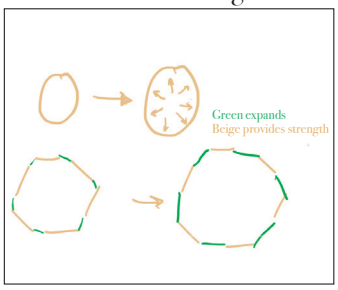


Balloon over needle

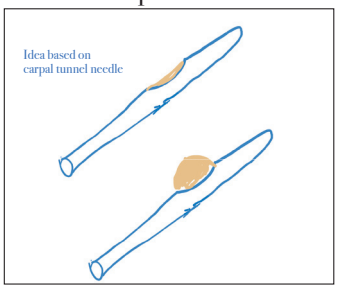
Flexible inner needle



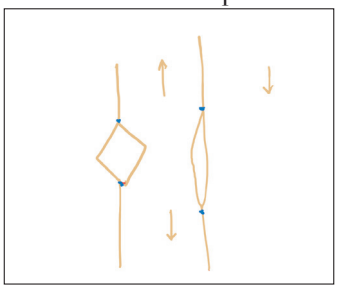
Balloon folding



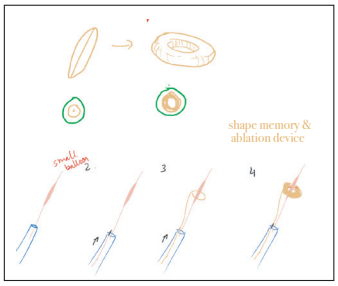
Carpal tunnel



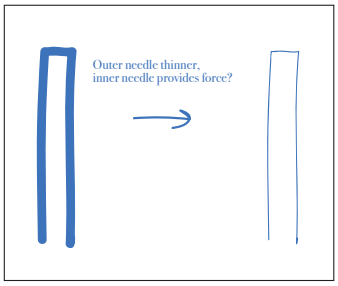
Diamond shape



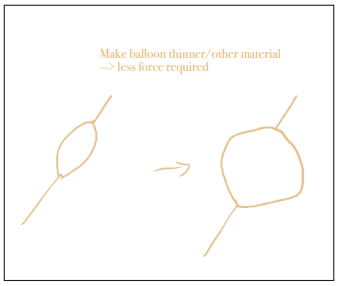
Donut balloon



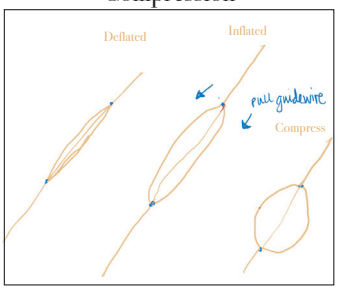
Needle material research



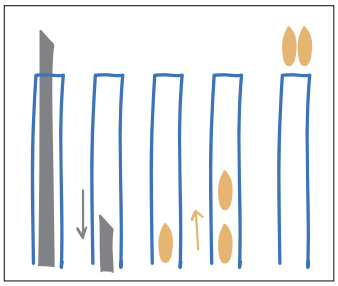
Balloon material research



Compression



Double balloon



Balloon optimization

Figure B.1: Generated ideas with illustrations for explanation

Appendix C

Concept 1 & 2

Concept 1: Compression

The compression started from the idea where a balloon would have some extra material in the length, and as the balloon is inflated it has not achieved its full diameter yet. To achieve extra circular diameters, the balloon would be compressed by pulling a guidewire. The idea was inspired on some existing medical instruments as shown at the right (Figure C.1). This idea led to two possible concepts.

The first concept was based on the compression of a solid material with the right properties. However, based on a SolidWorks simulation with a silicone rubber material it was determined that material compression at these dimensions will not cause the demanded material behavior. Therefore this concept was not worked out further.

The second concept possibility is based on the compression of multiple elements that would expand as shown in Figure C.2. However, a problem with the use of these so-called 'scoring' elements is that it would not provide a uniform pressure on the valve, which is an important requirement. Therefore the addition of an elastic material sleeve was explored. However, this all seemed far-fetched. Therefore an iteration on this concept was made. Braided nitinol has the ability to stretch and compress as shown in Figure C.3. Due to the thickness of nitinol and the use of such a structure, it is not likely that this would fit through a 20G needle, however by means of an iteration an interesting concept came of this.

In this concept, the tip of the outer needle consists of the braided nitinol material (Figure C.4). During puncturing, the inner needle provides sharpness and force just as it is happening right now. After puncture, the sharp inner needle is removed and the needle tip is positioned inside the valve. Optionally a guidewire is passed through the cannula beforehand which will help positioning. When positioned correct, the braided tip can be compressed which will allow for the material to expand in diameter and exert force on the aortic valve.

Key considerations to decide not to continue with this concept were the complexity, insecurity whether this would provide enough force and difficulties with controlling the shape. Next to that, the cannula would have to be able to position within the valve without causing any trauma, which is a task of which it is not sure whether it is possible.

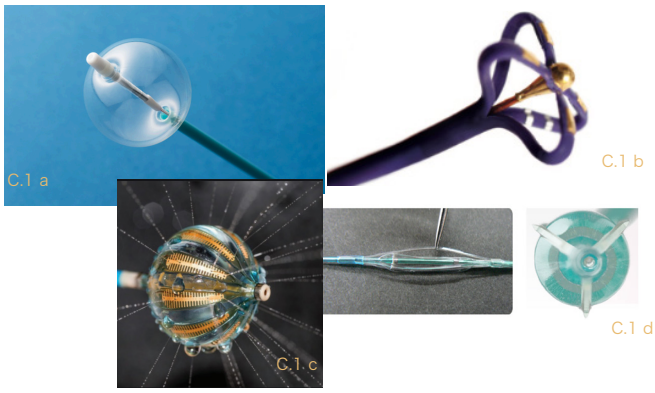


Figure C.1: Products that were used as inspiration for the idea. a) Satake HotBalloon™, b) Creganna Medical, mapping & ablation solutions. c) Biosense Webster's multi-electrode ablation balloxon. d) NSE Alpha balloon, NIPRO

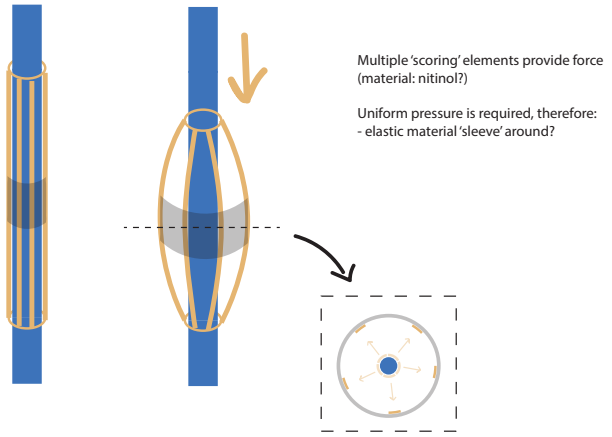


Figure C.2: First iteration for the compression concept.

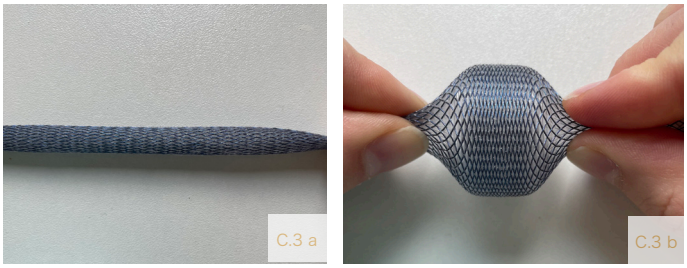


Figure C.3: Nitinol structure to illustrate stretching and compression behavior. a) fully stretched. b) fully compressed

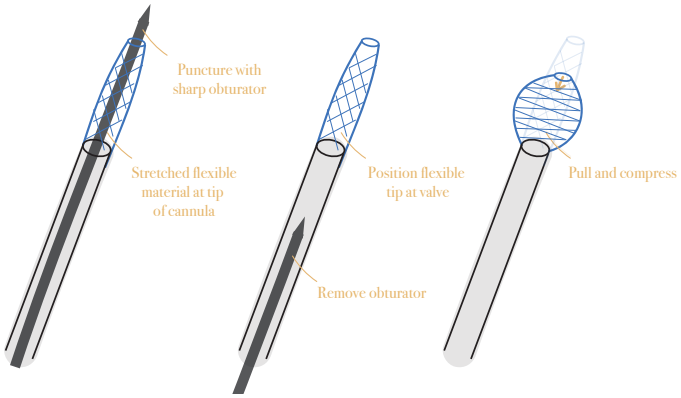


Figure C.4: Illustration of working principle of the 'compression' concept.

Concept 2: Double Balloon

The double balloon concept takes two small balloons as a starting point. The idea is that these two balloons together are able to reach the required 3 mm or more for dilatation, while upon insertion the balloons have a smaller crossing profile. To figure out whether this could work, research was done to the smallest balloon catheters. The idea was based on the NuMED Multi-Track™ which is developed for mitral dilatation, as is illustrated in Figure C.5 (B.Braun Interventional Systems Inc., 2020).

The concept of the Multi-Track catheter would be used, but changed towards the needs of FAV. The new concept would be that one of the guidewires is fixed to the coupling piece, while the second guidewire can slide through.However, te currently used guidewire is a 0.014" guidewire which equals 0.35 mm. Two of these guidewires parallel to eachother do not fit through the 20G cannula (Figure C.6). This would mean that smaller guidewires are needed.

The smallest balloons that could be found had a crossing profile of ± 0.5 mm. This means that the guidewire can not be larger than 0.1 mm (since the balloon always is advanced through the cannula while one guidewire is next to it). However, the problem with the found balloons is that they can only reach a diameter of 1 mm when the crossing profile is 0.5 mm (Orbus Neich Sapphire II Pro & SIS Medical NIC Nano Hydro). Therefore, both a very small guidewire and balloon would have to be designed since there are no suitable options currently on the market.

The final concept as shown in Figure C.7 is therefore difficult to realize. Some concerns regarding this concept are that the use of two seperate balloons complicates the procedure, since they have to be alligned perfectly for it to work. Next to that, the balloons would either have to have a half-cylindrical shape or the dilatation shape is oval. There is also an risk of the guidewire causing damage to the balloon when it is advanced through the cannula.

Lastly, an important consideration was that if a new balloon is designed with a smaller crossing profile, which is needed for this concept to work, it would be easier to just optimize 1 balloon catheter. Therefore, based on the dimensions and sizes, this concept would be very challenging.

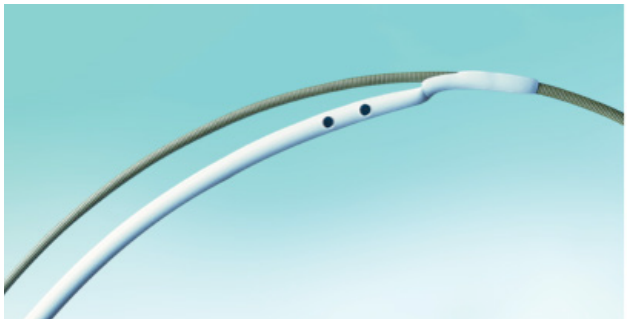


Figure C.5: NuMED Multi-Track™ by B.Braun. Source: B.Braun Interventional Systems Inc., 2020.

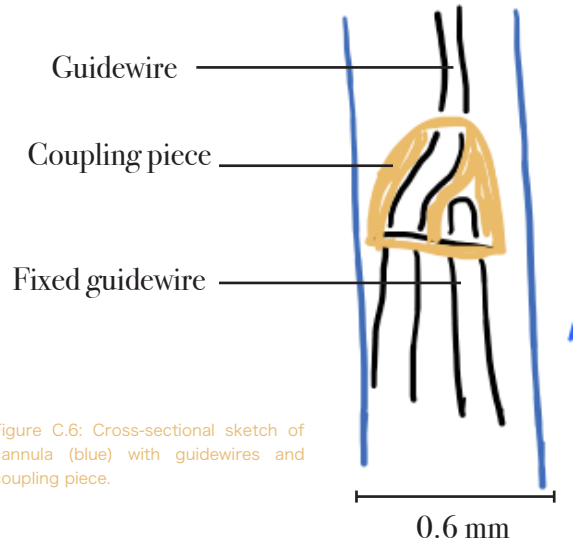


Figure C.6: Cross-sectional sketch of cannula (blue) with guidewires and coupling piece.

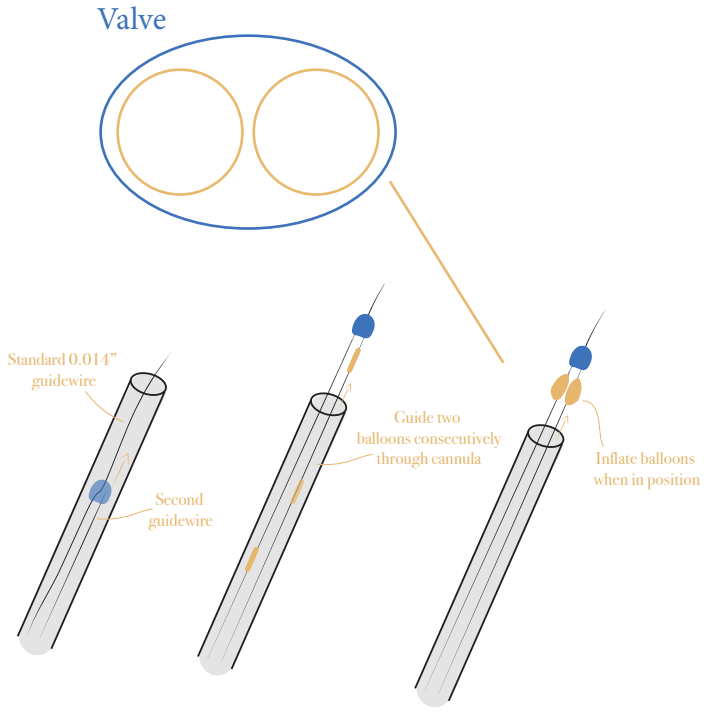


Figure C.7: Illustration of the working principle of the 'double balloon' concept.

Appendix D

Balloon folds

A quick search was done to figure out how many folds currently are applied to high pressure non-compliant balloons. This research is not exclusive, yet rather used for clarification on the current situation. As not many manufacturers provide information regarding this aspect of the balloon, not much data was found.

Table D.1
Overview of several non-compliant balloons with amount of folds related to diameter

Freeway 035 PTA balloon catheter, Eurocor Tech	
4 - 5 mm	4 fold
6 - 8 mm	5 fold
Passeo-35 PTA Balloon, Biotronik	
3 - 10 mm	5 fold
Senri® PTA Balloon Dilatation Catheter, Terumo	
2 - 6 mm	3 fold
7 - 8 mm	4 fold
Passeo-14 PTA Balloon, Biotronik	
1,5 - 4 mm	3 fold
Passeo-35 High Pressure PTA Balloon, Biotronik	
3 - 9 mm	3 fold
10 - 12 mm	5 fold
Everest PTCA catheter, Blue Medical	
1,5 - 4 mm	3 fold

Appendix E

Production parameters

This information is confidential as it describes the production procedure as developed in collaboration with MPT Europe. This datasheet shows the different parameters that were used for the iterative process of developing the balloon. If a balloon was succesful, it obtained the number of the attempt.

							Second pull			Heat setting				
	Nr	Temp (°C)	Time (sec)	Pressure (bar)	Pulling distance (mm)	Parison length (mm)	Pressure (bar)	Temp (°C)	Pulling distance (mm)	Temp (°C)	Time (sec)	Notes	Uitkomst	
day 1	1	80	200	24	10	5							Geen ballon, wel lucht door tube	
03-mei	2	90	200	30	14	5							kleine verdikking?	
mold 1	3	90	200	35	20	5						eerste microscoop foto	gebarsten, scheur in lengte	
	4	90	200	35	17	5						parison iets kleiner	gebarsten, scheur in lengte	
	5	90	200	35	14	5							gebarsten, scheur in lengte	
	6	90	120	30	7	5							niet gebarsten, kleine vorm verandering	
	7	90	120	35	7	5						microscoop foto	iets opgeblazen, geknapt	
	8	90	120	32	7	5							minder opgeblazen dan recept7, lengte geknapt	
	9	90	120	35	5	5							iets opgeblazen, niet geknapt, nog niet genoeg opgeblazen	
	10	90	120	38	5	5							vroeg geknapt, voor trekken	
	11	90	120	36	6	5							in lengte geknapt, druk omhoog of minder trekken	
	12	90	120	35	7	6						recept 7 reproduceren	lengte geknapt, iets opgeblazen (minder opgeblazen dan recept 7)	
	13	100	120	30	7	6							niet geknapt, vormverandering	
	14	110	120	30	7	4							BALLON	
	15	110	120	30	7	4						recept 14 reproduceren	ballon 2	
	16	110	120	30	8.5	4							ballon	
	17	110	120	30	12	4						meer kraaienpoten dan bij 16 door te veel strek	ballon	
	18	110	120	30	12	3							scheur in lengte, niet volledig gevormd ?	
day 2	19	110	120	30	12	4						herhaling recept 17	scheur in lengte, niet volledig gevormd ?	
04-mei	20	110	120	30	10	4						kraaivorming	ballon	dubbele wanddikte ± 0,075
	21	110	120	30	8	3.5	24	120	3	135	60	stappen toegevoegd	scheur bij eerste pull, parison te kort	
	22	110	120	30	8	4	24	120	3	135	60		scheur bij eerste pull	
	23	110	120	30	10	4	24	120	3	135	60	foto ballon in mal	ballon	dubbele wanddikte ± 0,04 gebruikt voor pleat test
	24	110	120	30	10	4	24	120	3	135	60	tweede pull langzamer	scheur bij eerste pull	
	25	110	120	30	10	4	24	120	3	135	60		scheur bij eerste pull	
	26	110	120	30	10	4	24	120	3	135	60		ballon	
	27	110	120	30	10	4	24	120	5	135	60	snelheid eerste pull van 150mm/s naar 100mm/s	scheur bij eerste pull	
	28	110	120	30	10	4	24	120	5	135	60	snelheid eerste pull van 150mm/s naar 200mm/s	scheur bij eerste pull	
	29	120	120	30	10	4.5	24	120	5	135	60	materiaal te warm	scheuren voor eerste pull	
	30	120	120	24	10	4	24	120	5	135	60		scheur bij eerste pull	
	31	110	120	30	10	5	24	120	5	135	60	mooi & strak, weinig kraaivorming	ballon	
mold 2														
	32	110	120	30	10	5	24	120	5	135	60	mold 2 ballondesign is 1 mm langer	scheur bij eerste pull	
	33	110	120	30	10	4.5	24	120	5	135	60		ballon	
	34	110	120	30	10	4.5	24	120	5	135	60		scheur bij eerste pull	
	35	110	120	30	10	4.5	24	120	5	135	60		ballon	
	36	110	120	30	10	4.5	24	120	5	135	60		ballon	
	37	113	120	30	10	4.5	24	120	6	145	60		scheur bij eerste pull	
	38	107	120	30	10	4.5	24	120	6	145	60		scheur bij eerste pull	
	39	110	120	26	10	4.5	24	120	6	145	60		niet genoeg geblazen, scheur bij heat set temp	
	40	110	120	28	10	4.5	24	120	6	145	60		niks geblazen	
	41	110	120	29	10	4.5	24	120	6	145	60		scheur bij eerste pull	
	42	110	120	34	10	4.5	24	120	6	145	60		plop bij opwarmen, wil al blazen bij opwarmen	
	43	110	120	32	10	4.5	24	120	6	145	60	mooi & strak, weinig kraaivorming	ballon	dubbele wanddikte ±0,037
	44	110	120	32	10	4.5	24	120	6	145	60		ballon	
	45	110	120	32	10	4.5	24	120	6	145	60		ballon	
	46	110	120	32	10	4.5	24	120	6	145	60		scheur bij eerste pull	
	47	110	120	32	10	4.5	24	120	6	145	60	luchtgaatje toegevoegd aan mal	scheur bij eerste pull	
	48	110	120	32	10	4.5	24	120	6	145	60		scheur bij eerste pull	
	49	110	120	33	10	4.5	24	120	6	145	60		plop bij opwarmen	
	50	107	120	33	10	4.5	24	120	6	145	60	kleine cone niet helemaal strak	ballon	
	mold 1													
day 3	51	107	120	33	10	4.5	24	120	6	145	60		plop bij opwarmen	
05-mei	52	107	120	33	10	4.5	24	120	6	145	60		scheur bij eerste pull	
	53	105	120	33	10	4.5	24	120	6	145	60	weinig kraaivorming	ballon	
	54	105	120	33	10	4.5	24	120	6	145	60		scheur bij eerste pull	
	55	105	120	33	10	4.5	24	120	6	145	60	meer kraaivorming	ballon	
	56	105	120	33	10	4	24	120	6	145	60		scheur bij eerste pull	
	57	105	120	33	10	4.5	24	120	6	145	60		scheur bij eerste pull	
	58	105	120	33	10	2	24	120	6	145	60		scheur bij eerste pull	
	59	105	120	33	10	4.5	24	120	6	145	60	kraaivorming 1 kant	ballon	
	60	105	120	33	10	4.5	24	120	6	145	60	minder kraaivorming	ballon	
	61	105	120	33	10	4.5	24	120	6	145	60		ballon	
	mold 2													
	62	105	120	33	10	4.5	24	120	6	145	60		ballon	
	63	105	120	33	10	4.5	24	120	6	145	60		scheur bij eerste pull	
	64	105	120	33	10	4.5	24	120	6	145	60		ballon	
	65	105	120	33	10	4.5	24	120	6	145	60		scheur bij eerste pull	
	66	105	120	33	10	4.5	24	120	6	145	60			

Appendix F

Prototyping materials

This table shows the materials that were considered for the production of the prototypes. To determine whether the material was suitable, the inner and outer diameter were reviewed, as well as the wall thickness and material. For the outer diameter, it had to be considered that the tube should have the ability to be stretched to an outer diameter of <0.6 mm. Wall thickness and material properties play a role in whether this can be achieved or not. The materials that are marked with an * are the materials that were eventually ordered. It was chosen to use 2 different materials with varying wall thicknesses. By doing this, the likelihood that one of them is usable is increased. The material selection was limited to the online availability of the supplier Nordson Medical. The item numbers refer to their material database.

Table F.1
Considered materials with corresponding properties

Material	Inner Diameter (mm)	Outer Diameter (mm)	Wall thickness (mm)	Item number	Expected wall thickness
Pebax 63D	0.406	0.914	0.254	115-0640	0.028
Pebax 70D	0.533	0.991	0.229	115-0881	0.029
Pebax 72D*	**0.559**	**0.813**	**0.127**	**115-0821**	**0.015**
Pebax 72D	0.457	0.965	0.254	115-1367	0.030
Pebax 72D*	**0.457**	**0.864**	**0.203**	**115-1366**	**0.023**
Nylon 12*	**0.419**	**0.851**	**0.216**	**115-0526**	**0.023**
Nylon 12	0.584	1.016	0.216	115-0529	0.029
Nylon 12*	**0.737**	**0.991**	**0.127**	**115-2588**	**0.018**
Nylon 12	0.406	0.660	0.127	115-2585	0.011
Pebax 72D				115-2584	
Pebax 72D	1.397	1.651	0.127	115-0578	0.033
Pebax 55D	0.737	0.991	0.127	115-2586	0.018

Note: Material properties (except for expected wall thickness) and item numbers refer to data retrieved from Nordson Medical (https://www.nordsonmedical.com)

The expected wall thickness of the balloon is also a very relevant property of the tubing. This was calculated based on the information of the inner and outer diameter and wall thickness. The material properties were left out of consideration in these calculations so it is not known whether the material will in reality be able to shape into this wall thickness. The expected wall thickness was calculated by using the following formulas:

In these calculations, it was assumed that the volume of the material stays the same. The length (h) is doubled, and the outer diameter of the balloon is 3.0 mm since that is the aimed balloon shape.

Based on these calculations, the values as shown in the Table above were acquired.

$$\pi * (rO_1^{\,2} - rI_1^{\,2}) * h_1 = V \quad (1)$$

$$\frac{V}{\pi * h_2} - rO_2^{\,2} = -rI_2^{\,2} \quad (2)$$

$$\sqrt{rO_2^{\,2} - \frac{V}{\pi * h_2}} = rI_2 \quad (3)$$

$$rO_2 - rI_2 = W_2 \quad (4)$$

where:

rO_1	= outer diameter of original tube
rI_1	= inner diameter of original tube
rO_2	= outer diameter of balloon
rI_2	= inner diameter of balloon
h_1	= length of tube
h_2	= length of balloon
V	= volume of material
W_2	= expected balloon wall thickness

Appendix G

Tested balloons

This table shows an overview of the balloons that were used for the different validation tests. The balloon numbers correspond to those in the datasheet in Appendix E: Production parameters.

Table G.1
Balloon numbers with indication of performed tests

Balloon nr	Clinical test	Mechanical test 1	Mechanical test 2	Mechanical test 3
17				
20		x		
33	x	x		
43	x	x		
44				
59	x	x		
60		x		
61	x	x		
62		x		
64		x		
45			x	
35			x	x
23			x	x
31			x	
53			x	x
26			x	
14			x	
16			x	
50			x	x
36			x	

Appendix H

Heart model

For the clinical validation test, a simplified model of the left ventricle of a fetus was made. The dimensions were based on literature (McElhinney et al., 2009; Luewan et al., 2011; Galindo et al., 2017). Table H.1 shows an overview of the measurements as described in this literature. These five key dimensions define the overall shape of the left ventricle. It is important to note that the values as provided by Luewan et al. (2011) are regarding a healthy fetal heart at 23 weeks of gestation. During the development of HLHS the left ventricle expands, and therefore it is understandable that their value for the diameter is lower.

Based on these measurements, the heart model with dimension as shown in Figure H.1 was produced. This was done by making the 3D model as also shown in Figure H.1 in SolidWorks. This model was then 3D printed with the Form 3 SLA printer. The material that was used is the Elastic 50A Resin of Formlabs. This is a flexible silicone like material with a low durometer and tensile strength (see Datasheet).

To allow for convenient use in the test set up, the heart model was printed on a square surface which allows for fixation by double sided tape and will keep the model in place during testing. See Figure H.2 for the printed heart models.

Table H.1
Data regarding LV dimensions from literature

	McElhinney et al., 2009	Luewan et al., 2011	Galindo et al., 2017
	HLHS	*Healthy*	*HLHS*
Aortic valve diameter	2.9 mm		2.7 mm
Mitral valve diameter			5.8 mm
Left ventricular inner diameter	12.6 mm	8.8 mm	10.5 mm
Left ventricular length	18.8 mm		16.1 mm
Wall thickness		2.2 mm	

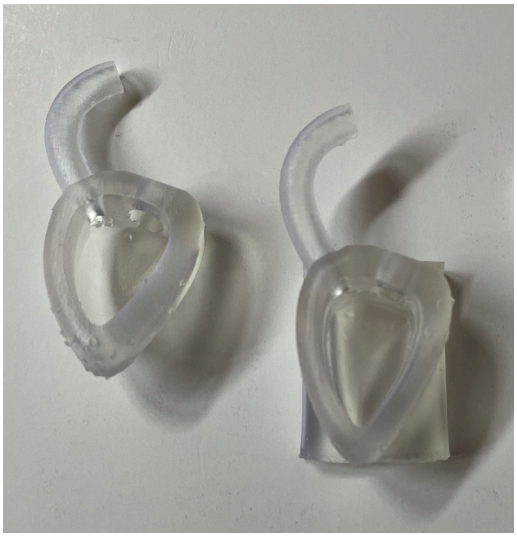


Figure H.2: 3D printed left ventricle models based on dimensions from literature. Without support square (left) and with support square (right).

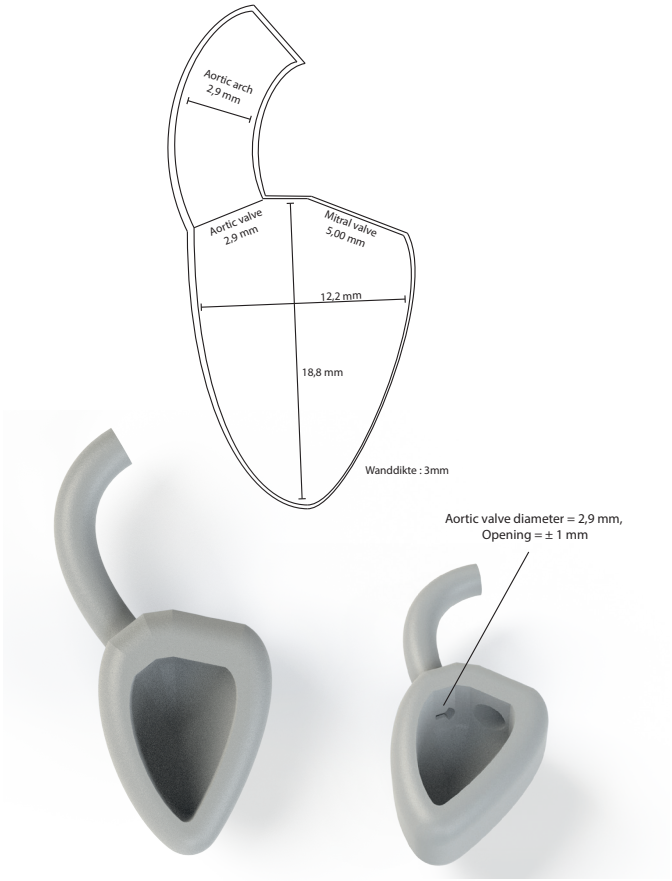


Figure H.1: Simplified heart model with dimensions and SolidWorks model.

Appendix I

Clinical test notes

Balloon 33

What	Yes/No	Notes
Advance balloon catheter through 18G needle	Yes	Advancing feels stable and smooth
Positioning in aortic valve	yes	Balloon needs to placed in center of marking. Needle requires slight retraction to allow for entire balloon to exert needle. Copper wire feels stiff so difficult with bend in aortic valve, normally this is not a problem.
Kinking or entrance mitral valve	No	
Inflation & deflation	Yes, 2 times	Inflates smoothly. At 1 bar deployment of balloon. Inflated up to 4 bar. Balloon is occluding valve totally. Rapid deflation.
Retraction through needle	No	Balloon could not be drawn vacuum entirely due to leaking connection system. Therefore retraction not possible

Balloon 43

What	Yes/No	Notes
Advance balloon catheter through 18G needle	Yes	
Positioning in aortic valve	yes	Little difference noticed regarding positioning between with/without guidewire through balloon. This one went easier due to more optimal needle placement. Steering mostly done through needle. Balloon only ahead.
Kinking or entrance mitral valve	No	
Inflation & deflation	Yes, 2 times	Inflates smoothly. At 1 bar deployment of balloon.
Retraction through needle	No	Balloon could not be drawn vacuum entirely due to leaking connection system. Therefore retraction not possible

Balloon 59

What	Yes/No	Notes
Advance balloon catheter through 18G needle	Yes	
Positioning in aortic valve	yes	Seems to fit more accurately than others. Balloon seems long in relation to LV. LV probably a bit smaller than in reality.
Kinking or entrance mitral valve	No	
Inflation & deflation	Yes	Inflates smoothly. At 1 bar deployment of balloon. Inflated up to 4 bar. Balloon is occluding valve totally. Air in inflation device. Deflation not smooth.
Retraction through needle	No	Balloon could not be drawn vacuum entirely due to leaking connection system. Therefore retraction not possible

Balloon 61

What	Yes/No	Notes
Advance balloon catheter through 18G needle	Yes	
Positioning in aortic valve	yes	Needle adjusted by retracting to give balloon enough space. Marking applied to balloon is useful, would want to see that on ultrasound. Entire balloon marked/coated is not preferred.
Kinking or entrance mitral valve	No	
Inflation & deflation	Yes	Deflation succusful, more vacuuum than others. Connection system works better now.
Retraction through needle	Yes	Due to successful vacuum, retraction was possible.

General notes

- Tip should not be longer than 15 mm
- Copper wire is too stiff, influences experience
- Retraction not tested properly
- Guidewire can be very thin and floppy, does not require force
- Steering mostly done by needle
- Model might be too small, therefore balloon is perceived to be too long
- Asymmetrical balloon is more difficult to position correctly