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Developing a realistic venous model for in-vitro application of the eduECMO trainer

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Declaration

I hereby declare that I have written this thesis independently. Only the sources and aids expressly named in the thesis have been used. I have marked as such any ideas taken over verbatim or in spirit.

Enschede, July 2th 2023

Place, Date Signature

Preface

Before you lies my master's thesis, marking the completion of my Master's in Biomedical Engineering at the University of Twente. Throughout my study I found myself more drawn towards the track medical device design, and after following the course 'Development of artificial internal organs' given by Jutta Arens, my curiosity regarding this research field grew. Once year later, I found myself getting the opportunity to finalize my study at the research group Engineering Organs Support Technologies of the department of Biomechanical Engineering at the University of Twente, under supervision of Jutta. I would like to thank Jutta not only for giving this opportunity, providing guidance and feedback throughout the thesis, but also for the warm welcome into the research group.

I would also like to thank Frank Halfwerk for providing me CT data and the accompanying software for segmentation, but also for the interesting conversations/discussions that let me think twice about certain topics. Furthermore, I would like to thank Gabriëlle Tuijthof for her feedback in the final phase of my master's thesis.

I would particularly like to thank Wytze Duinmeijer for being my daily supervisor. Aside from the support, weekly meetings, and all the feedback you provided me, I value the laughter and down-to-earth mindset. I am curious to see the further development of your PhD and what the future brings you.

Furthermore, I would like to thank Ana martins Costa for helping me in the blood lab, Quint Meinders for his support regarding activities in the Rapid Prototyping lab, and Danny van Galen as my (at the time) fellow graduate student for the fun conversations and weekly coffee breaks.

A special thanks to Nina Doorn and the whole research group CNPH for opening their office area to me and including me into their daily routine. I enjoyed working beside you.

Lastly, I want to thank my family and friends for the support throughout my study, especially with the rocky start I had. My mother would have been proud of who I have become.

Thank you for taking the time to read the preface and I hope you enjoy reading the rest of my thesis!

~ Seija van Lochem

Problem Definition

In critical cases where the cardiac and/or respiratory system of a patient no longer functions independently, Extracorporeal Membrane Oxygenation (ECMO) is often used. ECMO is a type of support system that allows the patient's body to recover. It is used as a last resort when other therapies are no longer feasible, as the procedure is invasive and highly complex: cannulas are inserted deep into the cardiovascular system to allow blood diversion to the ECMO system. The demand for ECMO treatment has increased over the past years, due to e.g. an aging population and the recent Covid-19 pandemic. Due to this increase, the need for innovation regarding ECMO treatment and cannulation techniques grows. It may also help to decrease the gap in clinical experience between personal in high- and low-volume ECMO centres, where the clinical demand is lower. These needs bring research challenges – such as new ways of cannula insertion, location and orientation, and the physiological response of the patient's circulation when insertion is applied –, but mainly ask for ways to train personnel. Hands-on ECMO simulators provide a suitable solution for such needs. Due to the current lack of high-fidelity ECMO simulators, most simulation-based training (SBT) is done through animal and cadaver experiments. The EOST-research group (University of Twente, Netherlands) is currently working on developing a SBT by creating a high-fidelity ECMO simulator, called the eduECMO. It will work as a practice device for physicians, nurses, and perfusionists for *in vitro* practicing of cannulation, and will make hemodynamic studies of the interaction between the ECMO system and a 'patient' more accessible. This simulator aims to include a realistic hands-on simulation environment of the cannulation path followed during VV-ECMO that represents anatomy and physiology of the vascular system, is not yet available.

Currently, no research specifies on developing realistic venous systems in ECMO simulators for cannulation training and realistic hemodynamic purposes [1]. Therefore, the aim of this master thesis is to develop a venous model that represents the anatomy and hemodynamics of the human venous system around cannulation sites of the eduECMO trainer. Parallel to this thesis, the eduECMO project will further focus on the development of components of the eduECMO, such as improving the mock cannulation sites. The initial focus is on VV-ECMO application, due to the large differences between types of ECMO and the increased demand of VV-ECMO in recent years (due to e.g., Covid-19). As this thesis is part of the eduECMO project, the development of the venous model will have to comply with current and future requirements of the eduECMO. Therefore, it must be:

- Applicable for VV-ECMO application,
- Easily adaptable for other applications that are desired in the future,
- Compatible with components of the eduECMO such as the mock cannulation sites,
- Highly accurate anatomical shape of the venous model as part of achieving high-fidelity,
- Incorporate the hemodynamics of the native vascular system,
- Adaptable to implementation of varying patient geometries,
- Time- and cost-efficiently to produce.

Abstract

Extracorporeal Membrane Oxygenation (ECMO) is a last resort treatment for when the cardiac and/or respiratory system of a patient no longer functions independently. With an increasing demand for ECMO treatment, a growing need for innovation arises, particularly ways to train personnel. Hands-on ECMO simulators provide a suitable solution for such needs, however there is a current lack of high-fidelity ECMO simulators.

This research designed and developed a venous model that represents the human anatomy and hemodynamics around cannulation sites, for future implementation into a high-fidelity VV-ECMO simulator. To create a realistic simulation environment, a thorough literature review was conducted to set a foundation for the model. CT patient data was used, to incorporate complex geometry of veins and cardiac structures into the model. To realize this, a segmentation method for veins was developed. A relatively easy and cheap production method is desired, so parts can easily be replaced whilst simulations remain affordable. This has resulted in using a 3D SLA printing method. Verification was done by testing the venous model against its functions, and through a survey gathering the opinion of experts (key-users).

The final product consists of seven components that together form the venous model. It contains a cannulation path which is used during simulation, and a supporting circuit for the hemodynamics. Testing confirmed that most components satisfy their requirements. However, during tests was found that the material used for the cannulation path appears not suitable for hands-on simulations, preventing hemodynamic tests to be carried out properly. This is because the material in combination with the thin-wall design is too brittle, causing the cannulation path to easily tear when it bends/folds or when local pressure is applied. First steps and recommendations for finding a more suitable material were made. The collective input of experts confirmed the importance of certain properties of the design and provided recommendations where to focus on in future work.

This thesis provides the literature foundation, verified design, and initial prototype of the venous model, thereby taking a significant stride towards realizing high-fidelity ECMO simulators.

Keywords

Extracorporeal membrane oxygenation (ECMO); Veno-venous (VV); hemodynamics; venous model; realistic simulation environment;

Content

1 Introduction

The vascular circulation is a crucial in providing the human body with needed substances and helps to dispose waist substances. In this circulation, the heart works as a pump to provide the driving force for blood flow and the lungs as a ‘membrane contactor’ for exchanging carbon dioxide and oxygen. When a patient suffers from lung and/or heart failure, the vascular circulation is affected which can lead to organ failure throughout the entire body. If this occurs, and long-term treatment is needed, Extracorporeal Membrane Oxygenation (ECMO) systems can be used as last resort [2]. These systems can temporarily take over the function of the lungs and/or heart fully or partially. This system allows recovery as it reduces the stress on the lungs and/or heart. According to the Extracorporeal Life Support Organization (ELSO) registry, ECMO has been used on more than 192,000 patients worldwide in 2022 [3]. This patient group is roughly divided into 25.0 % neonates, 18.4 % children, and 56.6 % adults. Since billions of people suffer from diseases – such as acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and heart muscle disease (decompensated cardiomyopathy), and with an aging population and the recent Covid-19 pandemic – the need for ECMO support increases even more [4].

This chapter will cover the background information needed to formulate objectives of this thesis. This includes the current ECMO system & cannulation methods, and the anatomy and physiology of the human vascular circulation.

1.1 Current ECMO system & cannulation methods

The ECMO system is used as a supportive therapy. In each type of ECMO treatment, deoxygenated blood is drawn out of the venous vascular system, led through several components of the ECMO system, and put back into either the venous or arterial vascular system [5]. This system consists of a pump supporting or maintaining the blood flow, an oxygenator with gas supply exchanging carbon dioxide and oxygen with the blood, cannulas to draw blood from and return blood to the body, and tubing to connect the components. The term ‘cannulation’ refers to inserting canulae into the blood vessel so it can travel through the vascular system until a desired location is reached. This is done to connect the ECMO system with a patient’s native circulation. A cannula is a catheter with a relatively large diameter that is directly inserted into a large vessel. Insertion is typically done under guidance of echography.

There are roughly two types of ECMO: Veno-arterial (VA) ECMO and veno-venous (VV) ECMO. The VA-ECMO provides both respiratory and hemodynamic support, whereas the VV-ECMO only provides respiratory support [6]. This thesis focusses on VV-ECMO. There are different cannulation methods that can be used to achieve VV-ECMO treatment. A commonly used method inserts a single-lumen cannula into the femoral vein that drains deoxygenated blood from the Inferior Vena Cava(s). To return blood into the Right Atrium, a second single-lumen cannula is inserted into the right internal jugular vein (IJV) [7, 8]. Another commonly used method used a dual-lumen cannula that allows parallel

drainage and return as two lumina, wrapped in one tubing. This cannula gets inserted into the right IJV, drains blood from the Vana Cava(s) and returns it into the Right Atrium [2]. To improve patient outcome during VV-ECMO support, the ProtekDuo cannula was introduced in recent years. It is a uniquely shaped dual-lumen cannula (inserted into the right IJV), that enhances blood flow dynamics for an efficient way of draining blood near the Right Atrium and returning it into the pulmonary artery [9]. Figure 1-1 gives a schematic visualization of types of cannulation methods used for VV-ECMO.

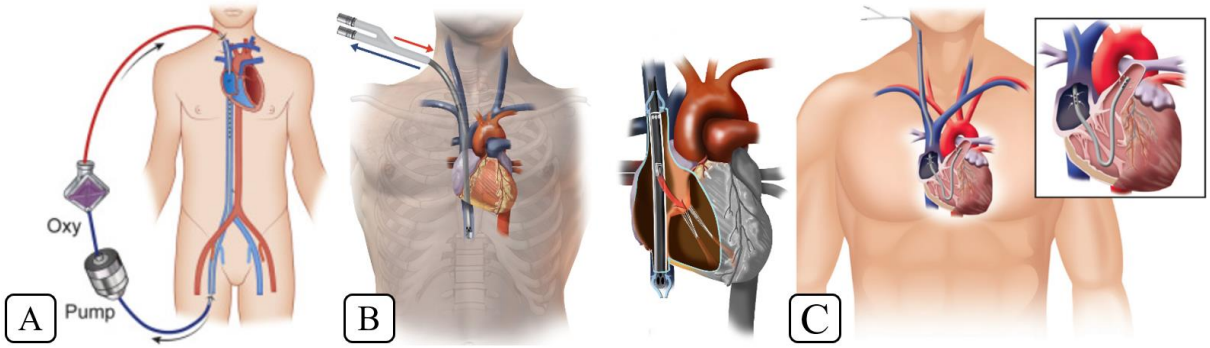

Figure 1-1: Type of cannulation methods for veno-venous (VV) ECMO treatment. (A) Femoral-jugular cannulation method where single-lumen cannulas are used to drain blood from the Inferior Vena Cava and returned into the Right Atrium [10]. (B) Classic dual-lumen cannula that drains blood from the Vena Cava(s) and returns it into the Right Atrium [11]. (C) ProtekDuo cannula drains blood near the Right Atrium and returns it into the pulmonary artery [9].

The oxygenated blood returning from the ECMO system gets mixed with the venous blood coming from the native circulation. VV-ECMO should not influence the hemodynamics of the native circulation, because the input cannula extracts an equal amount of blood from the body at the same location as that the output cannula returns blood [2]. Since VV-ECMO support relies on the patient's own circulation, it should not be used in case of multi-organ failure [7].

1.2 Properties of blood vessels

Blood vessels are active and dynamic organs, capable of contracting and expanding. Their main goal is to transport blood throughout the body. Most blood vessels share a similar structure consisting of three tissue layers containing different properties [12]. All these layers and properties can be roughly simplified into four building blocks that are used to distinguish blood vessels [13]. Endothelial cells form a single continuous layer that ensures a smooth surface and tries to prevent adhesion or thrombosis. Elastic fibres are a rubber-like material that accounts for the flexibility of a vessel. The more elastic fibres a vessel has, the less rigid it is. Collagen fibres are quite rigid as their main function is providing structure and strength to the vessel. Elastic and collagen fibres form a network, also helping to maintain flow direction. Vascular smooth muscle cells (VSMCs) exert primarily tension on an actively contracting blood vessel. The arrangement of these building blocks varies per blood vessel type as shown in Figure 1-2.

Blood vessels can be roughly categorized into arteries (arterial vessels both elastic and muscular, and arterioles), capillary vessels, and veins (venous vessels and venules) [12]. Since this thesis is focused on the veins, these will be highlighted. Veins transport deoxygenated blood. They carry waste products that need to be removed from the body, like carbon dioxide and other metabolic waste products. The big veins are called venous vessels and smaller vessels which culminate in these venous vessels are the venules. To support and maintain the blood flow unidirectionally, veins usually have venous valves.

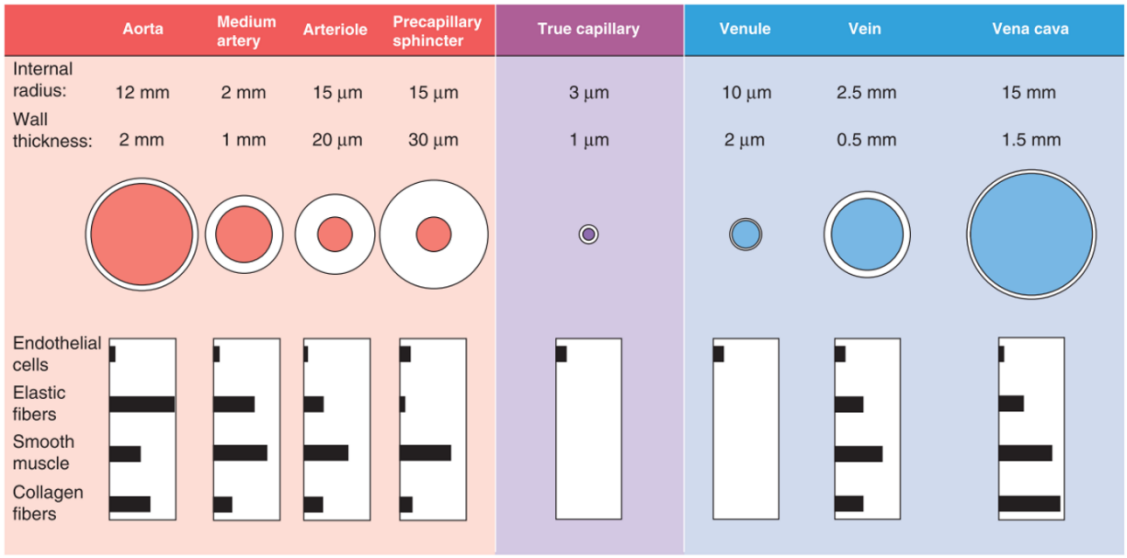

Figure 1-2: Overview of the variation in properties between blood vessels [13].

1.3 General physiology of the human vascular track

The physical behaviour of the cardiovascular circulation is called 'Hemodynamics', and can be used to understand the physiology of the cardiovascular system [13]. The cardiovascular system can be roughly divided into three basic functional parts; the heart functioning as the pump, the blood vessels work as a partially elastic tubing network throughout the body, and the blood is the liquid that circulates through this system.

1.3.1 Modelling the vascular track (Ohm's law)

To express the cardiovascular system mathematically, a modelling method can be used where all elements are described as a direct current (DC) electrical circuit (without the pulsatile characteristic of the heart). The electrical current represents the blood flow, and the voltages represent the blood pressures [14]. Ohm's law of hydrodynamics can be used to simply express the physiological workings of the vascular track [13]. Ohm's law for hydrodynamics reads as followed:

Equation 1-1: Ohm's Law of hydrodynamics.

$$\Delta P = Q \cdot R$$

with pressure difference [ΔP] between an upstream and downstream point [P_1, P_2] (mmHg), the blood flow [Q] (L/min) and the resistance [R] (Ω) between two points. This law holds at any instant in time, as long as the resistance is constant and the tubes are rigid, see Figure 3-1.

- The *pressure difference* between the beginning (the Aorta) and ending (the Vena Cava) of the systemic circulation is relatively constant over time (at rest). The flow and resistance, however, vary over time and are dependent on several parameters that will be discussed later in section 3.1.
- The *blood flow rate* can also be referred to as the cardiac output, which is the stroke volume (volume per heartbeat) times the heart rate (beats per minute).
- The *resistance* of a single vessel is for now considered to be a rigid tube with constant dimensions. Resistance is dependent on the relative arrangement of vessels with respect to each other, and the vessel radius. In reality, blood vessels are dynamic tubes with varying dimensions. The effect thereof on the hemodynamics will be discussed later (see section 3.1).

1.4 The heart

The heart is one of the most complex and important muscles in the human body as it generates the driving force of blood flow. It can be divided into a left and right side, both containing an atrium (inlet) and ventricle (outlet), see Figure 1-3.

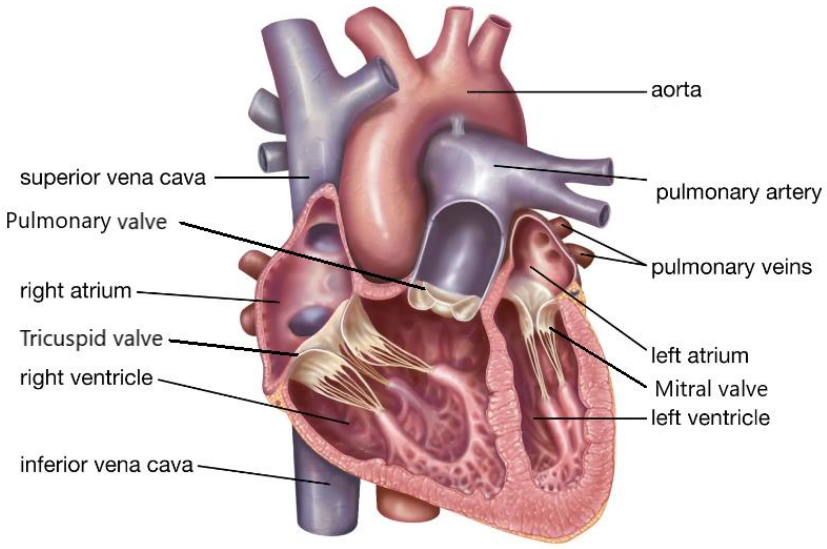

Figure 1-3: Animation of the human heart. Adjusted image from Encyclopaedia Britannica, Inc. [15].

The cardiac cycle creates the blood flow. The cycle moves through a sequence of mechanical events that are electrically actuated, but is commonly divided into the systolic and diastolic phase [13]. It starts with the *systole* – when the ventricles contract and blood is pushed out of the heart at a high velocity – followed by the *diastole* – when the ventricles are relaxed and are filled with blood again. The repetition of these phases causes the non-steady, pulsatile behaviour of blood flow. The systole occupies approximately 37.5 % of the cycle and the diastole approximately 62.5 % (based on a heart rate of 75 beats per minute) [13].

To create pressure inside a ventricle and to ensure unidirectional flow, two types of valves are found in the heart. The atrioventricular valves (Mitral and Tricuspid) divide the atria from the ventricles, and the semilunar valves (Aortic and Pulmonary) divide the ventricles from the connected arteries [16]. Atrioventricular valves are larger valves, made of thin, elastic flaps of tissue called leaflets. For support and to prevent prolapse, they are attached to the ventricle walls with fibrous cords. Semilunar valves are smaller valves, made of three slightly thicker leaflets. These valves are more similar to venous valves than to atrioventricular valves [13].

2 Objectives

The goal of this thesis is to develop a venous model that represents the anatomy and hemodynamics of the human venous system around cannulation sites of the eduECMO trainer, specifically for VV-ECMO. The venous model will consist of a cannulation path that represents the simulation environment, which is physically used by users. Other components of the venous model shall contribute to creating and maintaining this simulation environment.

A realistic simulation environment means mimicking the native venous system around cannulation sites until were cannulas travel to for blood draining/returning. The venous model should therefore:

- Incorporate the complex geometry of the parts of the vascular system that lie on the cannulation path. This includes large veins, the right side of the heart (hereinafter: right heart) with accompanying heart valves, and a part of the pulmonary artery. To realise this, CT patient data is provided with accompanying software for segmentation.
- Mimic hemodynamic properties. As described in section 1.3, important parameters to incorporate are pressure, flow, and resistance. Since the heart creates a pulsatile flow, compliance is another parameter to be considered. To preserve the hemodynamics, the venous model should be fluid tight. Furthermore, the working fluid has ideally properties representing blood. Elaboration of these properties is further discussed in section 3.1: The fundamentals.
- Have realistic behaviour of the cannulation path. This includes vessel behaviour such as flexibility of the vessel walls during a cannulation procedure, but also includes the contracting movement of the right heart.

The cannulation path of the venous model will physically be used by users during a simulation. This creates the potential risk for the cannulation path of getting punctured and/or damaged during use. A relatively easy, time- and cost-effective production method is therefore required to produce the cannulation path, and to ensure easy and quick replacement of parts whilst simulations remain cost effective.

To avoid potential complications that typically arise in custom-made designs, prefabricated parts will be considered for certain components of the venous model, only if these prefabricated parts meet all requirements, are compatible with other components, and are a cost-effective choice.

This thesis aims to develop a first version of the venous model with incorporated hemodynamics, to establish a foundation for future work of the eduECMO project. This report describes the iterative process of designing, developing, and verifying this thesis project. Prior to this process, a thorough literature review must be conducted to set a foundation for this model. After the foundation, the development methodology will be elucidated, as described in section 4.1, and this methodology is followed until the final product design is tested and verified. The results will thereafter be presented and discussed. The report is finally concluded, and prospects for future work will be described.

3 Fundamentals and state of the art

This chapter was created to gain further insight into the field of interest. Section 3.1 describes the hemodynamics of the vascular track in more detail, where important laws are used for a better understanding. This is followed by section 3.2 that describes the current state of the art and useful methods. How this all will be beneficial for this thesis will be discussed and concluded in the end.

3.1 Fundamentals

The hemodynamics of the vascular track as described in section 1.3.1 uses a simplified situation with assumptions of a rigid tube with a constant diameter. In reality, blood vessels are more complex. They vary in length, diameter, and rigidness. To create a more realistic representation of what occurs in blood vessels, the relationship between R, ΔP and Q – see Ohm's law (Equation 1-1) – will be further discussed. Finally, the properties of blood will be described.

3.1.1 Resistance

The *hydraulic resistance*, [R_H] (Ω), is a parameter that influences pressure and flow throughout the circulation. It defines the resistance to flow, and since the vascular system is a pressure-driven flow, this resistance can be described by the law of Hagen-Poiseuille [13].

Equation 3-1: Corollary of Hagen-Poiseuille's law.

$$R = \frac{8\mu L}{\pi r^4}$$

With the radius of the vessel [r] (mm), with $\pi r^4 = A^2$, the cross-sectional area of the tube [A] in mm^2, the viscosity [μ] (Pa · s), and the length of the vessel [L] (mm). Figure 3-1 (A) visualizes these parameters in a vessel. The resistance is proportional to the vessel radius to the fourth power and therefore, the vessel radius is an important parameter, as can be obtained from Equation 3-1.

The principle of vessels branching is a common phenomenon in the vascular system that influences the hydraulic resistance. A well-known example is the capillary bed. E.g., if an arteriole branches out into a capillary bed where multiple capillaries are lined up parallel to each other, the resistance decreases. A relation of this capillary bed can be made with electrical circuits, where parallel paths reduce the resistance whereas serial paths increase the resistance. As visualized in Figure 3-1 (B) – and taking Equation 1-1 into account – branching of vessels creates a resistance that causes a pressure drop in the vascular track. This form of resistance, created by the branching of vessels, will be referred to as the *peripheral resistance* [R_P] (Ω), since the accumulated cross-sectional area of a type of vessel increases as it moves further away from the heart.

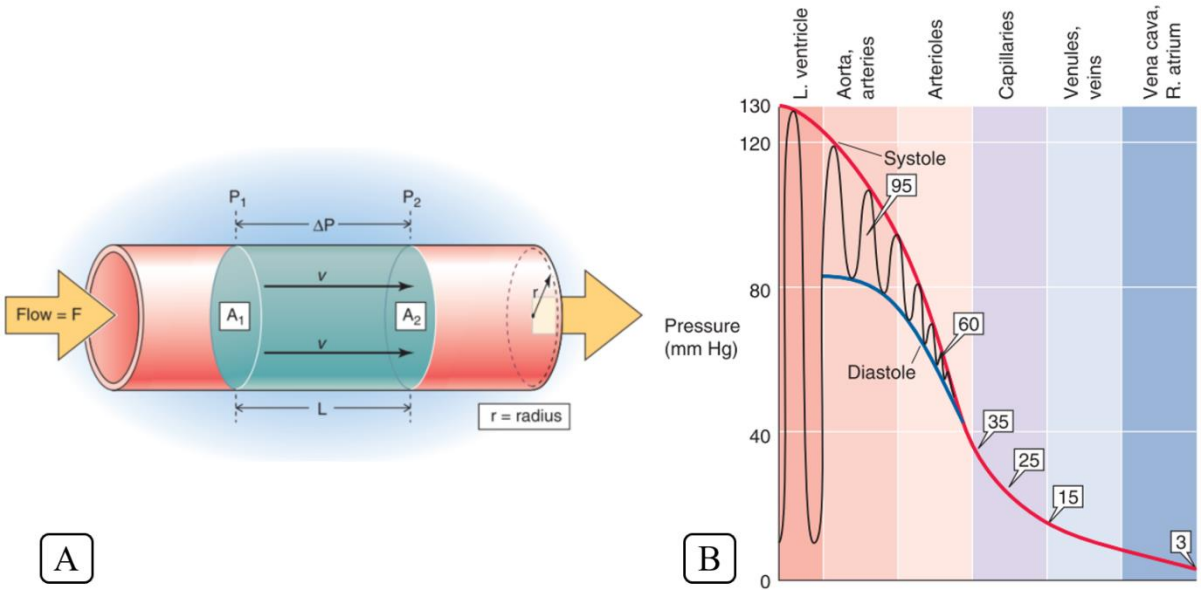

Figure 3-1: (A) Hydrodynamics of fluid flow through a straight tube [13].
(B) Pressure profile of the systemic circulation. The boxed numbers indicate the mean pressure [13].

During the branching of vessels, some frictional heat gets created between the particles in the blood and between the vessel walls and the blood [17]. Heat formation costs energy and cannot be converted back into pressure. Therefore, it contributes to the overall pressure drop. This form of pressure is called viscous flow pressure [P_V] (mmHg), but is considered as lost energy [17]. The assumption was made that this lost energy can be neglected as it will not play a significant role in the venous model since the accumulated cross-sectional area will not change as much as in the native vascular system.

3.1.2 Pressures

To understand the physics of energy conservation along a streamline, Bernoulli's law can be used [18]. A streamline is the path of a single fluid-particle through a vessel. Usually, two points on the streamline are compared.

Equation 3-2: Bernoulli's law.

$$\frac{1}{2}\rho v^2 + \rho g h + P = \text{constant} \rightarrow P_D + P_H + P_S = \text{constant}$$

With the velocity [v] (m/s), the density of the fluid [ρ] (kg/m^3), the acceleration due to gravity [g] (m/s^2), the height of the centre of the tube relative to a certain ground [h] (mm), and the pressure [P] (Pa). This law is built out of the following three terms:

- Dynamic pressure, [P_D] (mmHg), which represents the fluid kinetic energy (KE) per volume, as $KE = \frac{1}{2}\rho v^2$.
- Hydrostatic pressure, [P_H] (mmHg), which is pressure exerted by the fluid that elevates to a certain hight above a reference level, due to gravity.
- Static pressure, [P_S] (mmHg), which is the pressure of the fluid. This pressure is present even when there is no flow.

Bernoulli's law assumes that the working fluid is incompressible, meaning that the mass flow rate remains constant throughout the system as the mass must always be conserved. With a constant mass, the

law of continuity can be applied which states that the mass must always be preserved throughout the system. This can be applied to calculate certain parameters.

Equation 3-3: Law of Continuity

$$A_1 \cdot v_1 = A_2 \cdot v_2 \ (= Q) \rightarrow v_2 = \frac{A_1}{A_2} \cdot v_1$$

Figure 3-2 shows how this law translates into a real situation, in where 'the Bernoulli effect' occurs [13]. In this example a tube narrows its cross-sectional area to half the diameter of that of the two ends. The velocity in this middle part ([v_2]) must increase to a four-fold to maintain continuity (see Equation 3-3). This is because the flowrate of a certain mass must always be the same at any location in the system for an incompressible fluid [13]. Looking at Bernoulli's law, an increase of v_2 relative to v_1 causes a pressure drop between point 1 and 2 ($P_1 > P_2$). To minimize this effect, the radius throughout a system should change as little as possible.

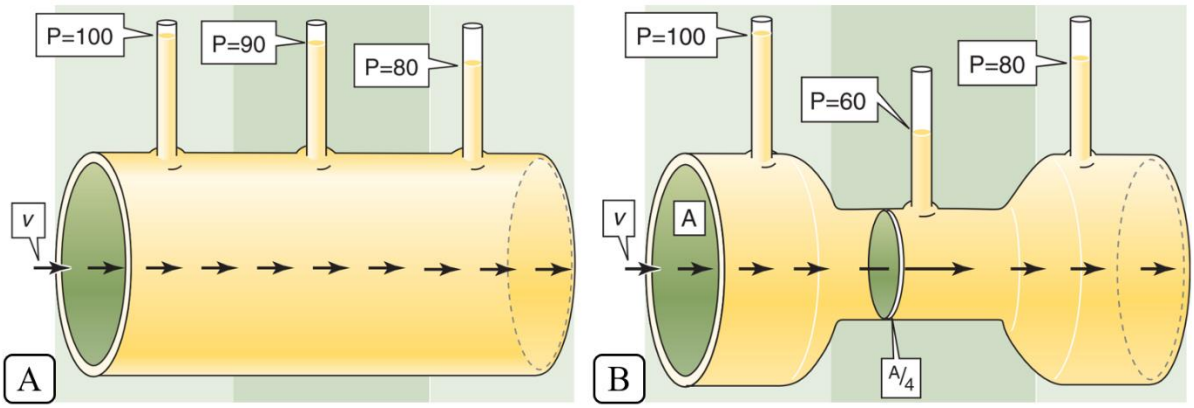

Figure 3-2: Bernoulli's effect.
(A) A tube with constant radius where the pressure decreases linearly along the length of the tube. (B) Same tube, but now with a constriction in the middle that reduces the pressure [13].

3.1.3 Flow pattern of venous system

For both the law of Poiseuille and Bernoulli (Equation 3-1 and Equation 3-2), the flow must be laminar. Laminar flow is defined by a fluid following a smooth path throughout a system. Flow through the vascular system is considered laminar if the Reynolds number [*Re*] (-) stays within a range of 10 to 2000. In the venous system, *Re* is generally low due to a typically large radius and slower flow velocity compared to arteries [13]. With this knowledge, the flow will be considered laminar in this thesis. Note that factors such as obstructions or differences in flowrate/radius can influence the flow pattern.

3.1.4 Properties of blood

The previously used laws to describe hemodynamics (Equation 3-1 and Equation 3-2) are only applicable if the working fluid is a Newtonian fluid, meaning that it has a constant viscosity. Blood, however, is a non-Newtonian fluid. This is partly due to viscoelastic properties which are dependent on elastic behaviour of red blood cells [19]. Newton's law describes viscosity as shear stress divided by shear rate. If this relation is linear, a fluid has a steady viscosity, and thus Newtonian behaviour. Figure 3-3 shows this relationship for (among others) blood, and that blood has a steady constant viscosity once the flow rate is high enough. This shows that blood can behave as a Newtonian fluid.

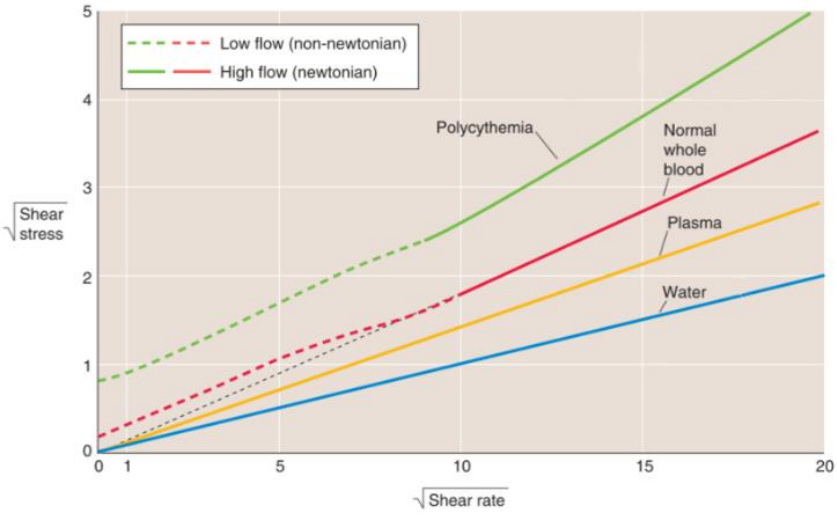

Figure 3-3: The viscosity of fluids based on Newton's law. The relation is shown for Polycythemia (in case of excessive red blood cell (RBC) production), normal whole blood, plasma (0 % RBCs), and water. Adjusted image from M. Walter et al. [13].

Aside from the flowrate, the viscosity of blood is dependent on: fibrinogen concentration, hematocrit, the vessel radius, and temperature [13]. Fibrinogen is a protein that influences the viscosity through interaction with red blood cells (RBCs). Hematocrit is the ratio of RBCs to the total blood volume, which varies per person [20]. For a realistic, but easy to implement simulation environment, a Newtonian fluid with a comparable viscosity to blood should be used in the venous model. Certain requirements must be met to achieve this:

- The vascular track relevant for cannulation contains only vessels with a radius > 1 mm, see Figure 3-4 (A).
- The average blood flow of a healthy adult is 4 – 5 L/min at rest [13]. As shown in Figure 3-4 (B), the flow must be > 2.4 L/min (40 L/min), for a linear shear stress to shear rate relationship.
- To ensure a steady temperature, this must be live monitored.

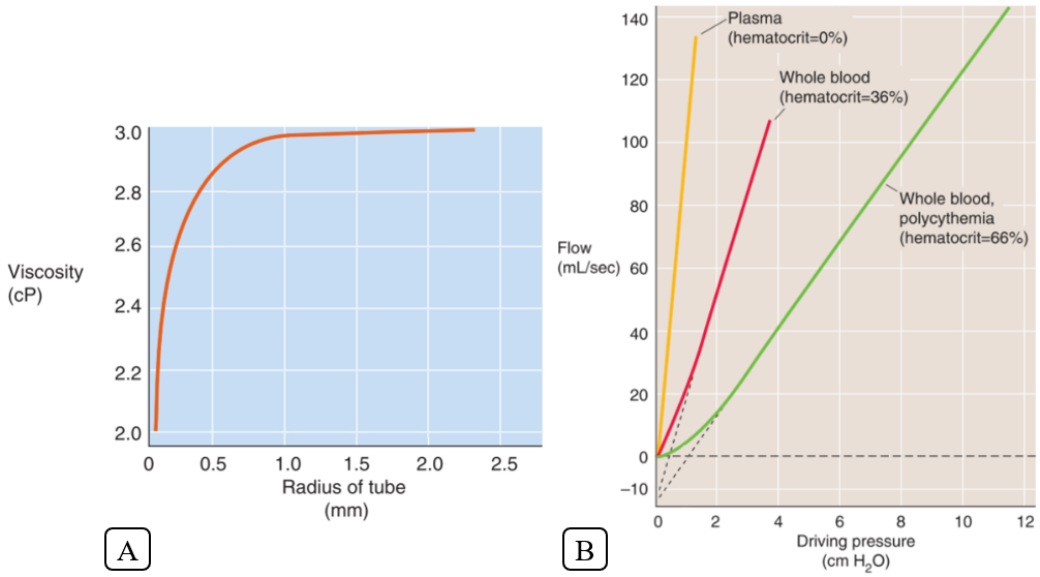

Figure 3-4: (A) Viscosity-radius slope that shows the viscosity reaches equilibrium once the radius is > 1 mm. (B) Flow-pressure graph that shows a linear slope once a certain threshold has been reached. Adjusted images from M. Walter et al. [13].

3.1.5 Biomechanical properties of veins

Because the mechanical behaviour of vessels is highly dependent of situation-specific factors such as age and health, there are large varieties in mechanical properties between individuals. This makes it hard defining reliable metric values for these properties. However, an indication of a vessel's behaviour can be made based on the ratio of building-block properties, see section 1.2. Figure 1-2 gives an indication of this ratio, as this ratio also varies between individuals. This shows that large veins such as the Vena Cava (VC) have thin walls with a high percentage of VSMCs, and a higher percentage of rigid collagen fibres to elastic fibres [13].

Two factors that constantly influence a vessel's behaviour are *stress* and *strain*. Stress describes the tension in a material due to transmural pressures, [P_T] (mmHg). The assumption is made that the wall thickness is constant for tension and stress to be the same. P_T defines the difference between the internal and external forces applied on a vessel's wall [13]. Strain describes the deformation of a material, the amount a vessel can stretch, due to stress. Therefore, strain can be used as an indicator for the relative volume (%). The linear relationship of stress and strain is called the *Elastic* or *Young's Modulus* (MPa) [21]. After a certain tipping point, this relationship is no longer linear, meaning the material is plastically deforming. During this phase, the material reaches its maximal stress capacity, which is defined as the *Ultimate tensile strength* (MPa) of a material. The moment the material fractures due to the applied forces, is commonly expressed with *elongation at break* (%), which indicates a material's ability to deform without failure [21]. Figure 3-5 shows a pressure-volume diagram that visualizes the dependency of the vessel's radius on P_T. The slope of this diagram represents the compliance. Compliance is an index of distensibility, which describes a vessel's ability to expand and contract throughout the cardiac cycle [22]. Since stress and strain are indicators for the relative volume and P_T, the Young's Modulus can be used as an indicator for compliance.

Figure 3-5 shows that the VC initially fills itself with blood over a wide radius-range before any stress develops (linear slope). This makes the VC initially look highly compliant. This initial rise of relative volume is in line with the fact that the VCs volume decreases with 20 % – 50 %, if it is removed from the body (meaning there is no P_T) [23]. However, once it is completely filled, the radius of the VC hardly changes while the P_T continues to build up (curved slope in Figure 3-5 A). This results in a stress build up that is applied on the VC's wall. This helps prevent excessive increases in venous pressure, even during e.g. exercise or change in body position.

The relationship between biomechanical and material properties is explained above. When looking for a material that can be used to mimic large veins such as the VC, the material should have the following properties:

- A low Young's modulus and ultimate tensile strength, to mimic the VC's ability to deform when pressure is applied (high compliance). Note however that the overall venous pressure is considered low and pressure differences are nihil, as shown in Figure 3-1 (right). This means that compliance should hardly be visible in the venous model. For an example of this, see Annex B Figure 12-1.
- A high elongation at break, so it can withstand lots of stress before rupturing, just like the VC.

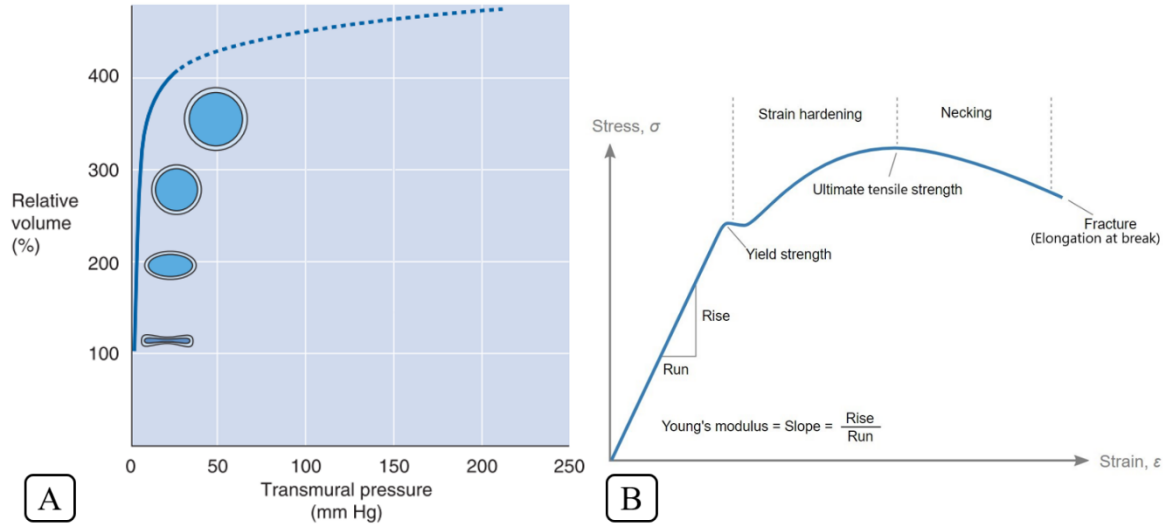

Figure 3-5: (A) Volume-pressure curve of the Vena Cava. It is used as an indicator for the vessel's elasticity. Relative volume of 100 % is set when the vessel is fully relaxed (Transmural pressure is zero). Adjusted image from M. Walter et al. [13]. (B) Standard stress-strain curve of low-carbon steel that shows all material properties that were determined through a tensile test. See abbreviation list in section 8 for definitions. Adjusted image from [24].

3.1.6 Conclusion of fundamentals

In section 3.1, the general fundamentals 'resistances', 'pressures', and 'blood properties' are described in detail. The knowledge gained from this section helps to have a better understanding of the hemodynamics and how this could influence the venous model. In section 3.1.5, a relationship is formed between material properties and the behaviour of veins. After an extensive reach, no viable metric material properties of large veins were found. The outcome of this section is used in the search for a compatible material to veins.

3.2 State of the art

A first review of the state of the art was done by using the scoping review on the fidelity of ECMO simulators by W.C. Duinmeijer et al. [1]. He created a method to objectively classify ECMO simulators as low-, mid- or high-fidelity, based on certain factors. According to this method, there are currently no high-fidelity ECMO simulators available. This explains that no information was found regarding research on the specific topic of creating venous systems for high fidelity ECMO simulators. Studies that could still be beneficial in this thesis are summarized in this section.

In 2010, Pantalos et al. [25, 26] focused on neonatal and infant mock simulators capable of producing realistic pressure and flow values. They were able to create a system that can be tuned to approximate key anatomical features and hemodynamic values of pediatric patients under normal and under heart failure conditions, see Figure 3-6 (A). This mock simulation can also be used to execute tests of various support systems such as the ECMO. For their method, they mimicked the compliance of the arteries by incorporating a single layer of Penrose Drain latex tubing, and a variety of pinch clamps were used to create vascular resistance. During their simulations, they used water or blood analogue fluids (e.g., 40 % glycerol-water mixture) as a replacement of blood. With this mock fluid, hemodynamic waveforms, blood pressure and blood flow mean values could be generated and measured.

In 2010, Kung et al. [27] focused on developing a physical model to recreate *in vivo* vascular flow for *in vitro* experiments. Although not all components of their setup are relevevant for this thesis, this study gives a great overview on how to translate components of hemodynamics into physical components. One of these components is a 'Flow resistance module'. They created a cylindrical channel filled with a large number of small channels as shown in Figure 3-6 (B), to mimic the peripheral resistance (explained in section 3.1.1). They were able to increase or decrease the pheripheral resistance in the system by placing multiple resistance modules in parallel and using control valves. Each module was designed in such a way that laminar flow was maintained throughout the module.

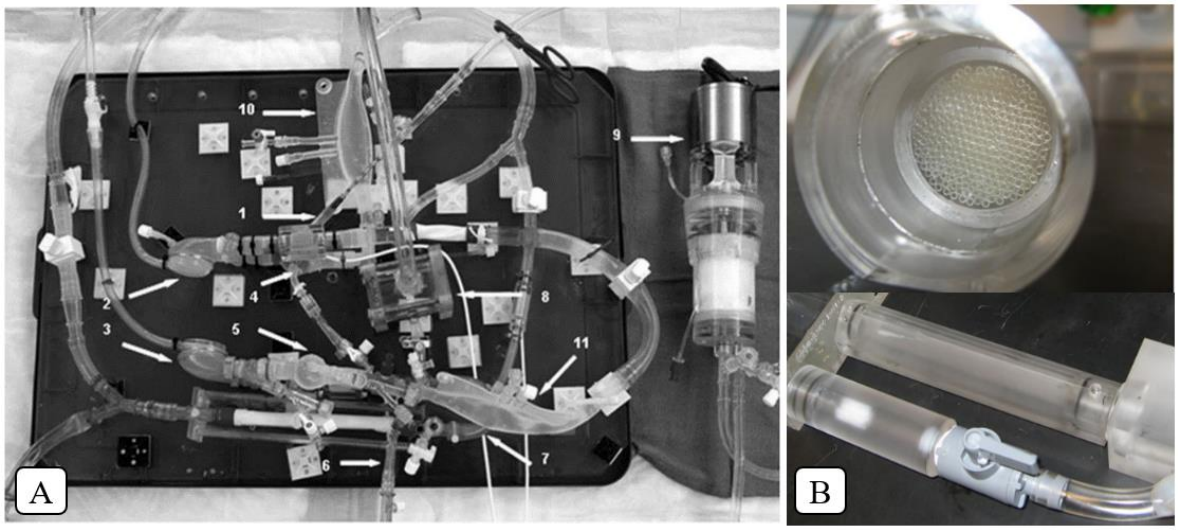

Figure 3-6: (A) The fully assembled pediatric mock circulation system from Pantalos et al. [25].
(B) Flow resistance module from Kung et al. [27]; (top) Construction of the peripheral resistance module with multiple small channels; (bottom) Switchable resistance setup.

The eduECMO strives to be as adaptable to specific situations (e.g., sex, age, body size, race, disease and/or anatomy, and BMI/fat percentage) as possible to reach high fidelity customization, according to the methodology from W.C. Duinmeijer et al. [1]. This results in a patient/situation specific simulator. For meeting this grade of customization when designing a venous model, 3D printing technology is a viable and widely used method (see Table 3-1). With this technology, a single, patient specific model can be realized in a relatively cheap and quick manner compared to other production methods. Table 3-1 lists several studies that created patient specific models to create vascular models and provides inside in the current state of the art of this field. Sommer et al. [28] used a multi-maker printer, meaning that multiple materials can be used in one print. This gives the opportunity to create solid, fluid tight connection at the end points whilst these are connected to soft, elastic, hollow veins through printing. Studies using a single material printer [29, 30] also concluded that mimicking tissue material properties is better achievable by making use of a multi-material 3D printing method.

In conclusion, no studies were found on specifically using realistic venous systems in ECMO simulators for cannulation training and realistic hemodynamic purposes. The state of the art shows current work in the ECMO simulator field, and in creating realistic, patient specific vascular models that could be used in hemodynamic studies. This can be used as inspiration for the design phase.

Table 3-1: Overview of studies that used patient data to create vascular models.

Reference	Anatomical site	Patient data type	Production method	Material	Assembling method	Aim of use	Hemodynamic studies
Parker et al. (2010) [31]	Vena Cava	CT	3D systems© ProX 950 SLA printer	Tango[3]	Glue	To compare different techniques for implementing filters in the IVC.	No
Wen Wen Lau et al. (2018) [30]	Heart	CCTA[1]	Stratasys© Object Eden 260VS SLA printer	Tango Plus[3]	N/A, one part fabrication	Investigating dimensional accuracy and value of 3D printed models.	No
Sommer et al. (2020) [28]	Coronary arteries	CCTA[1]	Stratasys© Object 500 multimaker SLA printer	Agilus[4] and Vero[5]	N/A, due to printer	Physiologically relevant flow simulations.	Yes
Meess et al. (2017) [29]	Abdominal aortic aneurism	CT	Stratasys© Object Eden 260VS SLA printer	FullCure 930 TangoPlus[3]	Silicone-glue	Image guided (X-ray) *in vitro* surgical planning and training.	Yes
Li et al. (2020) [32]	Normal aorta and aortic dissection aorta	CTA[2]	Not mentioned	Silicone	N/A, one part fabrication	Evaluating perfusion characteristics of a normal aortic and aortic dissection model.	Yes

[1]CCA = Coronary computed tomography angiography. [2]CTA = Computed tomography angiography. [3]Tango (plus) = a rubber-like photopolymer resin. [4]Agilus = a soft, elastic resin within the arterial compliance range. [5]Vero = a hard material.

4 Material and Methods

This chapter starts with a description of the chosen methodologies, and continues with the development process through ideation and conceptualizing. At the end of this chapter, a final concept is formed.

4.1 Methodology

As the final product must represent properties of the vascular track realistically, certain limitations arise regarding ideation. This is a research thesis where design is used to realistically translate human characteristics into a mechanical product. A suitable methodology for this assignment is the V-model [33]. This is a development and testing framework that forces a structured approach throughout the development process. It works with the level of detail that increases over time, see Figure 4-1. This figure gives a schematic overview of this thesis´ methodology, based on this framework. Each block represents a process-stage with, in blue, the title of this phase and in green, the products that are created during this phase.

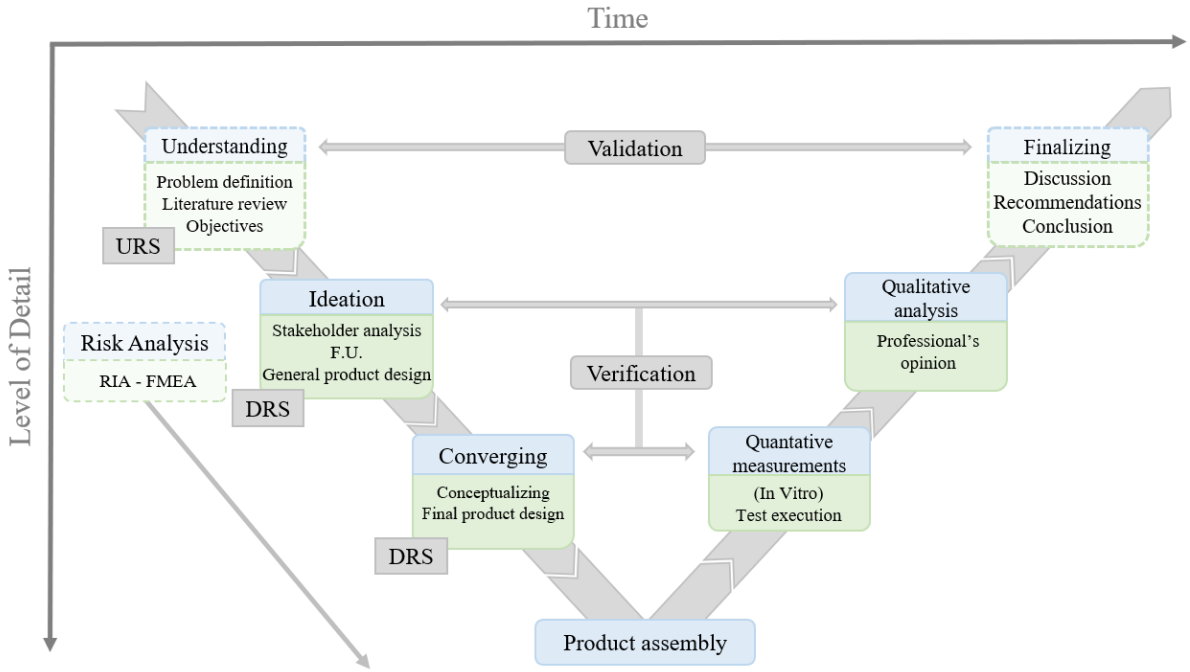

Figure 4-1: Schematic overview of the methodology used for this thesis. Blue blocks represent each title phase and in green the products of that phase. The blocks that are dotted are not part of the design procedures, but other phases of the thesis.

The initial stage (*understanding*) describes the concept orientation where a literature review is done to understand the fundamentals of hemodynamics and state of the art. Together with the user requirement specifications (URS) that describe the intended use of the venous model, an understanding of product

needs/constraints (objectives) is formed. The second stage is *ideation*, where the overall architecture of the design is formed. This is achieved through a stakeholder analysis, defining functional units (FUs), and translating the URS into technical requirements of the venous model, the design requirement specifications (DRS). This results in solving components that together satisfy all FUs and form the general product design. In the next stage (*Converging*), a final product design is formed. This is achieved through collecting and generating several solutions for components and followed by selecting/prioritizing the most suitable option for each component. Components are either prefabricated products or custom-made parts. Prefabricated products were compared with other product options through market and/or literature research and selected using a dedicated scoring system. For custom-made components, the Design Sprint methodology is applied [34]. This fast-past approach aims to quickly design, prototype, test, and validate ideas, to rapidly explore ideas, see Figure 4-2. In this thesis, this is a method translated into a trial-and-error process that continues until a suitable concept was designed and tested. Eventually, the product design is verified with a qualitative analysis through gathering the opinion of professionals (users). Once this is done, all components are assembled to form the final product. This is followed by verifying the final product. Here, the venous model's functioning is tested through quantitative measurements such as experiments. All findings and recommendations are discussed, and a conclusion is given in the discussion.

Alongside this development process, a risk analysis (RIA) is performed as a support tool to identify and prevent possible product failures. This results in new requirements for the DRS. The accompanying documents (URS, DRS, RIA) and their description on use are found in Annex E, section 12.5.

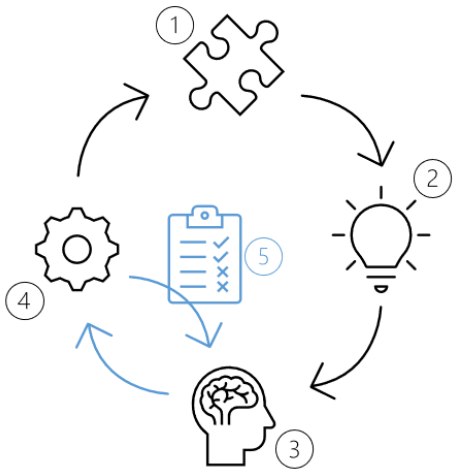

Figure 4-2: Schematic overview of the five phases of the Design Sprint Approach. (1) Design; gain insights and define the problem, (2) Diverge: collect/generate several ideas, (3) Converge: Select and prioritize the best ideas. (4) Prototype: create physical representations of the ideas. (5) Validate: test the prototypes and gather feedback. This figure is custom-made and based on literature [34].

4.2 Ideation

This section focusses on combining the gained knowledge from the literature review, the problem definition, and the needs from stakeholders, to identify the design's functional units (FUs). These FUs are then translated into distinct design components.

4.2.1 Stakeholder analysis

Several stakeholders are involved in the eduECMO project. The ones that influence this thesis are analysed. Figure 4-3 shows an overview of all involved stakeholders in a 'Power/Interest'-diagram. This diagram is used to divide all stakeholders into categories as these vary in amount of power and/or interest they have on the project. The division of stakeholders was done through analysing what their relationship to this thesis is. To define this, the characteristics, expectations, and possible impact and/or contribution to the thesis was determined. An overview of this analysis is shown in Annex C, Table 12-1. All stakeholders – but mainly the key stakeholders – are considered when creating the User requirement specifications (URS) and functional units.

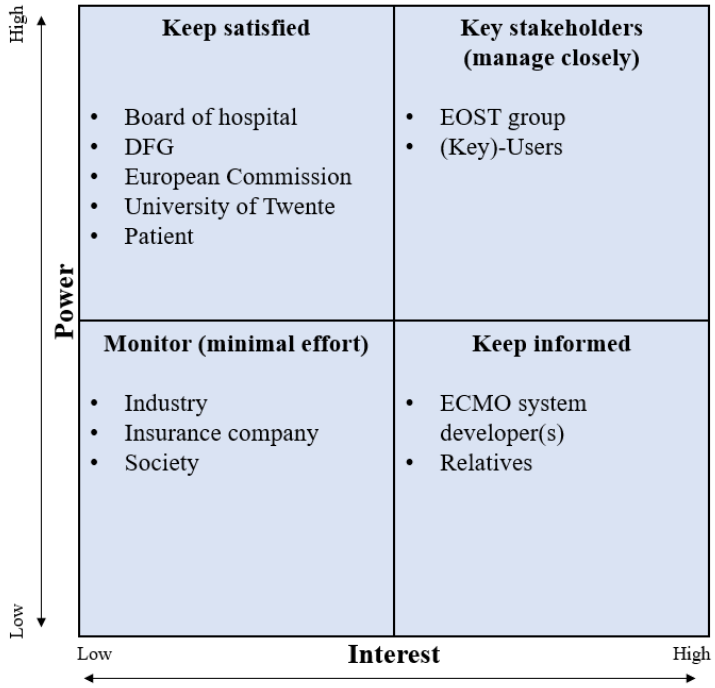

Figure 4-3: 'Power/Interest'-diagram of the stakeholder analysis.

4.2.2 Function analysis

Functions of products are described abstractly to allow multiple design solutions. This is usually done through two describing words; 1) defining the content (material/energy/information), and 2) defining what happens to it (transportation/transformation/storage/separation/combination).

The function analysis was performed with emphasis on combining the gained knowledge from the literature review, the objectives of this thesis, and the needs from stakeholders, to form the functions of the final product (FUs). In Table 4-1, all eight FUs are defined based on their describing words. These functions are considered key requirements of the venous model and are used to form distinct components, ensuring a clear and complete system design. Figure 4-4 shows a flowchart of how each component is a solution originating from corresponding FUs. It shows how fundamentals (parameters of hemodynamics) are used for solving and ensuring a complete system design.

Table 4-1: Functional units with corresponding specifications. The keywords of the FU are underlined for a quick overview of all FUs.

FUs	Function description	Specification	Describing words
FU-1	The product needs to incorporate clinically representative parts of the cardiovascular system, that can be visual during VV-ECMO.	For this, patient imaging data (CT) is used to create 3D models.	Storage of information
FU-2	The product must be adaptable for future modifications and/or expansions.	For this, the device must be adjustable so parts can be replaced/altered, and different situation or patients can be simulated in the future.	Transformation of information
FU-3	The product must be compatible with other components of the eduECMO simulator.	The venous model must have compatible diameters with the vein of the cannulation site to allow smooth connection. Currently, only the groin-connection site is produced.	Transformation of information
FU-4	The product must transport a fluid.	For this, a component is needed that can imitate flow conditions in the veins.	Transportation of material
FU-5	The product must be fluid tight.	For this, each component has to be fluid tight and must fit on the neighbouring component to prevent leaking.	Storage of material
FU-6	The product contains a circulating fluid that has some physiological properties of blood.	For a realistic blood representation during testing.	Storage of information
FU-7	The product must have physiological parameters that mimic the native hemodynamics realistically.	Focus will be on a realistic flow- and pressure-profile throughout the system.	Separation /Transformation of energy
FU-8	The product must be able to monitor the circuit on physiological parameters.	For obtaining flow and pressure data from the circuit.	Transformation of information

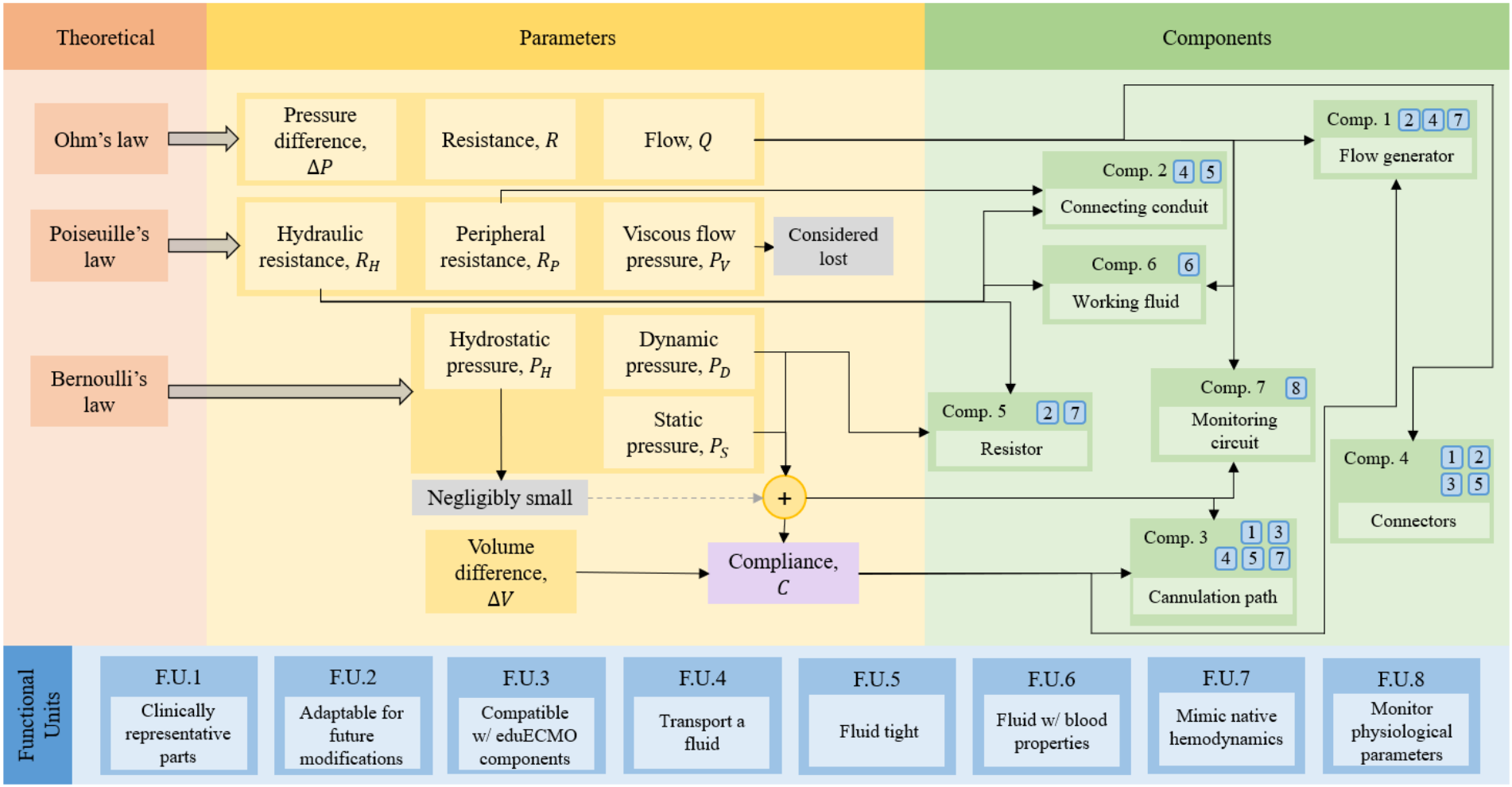

Figure 4-4: Flowchart of how fundamentals and functional units (FUs) are used to form seven distinct components of the general product design. The relation of a component to the FUs is visualized with blue boxes in the corner of each component, and to a parameter with black arrows. As described in section 3.1.6, one overall pressure is used. The three types of pressures are used to understand potentially originating deviations in pressure values.

4.2.3 Product design – General

The general product design of the venous model consists of seven distinct components. Figure 4-5 shows a schematic of the interaction between components. As the systemic circulation of the venous system is essentially a closed loop circuit, the venous model will also be developed as such.

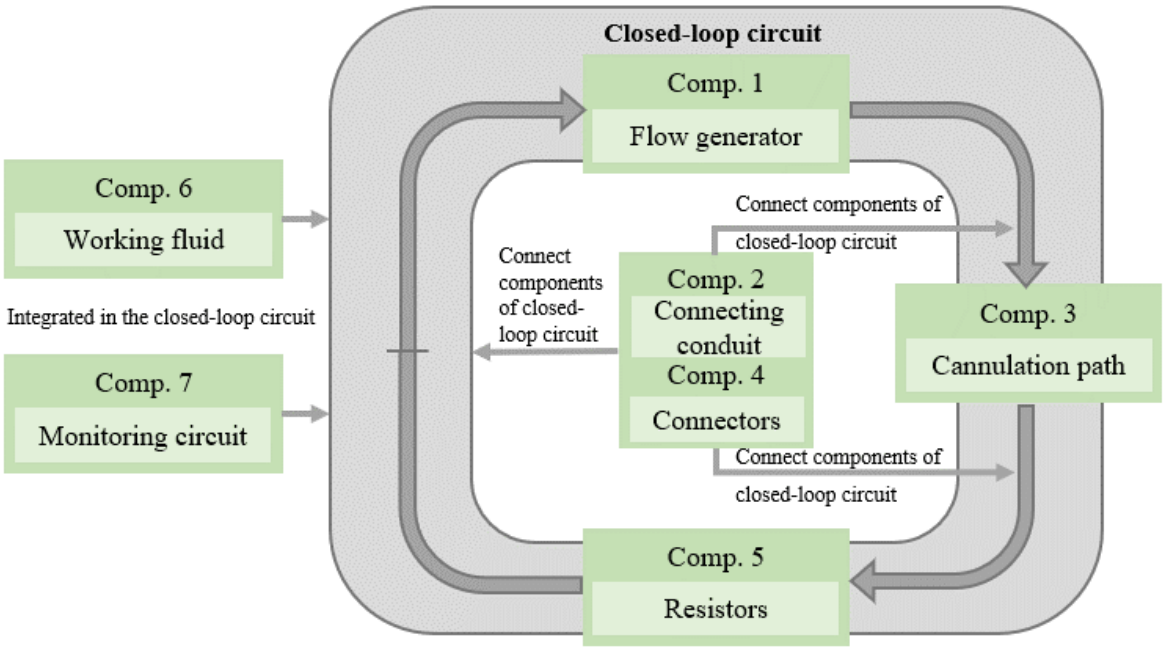

Figure 4-5: A schematic of the general product design of the venous model showing the interaction between components.

4.3 Conceptualizing general product design

Different methods were used to realize final product components. For component 1, market and literature research on several solutions was performed, and results were compared using a dedicated scoring system. Component 3 was realized by segmenting received patient data using a custom-made protocol. For component 4 and 5, a trial-and-error process was utilized that continued until a suitable component was designed and tested. For component 6 the literature review was used to find which substances are needed for a blood-analogue fluid, and how to produce it. Component 2 functions to transport the working fluid between components and component 7 monitors parameters. For both, viable options were available at the UT and therefore, no extensive research was done on these components. Lastly, a final product design was created.

4.3.1 Comp. 1: Flow generators

Key requirements: FU 2, 4 & 7

As shown in Figure 4-4, comp. 1 must satisfy FU-2 (Adaptable for future modifications), FU-4 (Transport a fluid), and FU-7 (Mimic native hemodyanmics). Furthermore, this component is most suited to generate the flow in the venous model. Note that the native pulse in veins is barely noticeable as graphically shown in Figure 3-1 (right), but is present because of the pumping method of the heart

(cardiac cycle, see section 1.4). Therefore, selecting a flow generator with a subtle pulsatile flow is not excluded. Based on these requirements, market and literature research was done to create an overview of what is available and could potentially be used. Several flow generators were compared, as described in Table 12-2 in Annex B. These were rated with a dedicated scoring system as shown in Table 12-3 in Annex B. Based on these two tables, three solutions for comp. 1 stood out (listed from highest to lowest rating).

- The roller pump (HL20, Maquet Cardiopulmonary/Getinge, Hechingen, Germany), as it was used for VV-ECMO systems in the past making it applicable for comparable applications such as this thesis. Using a 2-roller pump, the generated flow is given in a 2-phased cycle, causing the flow to be pulsatile. Depending on the size and design of the pump, it could represent the desired pulse. However, frequency and amplitude cannot be influenced independently in such a pump. A 2-roller pump is available for use at the UT.
- Rotaflow® centrifugal pump (Maquet Cardiopulmonary/Getinge, Hechingen, Germany), as it is commonly used for ECMO systems, making it applicable for comparable applications such as this thesis. This pump creates a continuous flow, which is applicable for the venous model. A Rotaflow pump is available for use at the UT.
- The ViVitro Labs© pulsatile pump [35] (ViVitro Labs Inc., Victoria, Canada), as this is specifically designed for *in vitro* testing and development of cardiovascular medical devices. This pump over-qualifies for this thesis product as it can accurately mimic arterial pressure flow whereas we concentrated on the venous system. If desired, this pump had to be purchased.

In agreement with the supervisors of the project, the choice was made to use the 2-roller pump as the flow generator component. As both the roller and Rotaflow pump were viable options, the eventual choice was made because the roller pump is the more cost-effective pump and requires less maintenance due to its more simplistic mechanism.

4.3.2 Comp. 2: Connecting conduit

Key requirements: FU 4 & 5

Connecting tubing shall be used to bridge any distance between other components whilst maintaining a fluid tight (FU-5) closed-loop circuit (FU-4). It is important to consider the peripheral resistance that gets created if any branching occurs. This will influence the pressure, not the flow. To recall from Equation 3-1 section 3.1.1, the hydraulic resistance [R_H] is proportional to the vessel radius to the fourth power. An efficient way to minimize R_H is by keeping radius differences throughout the circuit to a minimum. Doing this, the Bernoulli effect is minimized as well. Therefore, the choice was made to use one size connecting conduit throughout the circuit. The exact diameter size will depend on other component selections, which are yet to be defined. As both 3/8- and 1/2-inch tubing are used for adult ECMO treatment [36], these are preferred sizes. A new requirement that arised when making the choice for a roller pump is that the connecting conduit should be flexible enough for roller pump application.

At the UT, tubing is available varying in diameter and material, either polyvinylchloride (PVC) or silicone. Both types are commonly used in ECMO systems and are applicable with the roller pump. Silicone tubing is known for its flexibility and easier handling. PVC more commonly used in VA-ECMO as it can withstand high pressures. As the silicone is more user-friendly and no high pressures are involved, the choice was made to use this for component 2.

4.3.3 Comp. 3: Defining, segmenting, and designing the cannulation path

Key requirements: FU 1, 3, 4, 5 & 7

The cannulation path is the component that will physically be used by users during simulations. To recall, this component must be compatible with the eduECMO component 'cannulation sites' (FU-3). The cannula enters this component through its lumen, after it has been inserted into the simulator through the cannulation site. The cannulation path defines the part of the cardiovascular system that lays on the path during VV-ECMO cannulation. Section 1.1 is used to define this path (FU-1). Anatomical names of all vessels and structures within this path are listed in Annex B, section 12.2.2.2. Important characteristics of the cannulation path during a simulation are:

1. Realistic dimensions, correct branching, and anatomical shape – for users to learn with an accurate simulator.
2. Reusability – as simulations do not require puncturing the path, it can be reused.
3. Comparable compliance – As described in section 3.1.5, compliance is an important vein property, but should not be visible due to the constant pressure and flow profile.

Professional opinions are used for evaluation.

This component can be divided into two subcomponents: 3a) the venous track – representing all veins between the cannulation site and heart (the inlets of the cannulation path) –, and 3b) the right heart – representing the structures of the right heart, and pulmonary artery (the outlets of the cannulation path). See Figure 4-6 for a visualization of this division.

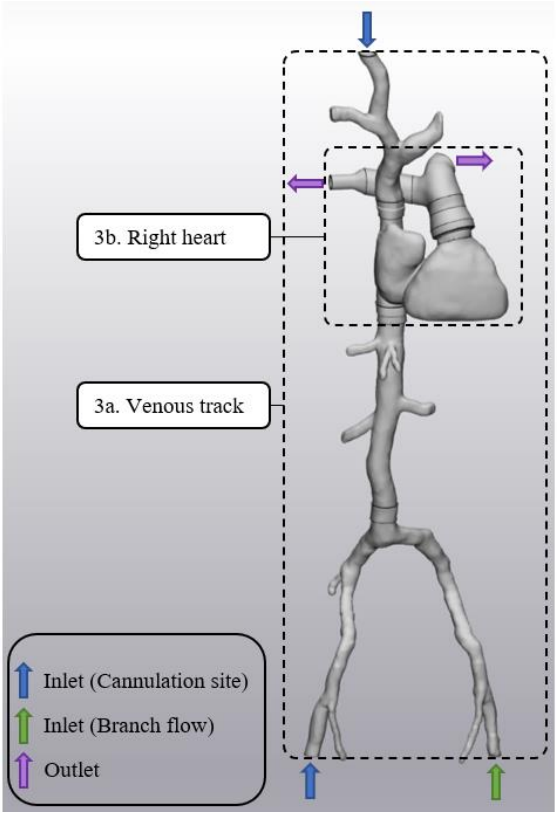

Figure 4-6: Overview of the subcomponents and the type of inlets/outlet. Image was taken in Materialized© 3-Matic and based on the patient's data.

As shown in Figure 4-7, the right heart is incorporated into the product design because it is part of the cannulation path of the ProtekDuo cannula (LivaNova PLC, London, United Kingdom), as described in

section 1.1. The distinction of subcomponents was made because of the challenging anatomy when passing through the right heart with a cannula. Note that these subcomponents are produced as one component.

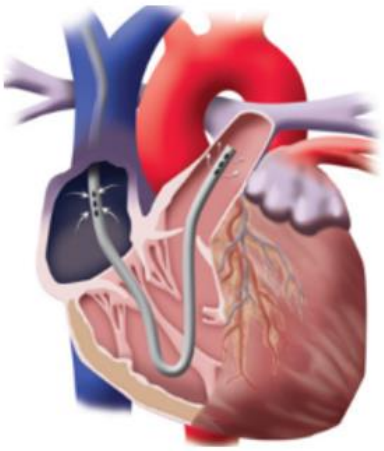

Figure 4-7: Visualization of the ProtekDuo cannulating through the right heart to return blood into the pulmonary artery [9].

4.3.3.1 Realizing cannulation path (comp. 3)

Data gathering

As described in the objectives (section 2), a highly accurate anatomical cannulation path is desired. There is no open-source dataset of the fully segmented cannulation path available. 'Z-anatomy.exe' is an open source, 3D single model of the full human anatomy. Even though this is a project of the University of Leiden and has great potential, the anatomical content is still under development. Therefore, the choice was made not to use this dataset. Instead, the cannulation path was custom-segmented, and is based on one anonymized patient-specific CT dataset (FU-1), provided by the 'Medisch Spectrum Twente' (MST) through Dr. F.R. Halfwerk.

Production method

Ideally, a suitable production method can produce the cannulation path that 1) represents realistic anatomy of patient specific data, 2) is fluid tight, 3) is hollow like veins, 4) is flexible for venous compliance, 5) can withstand native pressure and flow profiles, and 6) has the option for future alterations and modifications. As described in section 3.2, 3D printing technology seems to be the most commonly and viable method for such applications. Nevertheless, a brainstorm was conducted to compare several production methods that could possibly be used. An overview of this is given in Annex B, Table 12-6. Table 4-2 shows material properties of accompanying resin used in 3D printing. Each considered method was rated with a dedicated scoring system as shown in Annex B, Table 12-7. Based on these three tables, the most suitable method seems '3D Stereolithography (SLA) printing with the Stratasys© Object 280 printer' (Rehovot, Isreal), as it is available at the UT and used in comparable research, see Table 3-1. Unfortunately, the printer was malfunctioning during the development process of this thesis. Two other viable options were the Form 2© (Sommerville, USA) and Phrozen© (Hsinchu, Taiwan) SLA printers. These were compared based on their pros and cons, and compatible material (see Table 4-2). As stated before (section 3.1.5), no material properties of large veins are defined in literature. Therefore, even though Flex 82A resin has a lower elongation at break and higher ultimate tensile strength compared to other materials in Table 4-2, it is yet to be determined which ratio of material properties is suitable for

the venous model. The choice was made to collaborate with 3D Medical Support (3D-MS) (Enschede, Netherlands) – who work with the Phrozen© printer and a confidential material with comparable properties to Flex 82A resin – since they are located at the UT and have shown to be capable of printing multiple tailored products of the vascular system before. The main reason for not using the Form 2© printer is because experts advised against it for the production of the cannulation site, due to its size and complexity. At 3D-MS, comp. 3 could be printed in four parts.

Table 4-2: Material properties of resin with SLA compatibility. Data was gathered from vendor websites.

Resin	**White & Clear V4**	**TPU 95A filament**	**Flex 82A**	**Elastic 50A**	**TangoPlus™, FLX930**	**IORA Model Flex 30 A Black**
Vendor	**FormLabs© (Somerville, USA)**	**Ultimaker© (Utrecht, Netherlands)**	**Form-Futura® (Nijmegen, Netherlands)**	**FormLabs® (Somerville, USA)**	**Stratasys© (Rehovot, Israel)**	**iSquared2© (Lengwil, Switzerland)**
Compatible printer	FormLabs© Form 2 (SLA)	Ultimaker© 2+ or 3	Phrozen© (SLA)	FormLabs© Form 2 (SLA)	Stratasys© Object 280 (SLA)	Stratasys© Object 280 (SLA)
Ultimate tensile Strength (MPa)	65	39	12	3.23	0.8 – 1.5	2.2 – 3.0
Elongation at break (%)	106.2	55 – 580	135	160	170 – 220	180 – 250
Shore Hardness*	N/A	95 A	82 A	50 A	26 – 28 A	30 A
Note: No Yield's Modulus is listed because it was not provided on datasheets of most resins. A reason why this is commonly not included on datasheets of flexible materials, is because it is difficult to determine property for materials that have a large deformation response and no linear stress-strain curve [37].						
* Shore Hardness is an indication of the toughness of a material. The higher a material, the tougher and thus, more rigid it is.						

Image segmentation and post-processing

Segmentation of the CT patient data was done using Materialized© Mimics Innovation Suite software version 24.0 (Leuven, Belgium). In the software, several segment tools are provided to 'quickly' segment clear structures such as the Aorta by simply marking them on multiple slices in varying views (coronal, axial, or sagittal). Unfortunately, the desired cannulation path could not be segmented automatically, because the software could not clearly distinguish the desired veins as individual structures as shown in Figure 4-8. No tutorials or guidance of experts within reach were available. Therefore, skills regarding using this software were self-learned through videos of specific situations found on YouTube. This resulted in manually segmenting the full cannulation path with a custom-created method. For identification of structures, examples in medical literature were used. The segmented cannulation path was exported to Materialized© 3-Matic Innovation Suite software version 16.0 (Leuven, Belgium) to remodel and prepare the segmented path for printing. The final digital 3D model was hollowed and smoothed as much as possible before exporting in STL-format for printing. For visualization and a protocol on segmentation and remodelling of the cannulation path, see Annex B section 12.2.2.4.

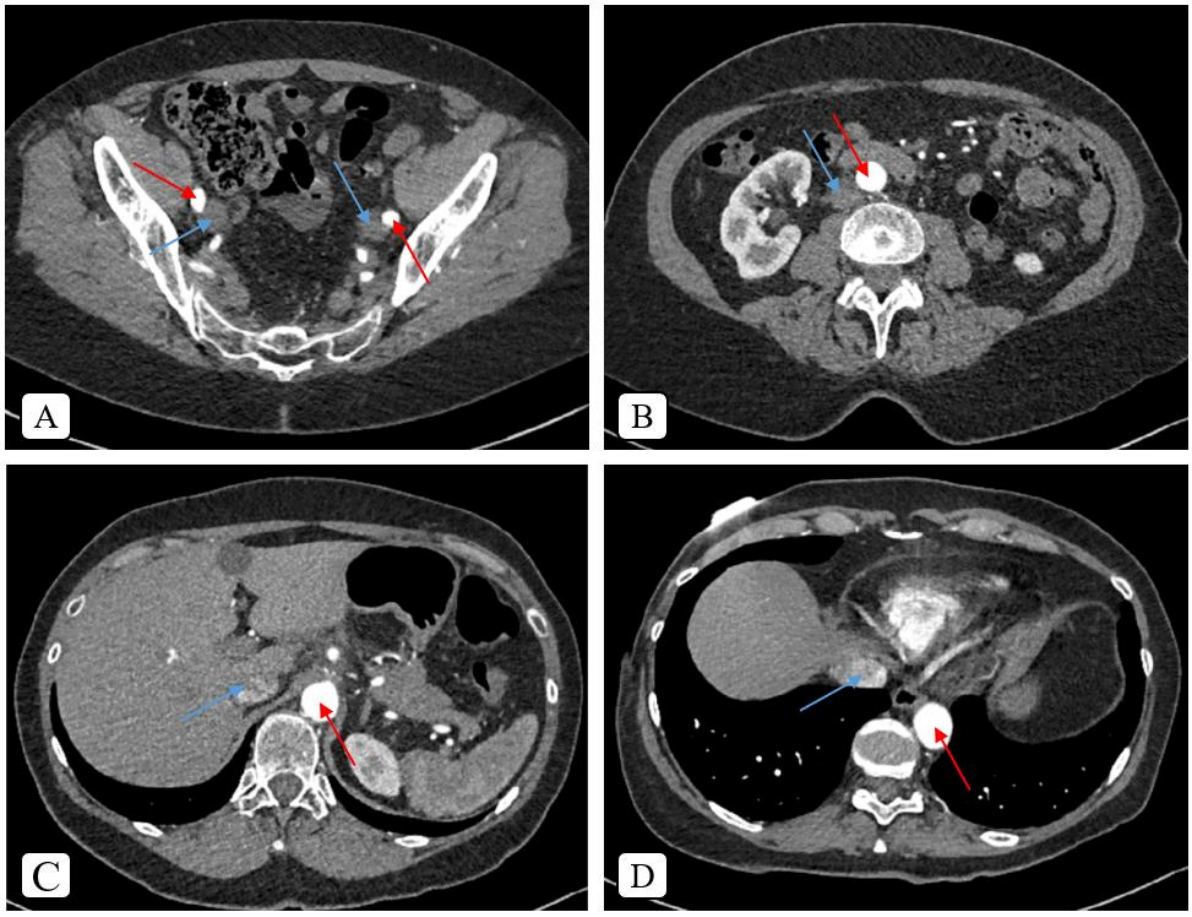

Figure 4-8: Four images of the CT data (axial) throughout the trunk (From A to D, from groin to neck), that form examples that segmenting the veins brought difficulties due to the lack of clear distinction between structures. With red arrows, the clear to distinct arteries are indicated. With blue arrows, the veins of the cannulation paths are indicated. Images were taken in Materialized© Mimics software.

4.3.3.2 Bridging obstacles of right heart cannulation (Comp. 3b)

The right heart is incorporated because during ProtekDuo cannulation application [9], the cannulation goes through the right heart as shown in Figure 1-1. This subcomponent is divided into four obstacles a user would encounter during simulation. They are ranked according to their importance for incorporation. For this, experts' opinions (EOST group) were asked.

1. Correct anatomical shape and making the angle between the Tricuspid and Pulmonary Valve – due to sharp angle between the valves (approx. 60 degrees, based on measurement in Mimics, see Figure 4-9 (A)), and little rotation space for the cannula in the ventricle. To satisfy these requirements, additional time was spent on segmenting the heart. The final digital 3D model made in 3-Matic was imported back into Mimics to overlap the model with the CT data for verification of accurate segmentation.

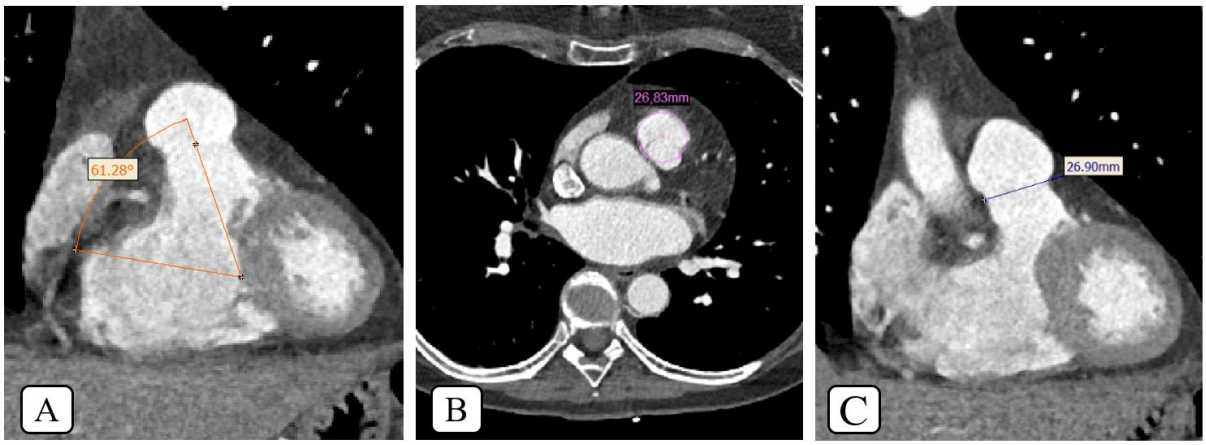

Figure 4-9: Measurement of CT patient imaging data, made in Materialized© Mimics software. (A) Coronal view of heart with angle measurement. (B) Axial view, and (C) coronal view of heart with Pulmonary Valve diameter measurement.

2. Going through the Pulmonary Valve – as this valve has a relatively small opening. To satisfy this requirement, an external valve was implemented. To define desired dimensions, measurements of the Pulmonary Valve diameter were made in Mimics, see Figure 4-9 (B & C). Through a free-sample set, a suitable valve was obtained: the cross-split silicone valve with a diameter of 27 mm (MiniValve©, Oldenzaal, Netherlands). This valve contains four cuspids forming the valve 'flaps' and ensures non-tortuous flow. To fixate the valve firmly in the desired position, a seating was designed and implemented into the final digital model of the cannulation path. The design is based on seating suggestions of MiniValve© and tested separately before implementing. For testing, the seating design was incorporated into a custom-made test part that was printed with Formlabs© Form 2 SLA printer in Clear V4 resin, see Figure 4-10. The final seating design was correctly placed and implemented into the final digital model of the cannulation path using 3-Matic software. The left pulmonary artery was opened to have a diameter of 20 mm, so the external valve could be implemented during assembly. Details on seating dimensions, the test setup, test results and images of correct seating placement into the final digital model can be found in Annex B, section 12.2.2.5.

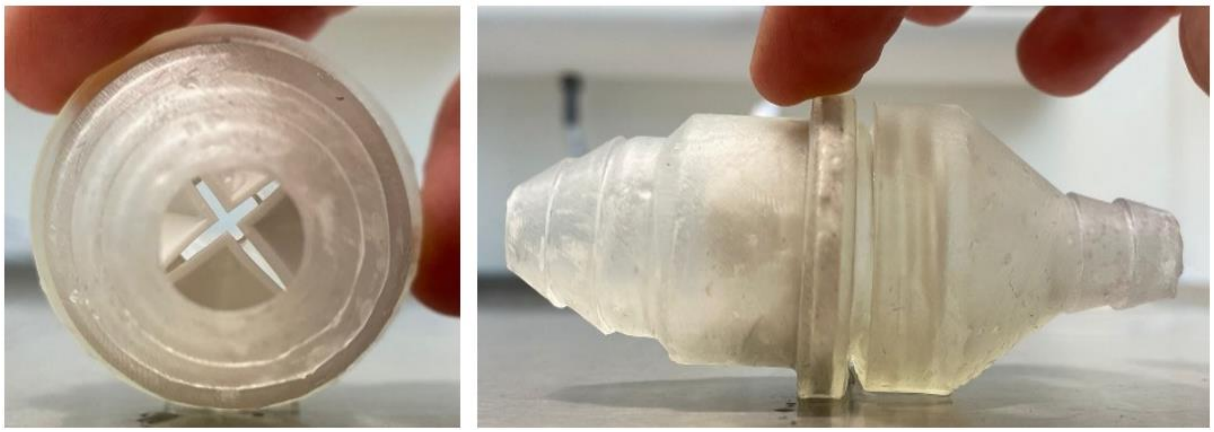

Figure 4-10: Views of the custom-made part to test the valve seating. Design was made in Solidworks® and printed with Formlabs© Form 2 SLA printer in Clear V4 resin.

3. Going through the Tricuspid Valve – as this valve has a relatively wide opening. This opening is roughly shaped as an ellipse as shown in Figure 4-11 (A). According to R. Kalyani et al. [38], the average circumference of a Tricuspid Valve is 108 mm in females. During remodelling in 3-Matic, such dimensions sometimes change. To verify the Tricuspid Valve opening in the digital model, combined examples

of literature [38] and the CT data in Mimics were used. Figure 4-11 (A) shows the final opening dimensions.

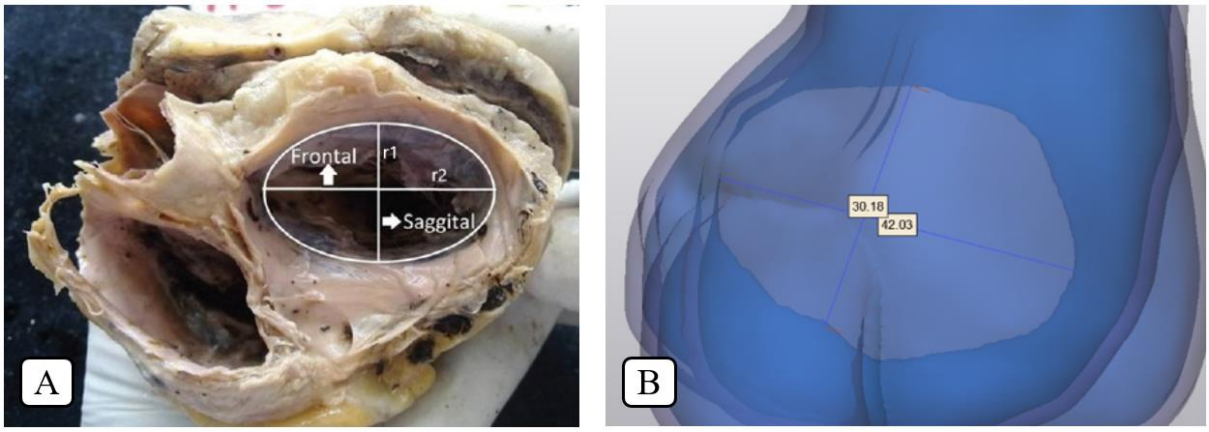

Figure 4-11: (A) Image from literature on the general shape of the Tricuspid Valve [38].
(B) Image of the Tricuspid Valve opening dimensions of the digital design made in 3-Matic.

4. Contracting movement of the Right Ventricle – for a realistic simulation. Some discussion arose between stakeholders regarding the need of a contracting Right Ventricle. Some argued its contribution to a realistic simulation. Others believed it would not be beneficial for a simulation, and incorporating a contracting element would only add redundant difficulty to the development process.

4.3.4 Comp. 4: Connectors

Key requirements: FU 1, 2, 3 & 5

Connectors can potentially cause disruptions such as turbulent flow or increase the hydraulic resistance [R_H]. To minimize such disruptions, some design requirements are imposed and considered such as smooth transition and minimal radius differences. Furthermore, key requirements (FUs) were considered for the design. Concept prototypes were designed in SolidWorks® (SW) 2020 student version and printed using FormLabs© Form 2 SLA printer because of its ability to 3D print parts highly detailed and fluid tight. Print preparation was done in FormLabs© PreForm 3.23.0 software. Resins used were either white V4, Clear V4 or Elastic 50A V1 resin from FormLabs©, see Table 4-2 for material properties. To test connection concepts without potentially damaging comp. 3, all ten connection sites were isolated, remodelled, and printed. Because of financial reasons, these 'test vessels' could not be produced at 3D-MS, and hence not with the same material as the cannulation path. Instead, the production was done with the Form 2 printer using Elastic 50A resin because of comparable material properties with Flex 82A Resin compared to other materials available (see Table 4-2) and easy access.

This component is divided into subcomponents as there are different types of connectors needed for this venous model. The four types of connections are:

- **4a. Connecting tubing (comp. 2) with each other.** The selected tubing (ECM Europe BV©, Gemert, Netherlands) has accompanying connectors. They vary in I-/Y-connector, and with/without luer-lock.
- **4b. Connecting the inlets of comp. 3 (venous track, 3a) with vein of cannulation site.** The cannulation sites must be detachable for adaptability and eduECMO compatibility (FU-2 & 3). There are three inlets (left/right iliac vein, right internal jugular vein), all needing connectors customized to their diameters. Note that these connectors lie within the path of the cannula. To

minimize flow disruptions, the internal radius is kept as constant as possible, the inside of the connector is smooth, and the length did not exceed 20 mm.

- **4c. Connecting tubing (comp. 2) with the outlets of comp. 3 (right heart, 3b).** These connections do not lie within the path of the cannula. Fewer requirements were therefore set for the design. There are two outlets: left and right pulmonary artery. The right pulmonary artery was altered in 3-Matic, so its diameter matches 3/8-inch. This way, a prefabricated 3/8-inch connector with luer-lock (Maquet Cardiopulmonary/Getinge, Hechingen, Germany) could be used. The left pulmonary artery needed a customized connector due to its large diameter (because it was opened to allow insertion of the Pulmonary Valve).
- **4d. Connecting parts of the cannulation path (comp. 3).** The cannulation path was printed in four parts and thus had three connection sites.

Trial-and-error processes were followed for connectors (Annex B Table 12-11) and connection methods (Annex B Table 12-12) to realize comp. 4b – 4d. Each concept has a label such as D.y/P.y., were 'D.y' is a detachable connection method and 'P.y' is a permanent connection method (e.g., connection method P.3 was used). A connection method describes which connector was used (from Annex B Table 12-11) and how this got attached onto comp. 2 and/or comp. 3. From now on, connections will be referred to by their label (label description is found in Annex B Table 12-12). This process let to the conclusion that connectors cannot be detachable, flexible, custom-made, and fluid tight all at once. This is because a detachable connection has to be pinched off to make it fluid tight and this requires opposing forces from both sides of the vessel/tube wall. A flexible connector cannot provide or withstand these forces. Therefore, all D-connectors are made from rigid material. P-connection methods allowed flexible connectors, which have less to no influence on the flow compared to rigid connectors. A method that was found to create strong and fluid tight connection is to use RS© Silicone Rubber Compound (SRC) (RS components, Corby, UK), which is used as an adhesive agent for permanent connection. The choice was made to use a combination of D- and P-connections for components 4b and 4c, because attaching these connectors permanently onto one side does not change the situation for a simulation and P-connections have proven to be stronger connection method.

Table 4-3 lists the final component selections of all subcomponents.

4.3.5 Comp. 5: Resistors

Key requirements: FU 2 & 7

Resistors are incorporated to influence the dynamic pressure [P_D] by applying resistance (FU-7), see Equation 1-1. This can be done through peripheral resistance [R_P] as seen in literature (see section 3.2, Figure 3-6 (right)), or through hydraulic resistance [R_H] by decreasing the radius (see Equation 3-1).

The choice was made to use clamps, thus having influence on the radius. For this, Bochem™ 'Hoffmann' stainless steel Pinchcock tube clamps (Bochem Instrumente GmbH, Weilburg, Germany) where used. They are manually adjustable (FU-2). Testing revealed that the printing material used for the cannulation path (comp. 3) cannot withstand the applied forces of the Pinchcock clamp, see Figure 4-12. Therefore, they are only used on connecting tubing (comp. 2).

Figure 4-12: Pinchcock clamp causing tears in branch of cannulation path.

4.3.6 Comp. 6: Working fluid

Key requirements: FU 6

Initial testing was done with water as working fluid. When the venous model proves to be a fluid tight circuit that can mimic and withstand fundamentals of hemodynamics (satisfying FU-4, 5 and 6), a fluid with properties of blood can be introduced. As described in section 3.1.4, blood can be considered a Newtonian fluid if the viscosity is constant. This can be assumed if the three boundary conditions listed in section 3.1.4 are satisfied. Using a working fluid with a similar viscosity will mimic blood with respect to flow properties sufficiently. In multiple studies [26, 27], a 40 % glycerol-water mixture is used for mimicking the viscosity of blood, as it has similar properties as blood within assumed boundaries. Glycerol and water are incompressible fluids, making this mixture a Newtonian fluid. The mixture has a viscosity of 0.046 g/(cm · s) and a density of 1.1 g/ml (at a temperature of 21 °C). For different concentrations or temperatures, the online calculator can be used made by A. Volk et al. [39]. His research shows that this mixture is highly dependent of temperature changes, so therefore temperature must be monitored. A liquid red dye (Hydra International Ltd, Milton Keynes, UK) is added to create a blood-like appearance. 5 ml of liquid dye treats 125 L of water. Given this ratio, the assumption is made that adding a droplet of dye will not influence the viscosity and density of the mixture. A protocol on preparing this mixture was made in preparation, see Annex B section 12.2.2.8.

4.3.7 Comp. 7: Monitoring circuit

Key requirements: FU 8

The circuit must be monitored on physiological properties to ensure that the venous model is mimicking native hemodynamics, and to understand when certain properties change. They are used to obtain metric results during testing. Three types of sensors are incorporated:

1. The 2-roller pump (comp. 1) provides a live flowrate that is based on the tube diameter and the RPM (revolutions per minute) of the rollers. To verify this sensor, an additional flow sensor is placed in the circuit. At the UT, a Transonic© flowmeter and a matching clamp-on sensor for 3/8-inch tubing (Transonic Systems Inc, Ithaca, USA) is available and will be used.
2. As stated in section 4.3.6, a temperature sensor must be incorporated simultaneously with the glycerol-water mixture to verify a constant temperature of 21 °C.
3. Pressure sensors are commonly used to monitor the pressure. They measure the total pressure in a system, which is the combined pressure of the static [P_S], hydrostatic [P_H], and dynamic pressure [P_D] (see section 3.1.2, Equation 3-2). To minimize the P_H, the requirement is introduced to avoid height differences throughout the cannulation path (comp. 3) as much as

possible. This matches the position a patient is in during cannulation. Other elevations throughout the circuit will not influence measurements since resistors can be altered. P_S is determined at $Q = 0$ L/min, and all pressure increasements once $Q > 0$ L/min represent P_D. Usually, the pressure values mentioned in literature represent a combination of P_S and P_D. Pressure sensors are placed at the in- and outlets of the cannulation path (comp. 3), so resistors (applying hydraulic resistance) can be altered to achieve a physiologic pressure range. The measured pressure is a combination of the static and dynamic pressure. Elevations throughout the circuit do not influence measurements, as long as there are no changes in height during measuring. All pressures are measured in millimetre of mercury (mmHg).

4.4 Intermediate design verification

A qualitative analysis was done to verify the cannulation path design, as this forms the simulation environment that will physically be used by users. This was realised through a digital survey that gathered the opinions of professionals (users) on what they believe is important to incorporate into a realistic venous track design for VV-ECMO simulator applications. From this cam intermediate results that were used for the final design.

4.4.1 Survey

The survey consists of 10 questions regarding the venous model. The full survey can be observed in Annex B, section 12.2.3.

Three questions (2a-b & 4) were included with regard to the overall eduECMO. Question 2c and 2d asked participants to rank properties that they think are important/challenging when executing a simulation with the venous model, see Figure 4-13. Question 2c specified on the venous track (comp. 3a), and question 2e on the obstacles of right heart cannulation (comp. 3b) (obstacle 1 was split into ‘Correct anatomical shape’ and ‘Making the angle between the two heart valves’). Both questions were followed with an open question asking whether they missed properties or had additional notes regarding the previous question (question 2d and 2f). Subsequently, question 3 focused on the importance of a realistic compliance in the model, and if a more rigid vessel would affect a simulation positively or negatively. The survey ended with a final open question asking for any additional ideas/notes on overall eduECMO design (question 4). Participants could optionally state their name, current job position.

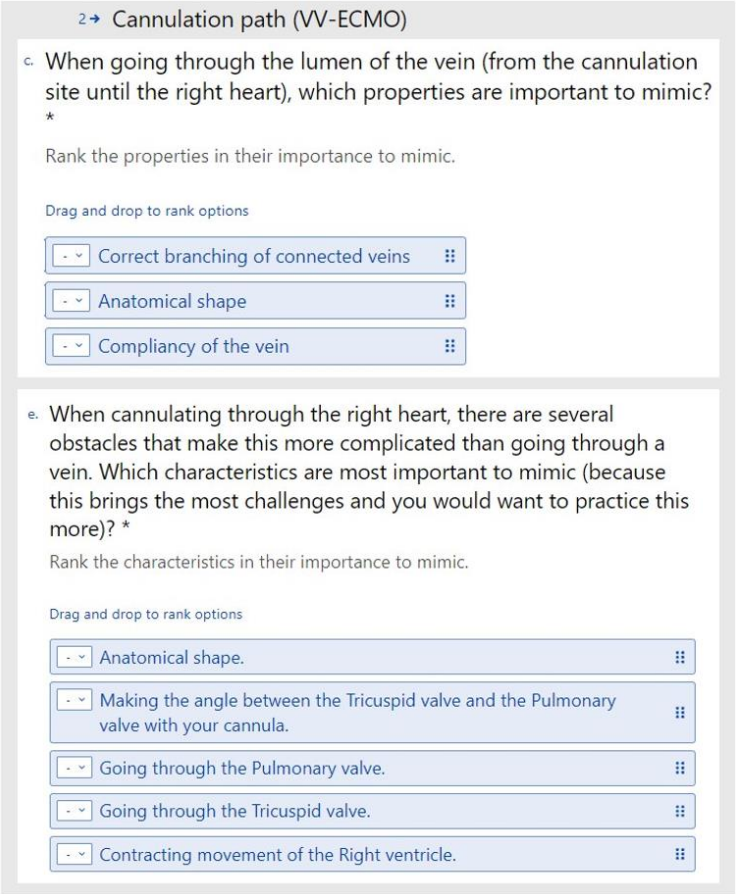

Figure 4-13: Survey questions where participants were asked to rank properties/characteristics on most to least important, based on their opinion.

4.4.2 Intermediate results – Survey

A total of 8 professionals/users within the field of ECMO or cardiovascular surgery participated in the survey. An overview of all survey results (both raw and combined) is given in Annex C, section 12.2.3.

Results on the ranking questions (question 2c and 2e, see Figure 4-13) were obtained and processed. Figure 4-14 gives an overview of the ranking of each participant, an average ranking based on all participants, one based on the key-users (clinical perfusionists and cardiac surgeon), and one based on the participants with technical knowledge. This division was made because the opinion of certain experts can way more than that from others regarding some topics. This will be used later on in the discussion (section 6). The outcome of question 2c of the combined opinion of all participants is not in line with the order of important characteristics initially set for the venous track (comp. 3a). They ranked the compliance of the veins as more important than the anatomical shape or correct branching. As for the right heart (comp. 3b), the results of question 2e verified the current order of important obstacles to focus on when designing, with a shared bottom position. The follow up questions (2d and 2f) did not give any new properties that should be considered for the design.

Participant's opinions regarding question 3 differed greatly. As hypothesized and verified by three participants, a less compliant vessel makes the simulation more difficult, and this would reflect positively on the training level. The participants who believed it would negatively reflect on the training level were concerned that the difference in compliance should not be too big, and that users should be aware that less pressure will be needed *in vivo* to prevent veins to rupture.

Through question 4, participants advised that the product should have an additional function to make it compatible with echography, as this is used for cannula placement.

	Question 2c			Question 2e				
Participants - Key users	Compliance of the veins	Anatomical shape	Correct branching of connected veins	the angle between the Tricuspid valve and	Anatomical shape	Going through the pulmonic valve	Going through the tricuspid valve	Contacting movement of the right ventricle
Participant A	1	2	3	1	4	2	5	3
Participant B	1	2	3	1	2	4	5	3
Participant C	2	3	1	1	5	3	2	4
Participant D	2	1	3	2	1	3	4	5
Participant E	1	2	3	3	1	4	5	2
Participants - Technical knowledge								
Participant F	2	3	1	2	1	4	5	3
Participant G	3	1	2	2	3	4	1	5
Participants - Other								
Participant H	1	3	2	1	2	4	3	5
SUM of:								
All_participants (n=8)	13	17	18	13	19	28	30	30
Clinical_experience_participants (n=5)	7	10	13	8	13	16	21	17
Technical_knowledge_participants (n=2)	5	4	3	4	4	8	6	8
Average ranking based on opinions of:								
Average ranking of all participants	**1,625**	**2,125**	**2,25**	**1,625**	**2,375**	**3,5**	**3,75**	**3,75**
Average ranking of key-users	1,75	2,5	3,25	2	3,25	4	5,25	4,25
Average ranking of participants with Technical knowledge	2,5	2	1,5	2	2	4	3	4

Figure 4-14: Combined results of the ranking questions (2c and 2e) of the digital survey. Average ranking is either based on the opinion of all participants (n = 8), on that of key-users (n = 5), or on that of participants with technical knowledge (n = 2).

4.4.3 Conclusion of intermediate design verification

Based on the outcome of this survey, the choice was made to print the venous track (com.3a) with a 1 mm wall thickness – as this is the minimum thickness for printing at 3D Medical Support and it is hypothesized that this will contribute to increasing compliance –, and the right heart (comp. 3b) with a 2 mm wall thickness to make it stronger – as it is assumed that the pressure in this part will increase due to the merging flow of the Superior and Inferior Vena Cava in the Right Atrium. Due to time and these results, the choice was made to initially focus on implementing the top three ranking obstacles of the right heart (comp. 3b) into the venous model. Some initial work was done on the other two obstacles. This is further discussed in section 6.

4.5 Product design – Final

Based on the substantiation and processes described in the previous section (4.3) and the intermediate design verification (section 4.4), final components were selected.

Table 4-3 gives an overview of these components with accompanying specifications and how they were realized (either prefabricated or custom-made). Figure 4-15 shows schematically how the components together form the final product design.

Additionally, a reservoir was added into the circuit. This way, the circuit has a user-friendly inlet, and provides a solution to filter out air that passes the reservoir. At the UT, a Maquet© venous hardshell cardiotomy reservoir with a capacity of 4200 ml (Maquet Cardiopulmonary/Getinge, Hechingen, Germany) is available for use. that can hold up to 4 litres is available for use. Fluid flows into the reservoir through the top and leaves it at the bottom.

Table 4-3: Overview of the selected final components. Section 4.3 describes the path of how these components were selected.

Component	Final component choices	Specification
1. Flow generator	2-roller pump	Realized: Prefabricated · Vendor: Maquet Cardiopulmonary/Getinge, Hechingen, Germany. · Compatible for 3/8-inch tubing. · Can generate flow up to 11 L/min.
2. Connecting conduit	3/8-inch silicone tubing	Realized: Prefabricated · Vendor: ECM Europe BV, Gemert, Netherlands. · To minimize hydraulic resistance, this size was chosen as it best matches the diameter of the inlets of the cannulation path. · Compatible with roller pump.
3. Cannulation path	· 3a Venous track · 3b Right heart	Realized: Custom-made · Segmented from patient CT data in Materialized© Mimics and remodelled in 3-Matic. · Produced at 3D-MS with Phrozen© 3D SLA printer using Flex 82A Resin. · Incorporated cross-split valve from MiniValve© (Oldenzaal, Netherlands).
4. Connectors	· 4a: ECM connector & D.1 · 4b: C.7 & D.3/P.5 · 4c (left PA*): C.10 & D.1/P.5 4c (right PA*): Maquet connector & D.1/P.5 4d: C.5 & P.4 (For details on connectors (C.x), see Table 12-11. For details on connection methods (D.y/P.y), see Table 12-12)	Realized: Custom-made/Prefabricated · 4a Product of ECM Europe BV (Gemert, Netherlands). · 4b Formlabs© Form 2 SLA printer using Clear V4 resin. · 4c Formlabs© Form 2 SLA printer using Clear V4 resin/Product of Maquet (Cardiopulmonary/Getinge, Hechingen, Germany) · 4d Formlabs© Form 2 SLA printer using Elastic 50 A resin.
5. Resistors	Bochem™ ‘Hoffmann’ stainless steel Pinchcock tube clamps	Realized: Prefabricated · Vendor: Bochem Instrumente GmbH, Weilburg, Germany. · Manually controlled.
6. Working fluid	40 % glycerol-water mixture + 1 droplet of red dye	Realized: Custom-made · Requires constant temperature of 21 °C.

	(For details and the preparation protocol, see section 12.2.2.8)	· Dye vendor: Hydra International Ltd, Milton Keynes, UK.
7. Monitoring circuit	· 1 flowmeter · 1 temperature sensor · 5 pressure sensors	<u>Realized: Prefabricated</u> · Flow: metric results in L/min, vendor: Transonic Systems Inc, Ithaca, USA. · Temperature: metric results in °C, vendor: Maquet Cardiopulmonary/Getinge, Hechingen, Germany. · Pressure: metric results in mmHg, vendor: Maquet Cardiopulmonary/Getinge, Hechingen, Germany.
* PA: Pulmonary artery		

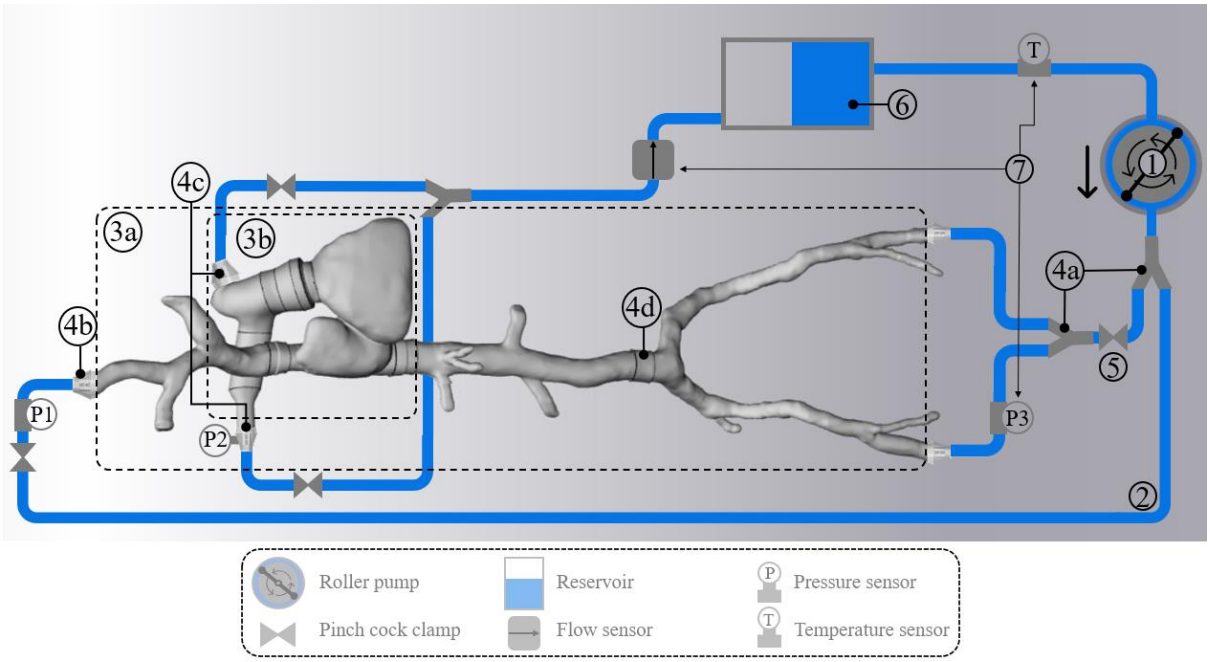

Figure 4-15: Schematic of product setup with legend of all parts. (1) Roller pump, (2) 3/8-inch tubing, (3a) venous track, (3b) right heart, (4a) tubing connector, (4b) detachable connector for inlet, (4c) permanent connector for outlet, (4d) permanent connector for comp. 3, (5) pinchcock clamp, (6) working fluid, (7) monitoring sensors. Image of cannulation path (3) taken from Materialized© 3-Matic software.

4.6 Product fabrication and assembly

For product assembly, the selected components as listed in Table 4-3 were used. For connecting the four parts of the cannulation path (comp. 3), connection method P.4 was used (see Annex B Table 12-12). These components were designed in Materialized© 3-Matic and printed with FormLabs© Form 2 SLA printer using Elastic 50A resin. Connection method P.5 was used on the inlets of comp. 3. Using connection method D.3, tubing (comp. 2) can be attached to comp. 3 for tests and simulations. Connection method P.5 was used on the outlets of comp. 3. Using connection method D.1, comp. 2 can be attached to comp. 3. The result is shown in Figure 4-16 (A). Once these components were attached, a full product

assembly was gained, see Figure 4-16 (B). A total of three pressure sensors are available to use at the location of testing. For this reason, comp.8 was altered from five to three pressure sensors. Pressure sensor 1 (measuring P_1) is placed at the top-inlet of comp. 3a (the right internal jugular vein), pressure sensor 2 (measuring P_2) is placed at the right outlet of comp. 3b (right pulmonary vein), and pressure sensor 3 (measuring P_3) is placed at the right bottom-inlet of comp. 3a (right iliac vein). A detailed logbook about the assembly of the cannulation path and accompanying connectors, can be found in Annex B section 12.2.2.8.

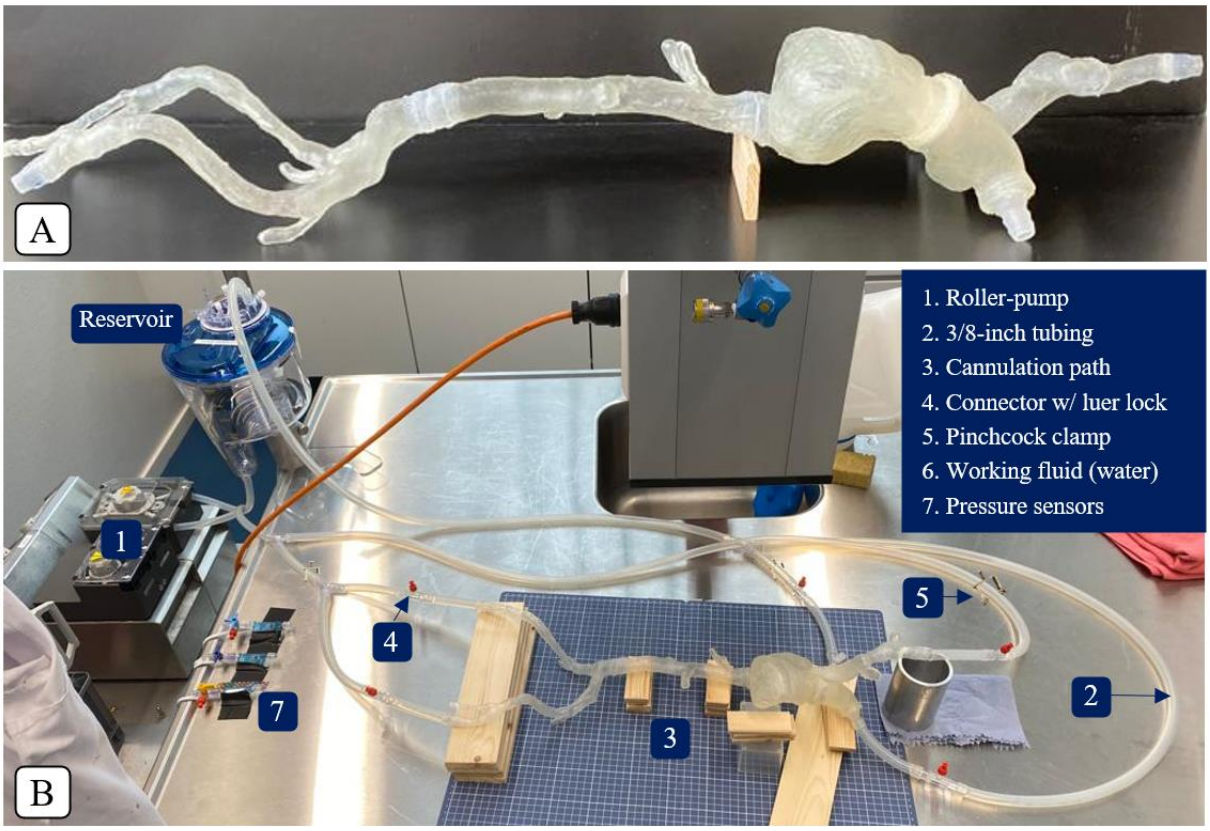

Figure 4-16: (A) Front view of fully connected cannulation path with accompanying connectors.
(B) Full product assembly with legend of corresponding components.

4.7 Product verification

Verification of the venous model is done through quantitative measurements by conducting in-vitro experiments to test the product on its functional specifications. Testing is considered successful if the product complies with the following requirements derived from the FUs (underlined words are used later in the report for referring to these requirements).

1. The product can be primed prior to testing. (FU-4)
    a. Satisfied when initially water fills up the product by replacing air.
2. The product shall maintain its shape once primed. (FU-1)
3. The product shall maintain fluid tight during testing. (FU-4 & 5)
4. The product can withstand flowrates of the corresponding native veins. (FU-4 & 7)
    a. Desired flowrate [Q] for tests: (4.5 ± 0.5) L/min. (See Annex B, Table 12-15).
5. The product must be able to monitor flowrates live during testing. (FU-8)
6. The product can withstand pressures of the corresponding native veins. (FU-7)

   a. Desired Pressure [*P*] in comp. 3a for tests: (10 ± 10) mmHg. (See Annex B, section 12.2.5.1).
   b. Desired Pressure [*P*] in comp. 3b for tests: (10 ± 5) mmHg. (See Annex B, section 12.2.5.1).
7. The product must be able to monitor pressures live during testing. (FU-8)
8. The product must be compatible with the width of cannulas used for VV-ECMO. (FU-3)
   a. Cannula width for right iliac vein entry must be ≥ 18 Fr. (See Annex B, section 12.2.5.2).
   b. Cannula width for right internal jugular vein entry must be ≥ 18 Fr. (See Annex B, section 12.2.5.2).
   c. Using ProtekDuo application, the cannula width for right internal jugular vein entry must be ≥ 29 Fr. (See Annex B, section 12.2.5.2).
9. The product is compatible with the groin-cannulation site component of the eduECMO simulator. (FU-3)
   a. Currently, only a cannulation site for the groin is developed by the eduECMO team. Therefore, no compatibility with a neck-cannulation site is required.
10. The product is compatible with a 21 °C, 40 % glycerol-water mixture. (FU-6)
11. The product must allow to monitor temperature live during testing. (FU-8)

In this order, tests were executed to satisfy individual requirements. Encountered problems and setbacks that arises were used to optimize the product. Substantiation on the specifications listed under requirements (such as the desired pressures), is described in Annex B, section 12.2.5.

5 Results

This section presents the quantitative measurement results of the final product. The text describes the methods used and accompanying findings. Interpretation and limitations are further discussed in the next chapter, section 6: Discussion.

A total of 7 tests were performed to verify if the requirements (derived from FUs, listed in section 4.7) were met. Requirements (Req.) were tested in chronological order of use (as listed in section 4.7), meaning that the first test focused on priming the product prior to testing. If this was satisfied with a test, the focus would shift to the next requirement and so on (in this example the next would be 'maintaining the products shape once primed'). Table 5-1 gives an overview of which requirements were tested during which tests and shows if the outcome was successful. A '+' indicates that the Req. was met, and a '–' indicates that the Req. was not met during that test. For each test, some details are listed. This table can be observed at the end of this section. A priming and test protocol, repair methods, and metric results of tests can be found in Annex C, section 12.3.1. Below, findings of all tests are briefly described.

Figure 5-1 (A) shows the rupture in the posterior surface of the ventricle that occurred during test 1 (lasting 25 min). This was repaired with Silicone rubber compound (SRC), a variant of connection method P.2. Figure 5-1 (B) shows that comp. 3a broke apart during test 2 (lasted 5 min). This was repaired with a custom-made sleeve (see Annex C, section 12.3.2.1) and attached using SRC, a variant of connection method P.4. This shows first signs that not all material properties of the used material seem to be suitable for a venous model used for ECMO simulations.

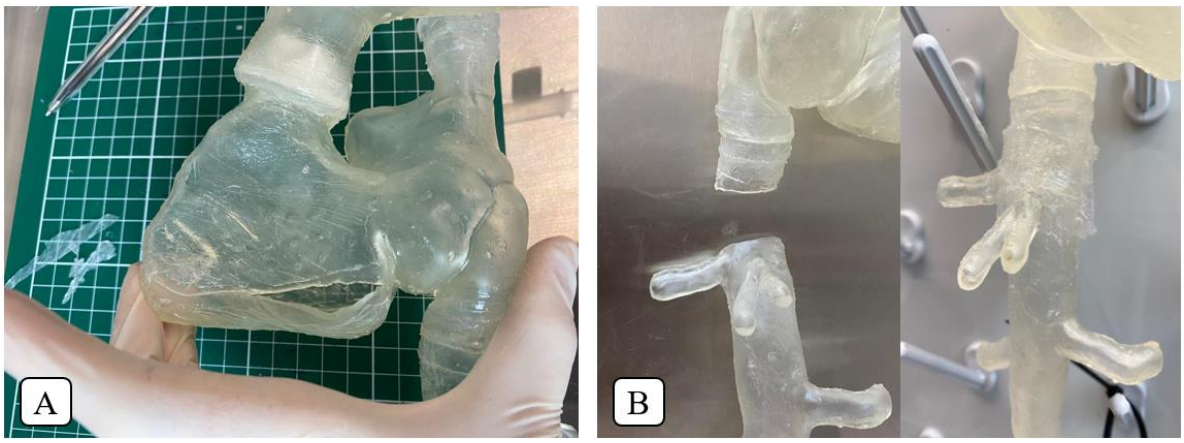

Figure 5-1: Images of comp. 3 being damaged during testing. (A) Test 1: Rupture in posterior surface of the ventricle. (B) Test 2: Comp. 3a broke apart at the Inferior Vena Cava, and this was repaired with a custom-made sleeve.

During test 3, priming went successful. Remarkably during this test, the ventricle dented at a previous repaired tear, and the Inferior Vena Cava (IVC) turned into a collapsed state, see Figure 5-2. This occurred after comp. 3 was primed and clamps were placed at each end of comp. 3, thus closing of access

to atmospheric pressure. This shows the effect of static pressure on the model as there was no dynamic pressure. This material reaction is compatible to the reaction of the Vena Cava when the transmural pressure is zero, see Figure 3-5 (A). The ventricle dented most likely due to the previous tear.

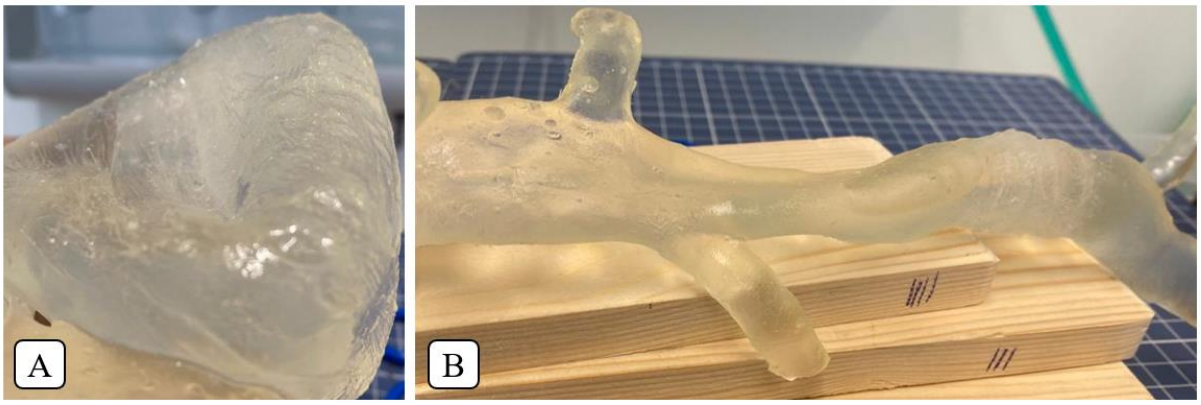

Figure 5-2: Material behavior of comp. 3 during test 3. (A) Dent in the Right Ventricle at a previous repaired tear location. (B) Inferior Vena Cava shows collapsing after priming.

During test 4.1, Req. 1 till Req. 5 were partly met (at a flowrate of 3.5 L/min) during a 30 min test. Test 4.2 is a continuing of test 4.1 as it uses the same (primed) setup. With no externally added resistance (of comp. 5), pressure in comp. 3 was higher than the desired pressure (36 mmHg > 10 ± 10 mmHg). The pressure in the conduit tubing (comp. 2) increased as reaction to reducing the pressure values in the cannulation path using the pinchcock clamps (comp. 5). This caused the tubing to detach from its connector (comp. 4a). Test 4.2 lasted 15 min.

Test 5 was done to satisfy req.8. Figure 5-3 shows how cannulation was tested through both the right iliac vein (rIV) and right internal jugular vein (rIJV). For the rIV cannulation, a Bio-Medicus® Femoral Arterial Cannula and Introducer of 19 Fr. x 18 cm (Medtronic, Minneapolis, USA) was used. For the rIJV cannulation, an Avalon Elite® Bi-Caval Dual Lumen Catheter 23 Fr. x 31 cm (Maquet Cardiopulmonary/Getinge, Hechingen, Germany) was used. This satisfies Req. 8.a and 8.b. Due to accessibility, no cannula with a size of 29 Fr. was available to verify Req. 8.c with. Instead, compatibility with a 29 Fr. x 40 cm silicone tubing was used, which also fitted through the rIJV opening. Each cannula was inserted five times to increase the accuracy of this verification. During all insertions, the cannulation model stayed intact.

Figure 5-4 shows that the product is compatible with the mock groin-cannulation site (test 6). The connection was tightened using connection method D.2. To test fluid tightness, a low flow (Q = 1 L/min) was applied. This verified a fluid tight connection (Req.3).

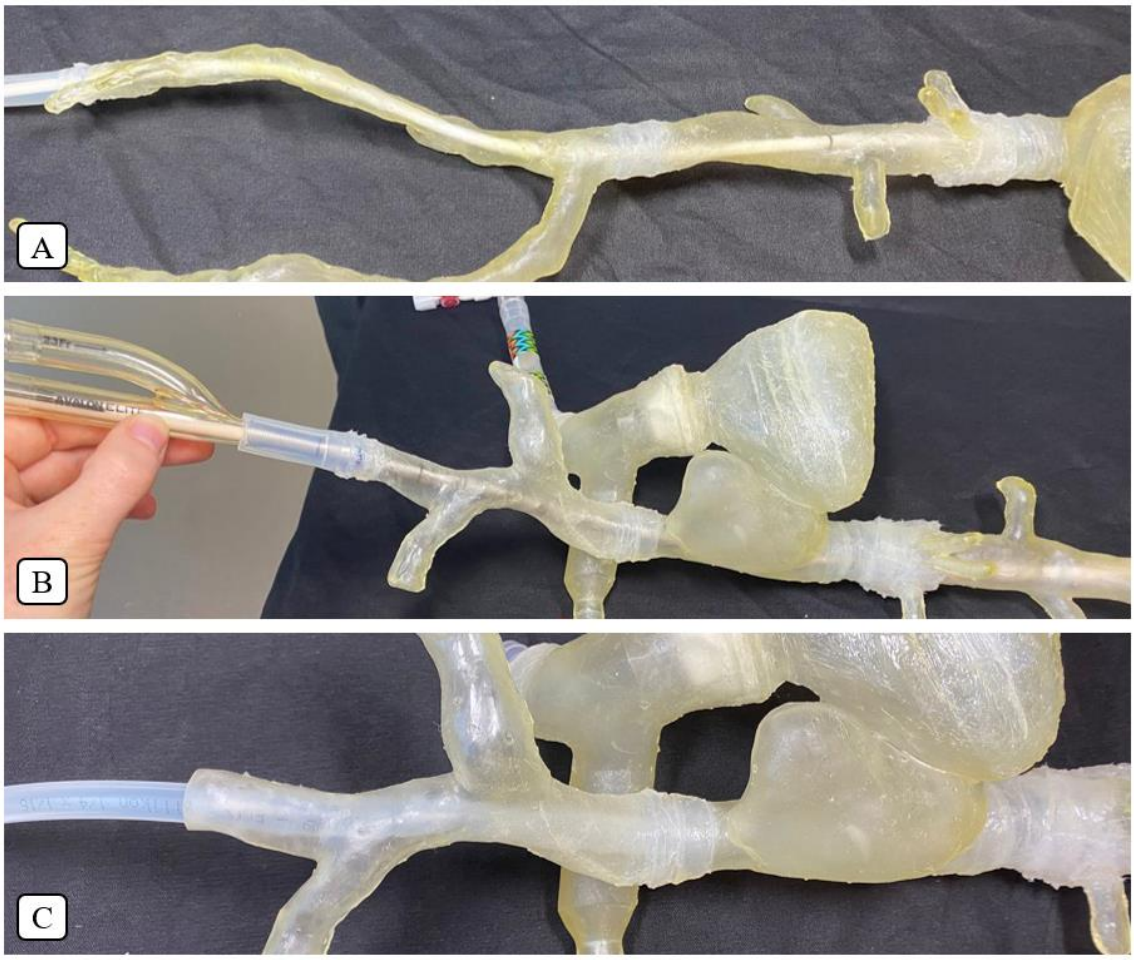

Figure 5-3: Pictures taken during test 5: compatibility with cannulas widths.
(A) Req.8.a: Cannulation through the right iliac vein (rIV) using the Bio-Medicus® Femoral Arterial Cannula and Introducer of 19 Fr. x 18 cm (Medtronic, Minneapolis, USA).
(B) Req.8.b: Cannulation through the right internal jugular vein (rIJV) using the Avalon Elite® Bi-Caval Dual Lumen Catheter 23 Fr. x 31 cm (Maquet Cardiopulmonary/Getinge, Hechingen, Germany).
(C) Req.8.c: Cannulation through the rIJV using a 29 Fr. x 40 cm silicone tube to test if the ProtekDuo® cannula (LivaNova PLC, London, United Kingdom) would fit.

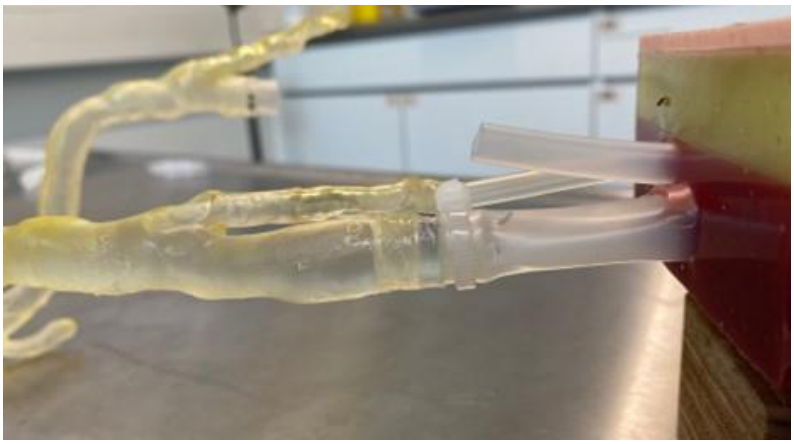

Figure 5-4: Compatibility of cannulation path with mock groin-cannulation site of eduECMO (test 6), whilst being fluid tight.

Table 5-1: Results per test if the requirements (Req.) were met. A '+' indicates the Req. was met, and a '–' indicates the Req. was not met during that test. Cells marked grey indicate that these Reqs were not tested during that test. Full Req. descriptions are found in section 4.7.

Test	1. Primed	2. Maintain shape	3. Fluid tight	4. Withstand flowrates	5. Monitor flowrates	6.a. Withstand pressures comp. 3a	6.b. Withstand pressures comp. 3b	7. Monitor pressures	8.a. Compatible w/ Single lumen	8.b. Compatible w/ Dual lumen	8.c. Compatible w/ ProtekDuo	9. Compatible w/ cannulation site	10. 40% - glycerol-water mixture	11. Monitor temperature	**Additional test details**
1	–	–	–												Rupture in comp. 3b during priming.
2	–	–	–												Comp. 3a broke apart during priming.
3	+	+	–	–	+										Puncture in comp. 3a due to increased pressure cause by flowrate of 5 L/min.
4.1	+	+	+	–	+										Successful w/ flowrate of 3.5 L/min. Continued with test 4.2 using same primed setup.
4.2	+	+	–	–	+	–	–	+							When increasing pressure in comp. 3, pressure increased in comp. 2. This caused comp. 2 to detach from comp. 4a.
5		+							+	+	+				At rIV*, tested w/ 19 Fr.** Femoral arterial cannula and introducer. At rIJV***, tested w/ 23 Fr. Dual lumen and 29 Fr silicone tubing.
6		+	+									+			Compatible with cannulation site.

* Right iliac vein. ** French. *** Right internal jugular vein.

6 Discussion

The results from the quantitative measurements (section 5) indicate that the venous model is applicable for VV-ECMO application regarding cannula insertion, compatible with the mock cannulation site of the eduECMO, a realistic representation of the anatomical shape of the cannulation path, adaptable for implementing patient specific geometries whilst produced in a time- and cost-efficient manner, and able to transport a fluid through a fluid tight model while monitoring the physiological parameters that occur in the model. During the cannula insertion test, some pressure could be applied onto the venous walls without it rupturing.

However, complications regarding the cannulation path arose when trying to prime the cannulation path or when mimicking the hemodynamics. A reason therefore is that the used material for producing this component (Flex 82A resin) appeared not to be suitable for simulation-based training applications as desired for the venous model. This conclusion can be drawn since several ruptures emerged during testing and/or when connecting connectors. Therefore, experimenting with other materials is necessary to find a material suitable for the cannulation path. A first step in experimenting with other materials was taken as described in Annex D section 12.4.1. In collaboration with research group RAM (University of Twente, Netherlands) – who have a Stratasys© Object 280 printer –, a part of the Inferior Vena Cava was printed (hereinafter: IORA prototype) using IORA Model Flex 30A resin and a water dissolvent material (Support706™) for the supports (both from vendor Isquared[2], Lengwil, Switzerland). Based on qualitative tests, this prototype seems to mimic the behaviour of large veins more realistically than the current cannulation path in flexibility and compliance, in both fully relaxed state and when flow is applied (fully expanded state). Also, connection methods P.4 and D.2 were verified to be compatible with this material. The IORA prototype was printed with a 1 mm wall thickness which led to production complications because small, not visible holes occurred in the prototype's wall during production. Because of this, no quantitative tests could be performed. The qualitative tests resulted in the hypothesis that using a 3D printing method is a more suitable production method for creating thin, fluid tight, anatomical accurate tubes with multiple branches, where a water-dissolvable support material is used in combination with a more flexible material than Flex 82A resin (such as IORA Model Flex 30A). It is recommended to verify this proposed 3D printing method and material for (connecting) larger, more complex parts of the cannulation path such as the iliac vein and right heart, and to test these parts against the requirements stated in section 4.7, in future research.

The outcome of question 2c of the survey regarding the venous track (comp. 3a) (see section 4.4.1) did initially not seem to verify the order of important characteristics initially set, see section 4.4.2, Figure 4-14. However, it is questionable whether clinicians considered the influence that complex geometry and branches have on the flow pattern. Studies that modelled parts of the venous return show that large branches of the Vena Cava – such as the right subclavian vein, left innominate vein, renal veins, and left iliac vein – influence the flow pattern [40, 41]. When focussing on the opinion of participants with technical knowledge, correct branching is considered to be more important than compliance. In the

current cannulation path, large branches have been incorporated into the design, but only the left iliac vein was opened for secondary flow from a branch in the product. This was done – with the research aim in mind to set a foundation for the venous model – to focus on the Vena Cava circulation during initial testing. Adding flow from branches will make the venous model more complex. The digital design currently holds the opportunity to open these closed branches by simply using the trimming and loft tool in 3-Matic (see protocol in Annex B, section 12.2.2.4). This fulfils the wish of technical participants of having a venous model comprising complex flow by adding flow from branches. This has already been partly applied for the IORA prototype by opening the renal veins as an initial test. As for the right heart (comp. 3b), the results question 2e of the survey verified the order of important obstacles, see section 4.4.2, Figure 4-14. However, when only looking at the results of key-users, a slight shift in importance can be observed. Users are of the opinion that when the top three ranking obstacles are successfully incorporated into the product design – which has been achieved with this version of the venous model –, the focus should be lied on implementing the contracting movement of the right heart rather than the Tricuspid Valve. Initial literature research was done on the contracting movement of the right heart (as briefly mentioned in section 4.4.3), which could be used as a starting point for future development to incorporating this obstacle, see annex D section 12.4. Also, contact was made with AdjuCor (Munich, Germany) regarding implementing their reBEAT® product as external contraction device, whereby future collaboration looks promising. With a contracting Right Ventricle incorporated, little pressure is added to the flow leaving through the Pulmonary Valve. This provides a solution to bridge the desired pressure difference between comp. 3a and 3b which was not realized during testing. To prevent backflow caused by this contraction, the Tricuspid Valve must be incorporated first/simultaneously with the contracting ventricle component. Annex D section 12.4.2 contains a preconcept that was made of a valve seating for the Tricuspid Valve.

One could argue that the material used for the cannulation path was not suitable for simulation-based training because the wall thickness of veins was too thin. To recall, 1 mm was used for the venous track (comp. 3a) and 2 mm was used for the right heart (comp. 3b). Attaching connectors onto the venous track (inlets) had to be done carefully due to its fragility which could cause ruptures. However, attaching connectors to the right heart (outlets) went effortless. The right heart is more stiff and therefore stronger compared to the venous track. However, both the right heart and venous track ruptured during testing. When using a more flexible material with a higher elongation rate, the wall thickness could likely be increased without fearing to lose the compliant behaviour. A wall thickness of 2 mm could be a more foolproof thickness. This is still close to the average wall thickness of the Vena Cava being 1.5 mm [13]. A thicker wall is also recommended for continuing research with the IORA prototype.

During test 4.2, see section 5, the connecting tubing detached from its connectors (4a) due to an increased pressure build-up. This pressure was > 60 mmHg since these connectors stayed connected during tests with such pressures (see Annex B, Table 12-8). A commonly used method to strengthen connections in circuits with high pressure rates is the addition of hose clamps to the connection. At the UT, steel hose clamps with a 9 mm Band Width and 8 – 16 mm internal radius from Javeka© (Almere, Netherlands) are available. Additionally, tests verifying the addition hose clamps to the connection is recommended once hemodynamic tests are continued. If necessary, these clamps can be added to connectors 4b and 4c as well, since hose clamps have a larger width compared to tie wraps. This reduces the chance of damaging the cannulation path as this distributes the pinching pressure over the width of hose clamps. However, due to the low pressure at these connection sites, this is likely not needed to use these for connectors 4b and 4c.

The focus of this thesis was lied on properties such as compliance and anatomical accuracy whilst creating a mock circulation of the venous system. As the foundation for a venous model still needed to be

formed, initial tests were executed with water as working fluid. Because of the complications with the cannulation path material, requirements regarding the hemodynamics could not be verified. Therefore, the 40 % glycerol-water mixture was not prepared nor tested since the hemodynamics were not yet achieved with water tests in a stable manner. For future work, a protocol on preparing this mixture was made and can be found in Annex B, section 12.2.2.8. Without using this mixture, monitoring the temperature was not needed. The temperature sensor is however available at the UT and its functioning was tested, so future work can easily implement this sensor.

Prior to each test that involved flow, the product had to be primed. This is done easily for all components except for the cannulation path, due to its organic and complex shape. Methods to remove air out of the cannulation path during priming were tapping against the vessel wall creating vibrations to force air bubbles into the flow, and by rotating the cannulation path since air has a lower density than water [42], the air bubbles would rise. As the dimensions of the cannulation path are 700 x 172 x 105 mm, and it inflects quite easily due to the thin walls and brittle material (low elongation at break), it was almost impossible to rotate and prime this component alone without it rupturing. Even with a second set of hands, priming remained challenging. However, this issue could potentially be resolved if other materials are used for the cannulation path (e.g., the IORA prototype was ‘flat’ when empty/at rest). If it remains an issue, it is recommended to design/purchase a holder for the cannulation path that allows easy rotation/tilting whilst the component is kept in position.

As stated in section 4.3.3.1, segmentation of the veins could not be automatically segmented because they cannot be clearly distinguished by the used software. This resulted in manually segmenting the full cannulation path using the custom-made protocol that can be found in Annex B, section 12.2.2.4. The final digital model had to be smoothened multiple times before a realistically vein-shaped model was formed. However, manually segmenting such large paths have an increased risk of human-made-errors. Therefore, if future research will use the protocol for segmenting comparable paths (from different patient data), it is of great importance to always verify the segmented data with the used imaging data before continuing with remodelling. For segmentation of the heart, advanced segmentation tools are purchasable specifically for the cardiovascular system. This tool provides quick, easy, and accurate segmentation. If in the long run more patient data need to be segmented – also for future VA-ECMO application –, it is advised to consider purchasing this tool as it will reduce the segmentation time immensely.

A first step in improving the venous model is taken by designing and producing the IORA prototype. While further testing and optimization is necessary to achieve a high-fidelity venous model that could be implemented in a simulation-based trainer for training personnel that apply ECMO treatment, this thesis provides the literature foundation, a verified design, and an initial prototype of the venous model, thereby taking a significant stride towards realizing high-fidelity ECMO simulators.

7 Summary and Outlook

To summarize, veno-venous Extracorporeal Membrane Oxygenation (VV-ECMO) is a support system that temporarily supports patients that suffer from respiratory system failure. In recent years, the demand for VV-ECMO treatment increased and therewith also the need for innovation, in particular ways to train personnel. The eduECMO project aims to fill this research gap between the stated need and the current lack of high-fidelity ECMO simulators. This thesis is situated within this project, where a venous model was designed and developed that represents the human anatomy and hemodynamics around cannulation sites. The final product is an assembly of seven components that together form the venous model. It contains a cannulation path which is used during simulation, and a supporting circuit for the hemodynamics. The outcome of this thesis is a literature foundation, verified design, and initial prototype of the venous model, that can be used for future research on high-fidelity (VV)-ECMO simulators.

During this research, focus was lied on creating a closed-loop, watertight venous model. Regarding the flow dynamics, it was assumed that the overall flow is laminar as is the case for flow through the venous system, according to literature [12, 13]. Because of this assumption, no in-depth research was done on the complex flow dynamics of the cardiovascular system. However, certain factors can cause turbulent flow. For instance, a study suggests that at sites where large veins merge, different flow patterns may occur [40]. Therefore, it is advised to continue in-depth research thereon and to translate this into the venous model. This will help identifying which branches have drastic influence on the main flow and thus have to be incorporated into the venous model. Other branches should be left closed based on the rationale not to make the venous model more complex than it should be. Monitoring flow behaviour can be done with methods such as echography and 4D flow MRI [40].

As advised by a participant of the survey and being a requirement for the eduECMO simulator, the cannulation path should be compatible with echography. Compatibility with echography depends on various factors such as trapped air in the product and comparable acoustic impedance between neighbouring materials [43]. When the venous model will be implemented in the eduECMO simulator, it would be wise to test compatibility of echography.

A big design change that needs to be made when incorporating VA-ECMO application into the eduECMO simulator, is the incorporation of a pulsatile flow component. A quick and easy solution therefore could be purchasing the ViVitroLabs© pulsatile pump as described in section 4.3.1. The pump must however be analysed in more depth before making such a decision as it is most likely an expensive pump. It was recently discovered that the TechMed Centre of the UT (Enschede, Netherlands) owns this pump. Collaboration with this party may be optional and would make using this pump more feasible. A widely used method throughout studies to model the arterial pressure and pulsatile flow is the Windkessel model. Initial literature research and preconcepts have already been made, see Annex D, section 12.4. This could be used as starting point for future research regarding this component.

Several research topics as mentioned above still need to be solved before final implementation of the venous model into a high-fidelity ECMO simulator can be realized. However, product optimization has been kicked-off by using a 3D SLA printing method (such as the Phrozen© or Stratasys© printers) in combination with a more flexible material than was used for the current version of the cannulation path (such as IORA Model Flex 30A resin). With the IORA protype test a suitable production method and material choice for hands-on simulators seems promising. It is therefore advised to continue research on this work. When proof of concept is achieved, it is recommended that testing the hemodynamic boundaries of the venous model are continued.

8 Terms and Abbreviations

8.1 Terms

Elongation at Break
Material property that is defined as the point a material fractures due to the applied forces (%).

Pressure, dynamic
The pressure created to the fluid kinetic energy.

Pressure, hydrostatic
Pressure exerted by fluid that elevates or drops, due to gravity.

Pressure, static
Pressure of the fluid. This pressure is present even when there is no flow.

Resistance, peripheral
Resistance due to changes in number of branches and cross-sectional area of the vessel.

Resistance, hydraulic
Resistance that exerts on the fluid when it flows.

Stress
Pressure that arises from externally applied forces perpendicular to a materials cross section.

Strain
The measure of how much an object is stretched or deformed. It is mostly expressed as a change in length or circumference of a material.

Ultimate tensile strength
Material property that is defined as the maximal stress capacity a material can reach (MPa).

Young's Modulus
Material property that is defined as the linear relationship of stress and strain (MPa).

8.2 Abbreviations

- 3D – three dimensional
- 3D-MS – 3D Medical Support
- ARDS – Acute respiratory distress syndrome
- C.x – Connector concept
- Comp. 1 – Flow generator
- Comp. 2 – Connecting conduit
- Comp. 3 – Cannulation path

- Comp. 3a – Venous track
- Comp. 3b – Right Heart
- Comp. 4 – Connectors
- Comp. 5 – Resistors
- Comp. 6 – Working fluid
- Comp. 7 – Monitoring circuit
- COPD – chronic obstructive pulmonary disease
- CT – Computed tomography
- D.y – Detachable connection method concept
- DRS – Design requirement specifications
- ECMO – Extracorporeal membrane oxygenation
- eduECMO – The ECMO & cannulation trainer is the outcome product of the eduECMO project. This product is under development of the EOST group.
- ELSO: Extracorporeal Life Support Organization
- EOST – Engineering Organ Support Technologies
- Fr. – French
- FU – Functional Units
- IJV – internal jugular vein
- MRI – Magnetic Resonance Imaging
- MST – Medisch Spectrum Twente
- P.y – Permanent connection method concept
- RBC – Red blood cells
- RIA – Risk analysis
- SBT – Simulation-based training
- SLA – Stereolithography
- SRC – Silicone Rubber Compound
- STL – Stereolithography CAD files that contain 3D printable designs
- SW – Solidworks® 2020 student version
- URS – User requirement specifications
- UT – University of Twente
- VA – Venoarterial
- VC: Vena Cava
- VSMCs – Vascular smooth muscle cells
- VV – Venovenous

9 List of Figures

10 List of Tables

11 References

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Annex

12.1 Annex A: Additional background information

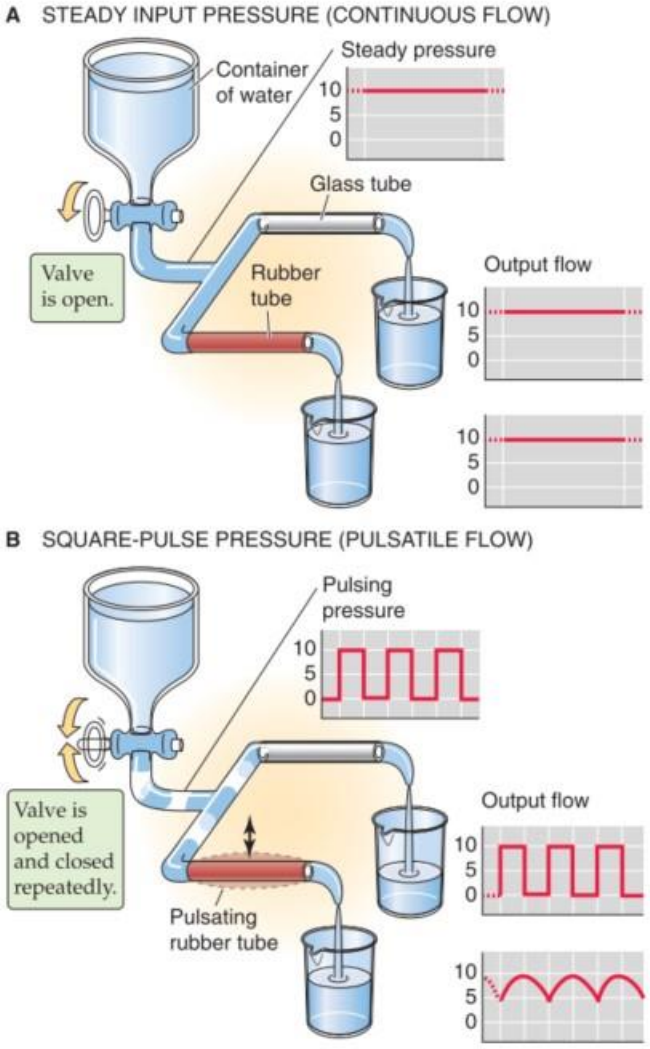


Figure 12-1: Example of no pulse in the veins if the flow has a nihil pulse.
(A) If a steady flow goes through a compliant rubber tube, it will act as a rigid tube, just like the glass tube.
(B) If A pulsatile flow is pushed through the rubber tube, it will show compliant behaviour [13].

12.2 Annex B: Additional to development process

12.2.1 Detailed overview of stakeholder analysis

Table 12-1: Overview of all stakeholders relevant for this thesis. Each stakeholder's characteristics, expectations of, and impact/contribution to the thesis are listed.

Stakeholders	Characteristics	Expectations	Impact and contribution to the thesis(-product)
Board of the hospital	Interested in providing the best treatment to patients and being able to supply employees with training gear.	The product should have value towards the current procedures.	Can be asked to give feedback on the product and what chance it has on adding value. No direct contribution on this thesis is expected.
Deutsche Forschungsgemeinschaft (Funding)	This project is funded by the Deutsche Forschungsgemeinschaft (DFG), which is a German Research Foundation. There are no strings attached through this funding on this thesis.	Research that contributes to the field eduECMO is involved in.	The main 'big costs' are materials for production and testing. Funding is needed for personal and materials for production and testing.
EOST group (Development team of the eduECMO	Designing the ECMO & cannulation trainer is one of the projects of the EOST group.	They want an efficient, quality and working design.	Since each team member has a different contribution to the eduECMO project, they can learn and help each other.
ECMO nurses, bedside nurse simulation trainers and other potential users (Users)	The users of the eduECMO, mainly for assisting and educating purposes.	Strives to improve for the best treatment of patients. This can be improved by more training possibilities to improve their role in ECMO therapy.	Can be asked to give feedback on the product or design, and if optional, to test the product.

ECMO system developer(s)	To improve ECMO systems and more easily test designs/products on a 'human' circulation, so acute animal experiments can be reduced.	They want a product that can be used for ECMO system testing.	Supply ECMO system parts like the oxygenator or cannulation tubes. No direct contribution on this thesis is expected.
European commission	Controlling body that will eventually have interest in the eduECMO project, not this thesis yet.	Interested in new, safe, and efficient innovations.	Need to accept the product as a quality training device for perfusionists and physicians, which can assurance profit. Not yet applicable for this thesis.
Industry	Interested in innovating products and research.	They want a product with a good margin of profit and efficient innovating qualities (such as reducing animal testing).	Provide knowledge through e.g., the state of the art or executed studies. In this thesis, this is used to gain knowledge regarding the current research field.
Insurance company	They provide insurance for potential patients. If the eduECMO results in a cheaper treatment, they would be interested.	Induced medical costs due to a higher training level and therefore an improved treatment outcome.	No direct contribution on this thesis is expected.
Patient (in need of ECMO therapy)	Wants the best possible treatment.	An increased positive patient outcome.	Give permission to use patient imaging data.
Perfusionists, physicians, cardiac surgeons (Key-users)	The users of the eduECMO, mainly for training purposes.	Strives to improve for the best treatment of patients. This can be improved by more training possibilities to achieve a higher training level.	Can be asked to give feedback on the product or design, and if optional, to test the product.

Relatives (Patient's family, caregiver and/or friends)	Wants the best possible treatment for their loved one and want to help in any way possible.	An increased positive patient outcome.	If a patient is incompetent, relatives are asked permission to use patient imaging data.
Society	This includes everyone that is not necessarily involved with eduECMO but do have an opinion, for example politicians, civilians, etc.	Demands a low number of patients and low health care costs and want quality and life improvement. The product must also have little to no negative impact on the environment.	This product is needed by society in order to bring it on the market and for it to be used. No direct contribution on this thesis is expected.
University of Twente	Supervision on, and facilitating of the development team is provided from within the University.	Is interested in innovations that are created within the University, and to provide a work environment for students and employees.	Provide a working place, including laboratories to produce and execute tests.

12.2.2 Conceptualizing

12.2.2.1 Component 1: Overview of market and literature research

Table 12-2: Overview of market and literature research regarding for component 1. Additionally, personal opinion/findings/pros/cons were listed. Together with this and the rating done in Table 12-3, a final component selection was made.

Name [Ref.]	Product elaboration	Personal opinion/findings/pros/cons
Vivitrolabs pulsatile pump [35]	Specifically designed to replicate a beating heart for *in vitro* testing and development of cardiovascular medical devices. Highly accurate. Accessories such as 1/2-inch connectors are available.	Company (located in Canada) specializes in cardiovascular device testing equipment and services. Pumps looks user-friendly. Pump is used in various research.
Trando-med pulsatile pump [44]	Designed to support *in vitro* experiments of cardiovascular models. Pressure at pulsation output end: 20 – 350 mmHg. Supporting liquids: Water, brine, and PBS.	Company (located in China) does not specialize in making pumps, but in 3D reconstruction of CT/MRI images and 3D printing of silicone mock models.
Cardiac Bioreactor [45]	Complex setup with a pump and three dual-chamber actuators (with a membrane between). With applied air pressure in one chamber, the fluid gets displaced in the other.	For their aim it is a nice product. However, for this thesis, this device has too many parts that have to be custom-made, all with multiple risks. As it still needed improvement, neither the product nor design is a final version that could be easily reproduced.
Membrane pump [46]	Dual-chamber pump. Advised to only use clean water. Maximum flow is 3.8 L/min.	Cheap product (41 €). This is a commercialized product, originally made for Drinkwater home application.
Roller pump [47]	Rotating rollers are forced into flexible tubing, creating flow inside the tube. This creates a pulse. Generate flow up to 11 L/min.	In the past, a used pump for ECMO systems. Pulse is not adjustable separately from the flow (rotations per minute). A motor-actuated pump is available at the UT for use. Simple design, little maintenance required.
Rotaflow centrifugal pump [48]	Pump functions by utilizing a spinning rotor and curved impeller blades to create a centrifugal force. This generates a continuous flow.	Currently, a commonly used pump for ECMO systems. Both manually and motor-actuated pump are available at the UT for use. Design has multiple moving parts, thus requires maintenance.

Piston pumps [49-51]	Piston pump using a linear actuator (servo motor) to drive the piston inside a cylindrical chamber.	Relatively simple hardware design for a creating a pulsatile flow. If software is correct designed, accurate control can be achieved.
Cam plate-driven piston pump [52]	The drive-unit (actuating the piston of a syringe), consist out of a stepping motor, controller, and cam disc. This specific design is for low-volume flow.	Relatively simple hardware design for a creating a pulsatile flow. The cam plate is patient specific, so not adjustable for all future modifications.
Gear pump [32]	A gear pump is driven by a servo motor. Gear pumps typically give pulse free flow. Additional components used for pulsatile flow generation.	Relatively simple hardware design for a creating a pulsatile flow. If software is correct designed, accurate control could be achieved.

Table 12-3: Rating of considered products for component 1. All findings are rated with respect to satisfying relevant functions (FUs), and other important factors based on objectives. Rating is from 1 (poorly/not satisfied) till 3 (Fully satisfied), relative to the other considered products. These rates are multiplied with a weight factor (1 till 3), based on their value to this project.

Solution [Ref.]	**Vivitrolabs pulsatile pump [35]**	**Trando-med pulsatile pump [44]**	**Cardiac Bioreactor [45]**	**Membrane pump [46]**	**Roller pump [47]**	**Rotaflow centrifugal pump [48]**	**Piston pumps [49-51]**	**Cam plate-driven piston pump [52]**	**Gear pump [32]**	**Weight factor**
FU-2: Adaptable for future modifications	3	2	2	1	3	3	3	1	2	3
FU-4: Transport a fluid	3	3	3	3	3	3	3	3	3	3
FU-5: Fluid tight	3	3	3	2	3	3	2	1	2	3
FU-7: Mimic native venous flow (minimal to no pulse)	3	2	2	1	3	3	2	2	2	3
FU-8: monitors flow	3	3	2	1	3	3	1	1	1	1
Cost-effective	1	1	1	3	3	2	3	3	3	2
Availability: at UT (3), purchasable (2) or not purchasable (1)	2	2	2	2	3	3	2	1	1	2
Requires additional production process (yes=1, no=3)	3	3	3	3	3	3	1	1	1	2
Total	**51**	**45**	**44**	**38**	**57**	**53**	**43**	**32**	**38**	

12.2.2.2 Component 3: Cannulation path

Defining cannulation path

Table 12-4: Overview of cannulation sites and endpoint used during VV-ECMO treatment.

Cannulation sites	Endpoint of cannula tip	Ref.
Right femoral vein (optionally left femoral vein)	Right Atrium, near the IVC junction.	[8]
Right internal jugular vein	Right Atrium, near the SVC junction. ProtekDuo cannula: Pulmonary artery, approx. 5 cm when passing the Pulmonary Valve.	[8] [9]

Defining the veins and heart structures between the locations stated in Table 12-4, the cannulation path will consist of the following, listed in Table 12-5.

Table 12-5: Overview of all veins, heart structures and branches that will together form the cannulation path. The table starts superior at the cannulation site in the neck and goes caudal towards the cannulation site in the groin.

Name of vein/heart structure	Name of branches
Cannulation site in neck: Right internal jugular vein	
Right innominate vein	Subclavian vein
Superior Vena Cava	Left innominate vein
Right Atrium	-
Tricuspid Valve	-
Right Ventricle	-
Pulmonary Valve	-
Pulmonary artery	Branches into left and right pulmonary artery
Inferior Vena Cava	Hepatic veins (three branches), renal veins (two branches)
Common iliac vein	Internal iliac vein
External iliac vein	-
Cannulation site in groin: Common femoral vein	

12.2.2.3 Component 3: Comparing production methods for cannulation path

Table 12-6: Overview of production methods that were considered to realize component 3. Each method is shortly described. Pros and cons are listed. These are based on findings or personal opinion.

Production method	Short description	Pros (+) and cons (-)
Injection Moulding	Injects molten material into mould cavity. Widely used for mass-production of rigid plastics.	+ Thermoplastic elastomers can be processed through some injection moulding machines. - Complex mould because of hollow structure. - Optimization of product would require producing new mould.
Liquid casting	Pouring elastic material (silicone) into a mould.	+ Viable option with what is available at UT. - Complex mould because of hollow structure. - Optimization of product would require producing new mould.
Purchasing silicone mock model [44]	Trando-Med specializes in 3D reconstructing of CT/MRI images and 3D printing of silicone mock models.	+ Within one week delivered prototype. - Examples on their website did not look highly accurate, only basic contours. - Little details on parameters and material option could be found. - No prove of working through research.
3D SLS printing	Selective Laser Sintering (SLS) is a powder-based 3D printing method that fuses powder particles using a laser.	+ Highly accurate and complex products. + Available at Rapid Prototyping Lab (UT). + Easy to use. + Compatible with semi-flexible materials such as Thermoplastic Polyurethane (TPU). - Cannot guarantee fluid tightness.
3D FDM printing w/ Ultimaker 2+ or 3	Fused Deposition Modelling (FDM) is a 3D printing method that uses a heated nozzle that extrudes a thermoplastic material (filament) in a certain shape. Prints in layers.	+ Fast production. + Compatible with semi-flexible materials such as TPU or Thermoplastic Elastomers (TPE). + Available at the Rapid Prototyping Lab of the UT (Enschede, Netherlands). + Affordable option. + Easy to use. - No high level of detail. - Support structures sometimes hard to remove. - Cannot guarantee fluid tightness.

3D SLA printing w/ FormLabs© Form 2	Stereolithography (SLA) is an additive production process that uses a UV laser to selectively solidify liquid resin layer by layer. These three printers differ in with which resin they are compatible, dimensions, and vendor (therefore maybe differ in quality).	+ Available at the Rapid Prototyping Lab of the UT (Enschede, Netherlands). + Elastic resin available: Elastic 50A resin. + Can produce highly detailed, accurate 3D objects that are fluid tight. - Limited in dimensions. - Lab technician is convinced that this printer cannot realize complex, large prints that are desired.
3D SLA printing w/ Stratasys© Object 280		+ Available at research group RAM of the UT (Enschede, Netherlands). + Flexible resin available: IORS Model Flex 30 A Black. + Can produce highly detailed, accurate 3D objects that are fluid tight. + Used in comparable research, see Table 3-1. - Printer is malfunctioning during the development process of this thesis.
3D SLA printing w/ Phrozen© 3D SLA printer		+ Start-up company (3D Medical Support©, Enschede, Netherlands) focusses on creating tailored products for medical professional support. + Prior to the thesis, collaboration possibilities for this thesis were discussed. + Flexible resin available: Confidential but comparable to Flex 82 A Resin. + Can produce highly detailed, accurate 3D objects that are fluid tight. - Used material is confidential. - Developer will become dependent of this company.

Table 12-7: Rating of production methods that were considered to realize component 3. All methods were rated with respect to satisfying relevant functions (FUs), and other important factors based on objectives. Rating is from 1 (poorly/not satisfied) till 3 (Fully satisfied), relative to the other production methods. These rates are multiplied with a weight factor (1 till 3), based on their value to this project.

Production method	**Injection Moulding**	**Liquid casting**	**Purchasing silicone mock model [44]**	**3D SLS printing.**	**3D FDM printing.**	**3D SLA printing w/ FormLabs© Form 2**	**3D SLA printing w/ Stratasys© Object 280**	**3D SLA printing w/ Phrozen© 3D SLA printer**	**Weight factor**
Produce fluid tight products	2	3	3	2	2	3	3	3	3
Produce products with complex geometry	1	3	2	3	2	3	3	3	3
Produce hollow products	3	3	3	3	3	3	3	3	3
Produce flexible products	2	2	3	2	2	3	3	3	3
Produce large parts (200 x 150 x 150 mm)	2	3	3	3	1	3	3	3	3
Easy modifications to design possible	1	1	2	3	3	3	3	3	3
Easy to use	1	1	3	2	3	3	2	2	1
Quick production	2	1	2	3	3	3	3	3	2
Cost-effective	1	3	2	3	3	3	2	2	3
Availability: at UT (3), purchasable (2), or custom-build (1)	2	1	2	3	3	3	3	2	2
Total	**45**	**59**	**65**	**71**	**63**	**78**	**74**	**72**	

12.2.2.4 Component 3: Protocol on segmentation and remodelling method

Segmentation of the CT patient data was done using Materialized© Mimics Innovation Suite software version 24.0 (Leuven, Belgium). Remodelling the segmented model was done using Materialized© 3-Matic Innovation Suite software version 16.0 (Leuven, Belgium).

Segmentation in Mimics

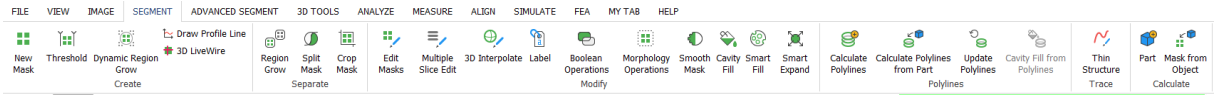


Figure 12-2: Image of the segment toolbar in Materialized© Mimics Innovation Suite software version 24.0. This toolbar is the most referred to in this protocol.

The segmentation protocol refers to tools that can be found in the toolbar at the top of the screen when using the software, see Figure 12-2. If parts of the protocol are still unclear such as using a certain tool, there are videos of specific situations found on YouTube that use these tools.

1. Import the CT images.
2. Segment > Threshold: set the Hounsfield Units (HU) from -60 to 2326. This way, clearly distinguished parts, and extreme soft tissues such as fat tissue are filtered out.
    a. Select Segment > Region grow, to filter out floating structures.
    b. Optional: Segment > Threshold: select predefined bone (CT) threshold and continues with a region grow operation. This is used to identify clearly distinguished parts in the images, such as bones, parts of the heart, the aorta etc. It is now still one parts (one colour). This was used so several structures (e.g. Aorta) are clearly shown in the imaging data (because of the colouring labelling). When comparing this CT data with literature, these structures help for quicker identification of other structures such as the Vena Cava.
3. Segment > Split Mask: Split mask into multiple masks. Select Mask made in previous step and label the regions as e.g.: vascular system and other. Through marking all structures of the selected mask with the colour of the desired region, you add that part of the mask to that region. The entire mask has to be divided into a region. Markings have to be made in multiple views on multiple slices (axial, coronal, sagittal). Markings do not have to be accurately placed.
    a. This mask now has parts of the desired vessel.
    b. Figure 12-3 shows an example of how to use this tool.

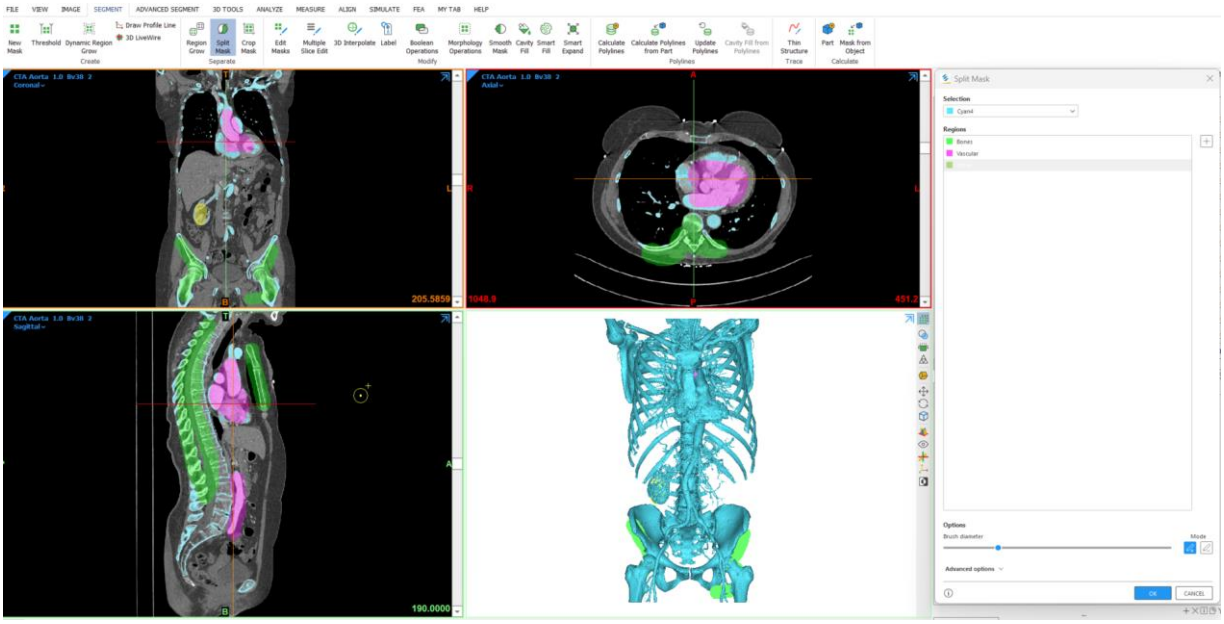


Figure 12-3: Example on how to use the Mask Split tool in Mimics.

4. Segment > Edit Masks: Select your mask.
    a. Operation: Remove
    b. Option: Lasso.
    c. In your 3D mask image, use the lasso tool to remove any small undesired structures and artifacts.
    d. Once done, apply a Segment > Region grows and select your mask in the 3D mask image. This way, floating structures are filtered out.
5. Segment > Split masks: Do the same for your vascular system Mask as it still has to many artifacts. If desired, you can add regions to split if e.g. the aorta is in your Mask.
6. Segment > Multiple slice Edit: Select the vascular system mask made in the previous step. This can be used to add or remove parts of the mask.
    a. As it is desired to have a smooth vessel, it is advised to use the Option: Ellipse and adjust size/shape accordingly to the vessel you want to segment.
    b. Activate: Auto-Interpolate.
    c. Choose a view (axial is advised) and a start point, e.g. the lowest image slice.
    d. Accurately mark the entire vessel.
        i. If the vessels will move a lot throughout slices, make small steps: Move 3 – 5 slices up by using the arrow button on your keyboard.
        ii. If the vessel stays in position throughout slices, make bigger steps: Move 5 – 10 slices up by using the arrow button on your keyboard.
    e. Again, accurately mark the entire vessel once moving several slices. Click on: Interpolation in the toolbox. This connects the markings on slices whilst trying to follow the vessel (based on your markings).
    f. If this went well, you could make multiple markings before interpolation.
    g. Once done, click OK. Now you will have a rough version of your vessel, see figure for example.
7. For the heart, repeat all previous steps with a new HU range of 179 till 1163.
    a. Because this is one organ, it is hard to distinguish parts of it such as the myocardium, atriums, and ventricles. Therefore, it is advised to first segment the heart as a total and then, use the small step method when using the ‘Multi slice edit’ tool. Apply this tool on the heart from different views.

   b. Process of segmentation of the heart is shown in Figure 12-5.
8. To improve the rough shape of the vessel, the Segment > Multi slice edit tool is again used. Now the aim is to improve the parts that are incorrectly incorporated into your mask. This tool has an on and off mode (below indicate view), which can be used to remove markings if needed.
   a. Repeat the process of smoothening your vessel by using this tool until you are satisfied.
   b. Adding branches can also be done with this tool.
9. Segment > Split Mask tool is used on the heart Mask to divide it into parts such as the atriums, ventricles, pulmonary artery, and myocardium.
10. Use Segment > Multi slice edit tool to improve/smooth the masks of the Right Atrium, Right Ventricle, pulmonary artery.
11. Once you are satisfied, go to 'File > Export > 3-Matic… With this, you finalized mask is exported to 3-Matic software for remodelling the mask.

The process of segmenting the veins of the cannulation path (comp. 3a) is shown in Figure 12-4, and the segmentation process of the right heart and pulmonary artery (comp. 3b) is shown in Figure 12-5.

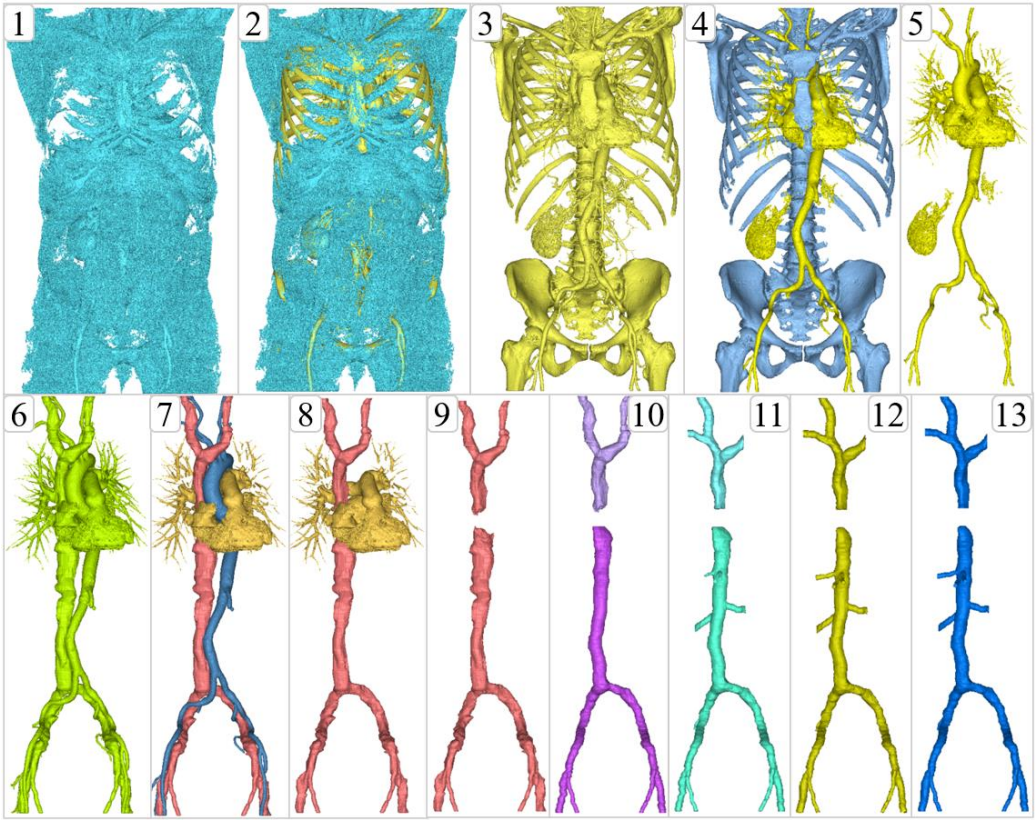


Figure 12-4: Visualization of the process of segmenting the veins of the cannulation path, from image 1: defining the Hounsfield Units, until image 13: a smoothed finalized mask.

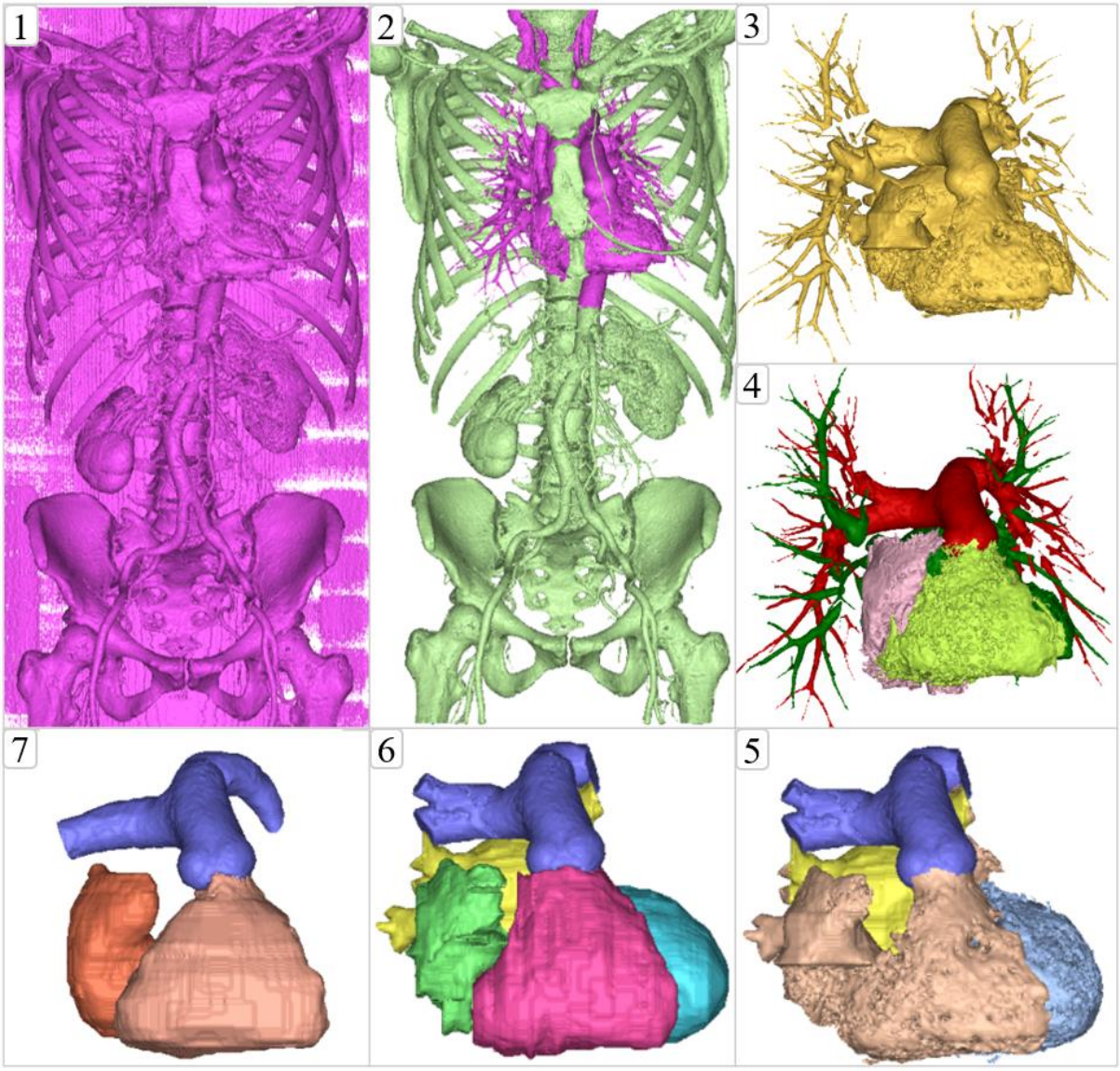


Figure 12-5: Visualization of the process of segmenting the right heart and pulmonary artery, from image 1: defining the Hounsfield Units, until image 7: a smoothed finalized mask.

Remodelling in 3-Matic

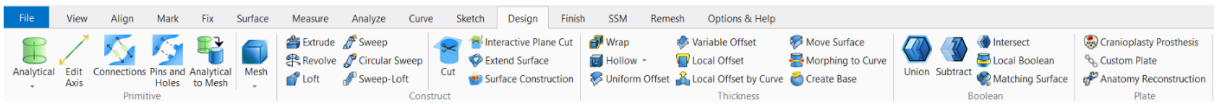


Figure 12-6: Image of the design toolbar in Materialized© 3-Matic Innovation Suite software version 16.0. This toolbar is the most referred to in this protocol.

The remodelling protocol refers to tools that can be found in the toolbar at the top of the screen when using the software, see Figure 12-6Figure 12-2. If parts of the protocol are still unclear such as using a certain tool, there are videos of specific situations found on YouTube that use these tools.

1. Import your segmented masks. In the previous example, there were 5 masks (see Figure 12-4(13) plus Figure 12-5 (7)) in total collectively referred to as ‘the model’.
2. Finish > Local Smoothing. This tool is used to smooth the imported masks.
    a. Adjust the Parameters of the smoothing tool to:

        i. Smoothing diameter: 5 – 15, depending on which area you are smoothing. Larger areas can be smoothed with a larger diameter.
        ii. Smoothing strength: 1.0.
    b. Left click and drag the curser over the surface of the masks. Do not smooth the connection sites between the masks as this will influence the connection in later stages.
    c. See Figure 12-7 (1).
3. Design > Wrap. This tool is used to eliminate small features in and resurface the model.
    a. Select all masks as entities.
    b. Adjust the wrap parameters to:
        i. Gap closing distance: 0.0.
        ii. Smallest detail: 0.50.
        iii. Rsulting offset: 0.0.
        iv. Only mark the option ‘Reduce’. (If you do not have this option, activate the ‘Expert mode’ by clicking on the bottom ‘Expert mode: OFF’ in the bottom of your screen).
    c. Now, you have copies of you mask files in your object tree with the word ‘wrapped’ behind it.
    d. Hide the masks that were used as entities by right clicking on them and selecting ‘Hide’.
    e. See Figure 12-7 (2).
4. Design > Boolean Union. With this tool you can merge masks as one mask.
    a. Select the following masks to form the venous track (component 3a):
        i. Superior Vena Cava (SVC),
        ii. Inferior Vena Cava (IVC),
        iii. Right Atrium.
    b. Select ‘create new part’ as parameter and make sure you did not select ‘remove original’.
    c. Hide the masks that were used as entities by right clicking on them and selecting ‘Hide’.
    d. See Figure 12-7 (3).
5. Design > Wrap.
    a. Select the newly made mask (step 4) as entity.
    b. Adjust the wrap parameters to:
        i. Gap closing distance: 1.5.
        ii. Smallest detail: 0.5.
        iii. Resulting offset: 0.0.
        iv. Only mark the option ‘Reduce’.
    c. Hide the masks that was used as entity by right clicking on them and selecting ‘Hide’.
    d. See Figure 12-7 (4).
6. To remove floating shells in the mask:
    a. Mark > Shell. Click on the previous wrapped mask (Step 5) in your work area.
    b. Mark > Invert.
    c. If there appear ‘Marked Triangles’ in the mask list of the object tree, delete these. If there are no ‘marked triangles’, then there were no floating shells in the mask.
7. Duplicate the previous made mask. Rename it to: VenousTrack_lumen_final.
8. Design > Hollow.
    a. Select the VenousTrack_lumen_final mask as entity.
    b. Adjust reduce parameters to:
        i. Hollow type: outside
        ii. Distance: 1.0 (this is the wall thickness)
        iii. Smallest detail: 0.5

iv. Mark the options ‘Reduce’ and ‘Clean-up at border’.
c. Rename the part to: VenousTrack_hollow
d. See Figure 12-7 (5).

9. Finish > Local Smoothing. This tool is used to smooth the mask.
    a. Adjust the Parameters of the smoothing tool to:
        i. Smoothing diameter: 5 – 10
        ii. Smoothing strength: 1.0
    b. Left click and drag the curser over the surface of the masks. Focus on connection sites and branches. These are usually places that are not smooth yet. Do not smooth the ends of vessels/branches as this can lead to holes in the mask.
10. Finish > Trim. With this tool parts of a mask can be removed.
    a. Select the VenousTrack_hollow mask as entity.
        i. As trimming method, select ‘remove inner’.
    b. Zoom in to the inlets of the venous track.
    c. You can make a trimming region by left clicking multiple points within the working area. Once the area is closed, these colours the inner area green. This is the trimming area. With this, you can open the ends of the vessels by clicking ‘Apply’. Now you have an entrance of your vessel.
    d. See Figure 12-7 (6a - b).
    e. Repeat this for all three entries.
11. Repeat step 6 to remove floating shells in the mask.
12. For the right heart (component 3b), repeat step 4 until 11, but now for:
    a. Step 4: Select the following masks to form the right (component 3b):
        i. Superior Vena Cava (SVC),
        ii. Inferior Vena Cava (IVC),
        iii. Right Atrium (RA),
        iv. Right Ventricle (RV),
        v. Pulmonary Artery (PA).
    b. Step 8: Set the distance (wall thickness) to 2.0.
    c. Step 9: Trim the mask.
        i. Now you trim the mask:
            1. Approximately 5 cm before the SVC enters the RA (see Figure 12-7 (7a)). This means you also trim the right PA partly,
            2. Approximately 5 cm before the IVC enters the RA see Figure 12-7 (7b),
            3. The PA on both left and right branch as shown in Figure 12-7 (7c).
        ii. This results in a final right heart model, see Figure 12-7 (8).
13. Show both final masks of the venous track (step 11) and the right heart (step 12).
14. Finish > Trim.
    a. Select the venous track mask as entity.
    b. Make a trimming area such that the overlapping part of the two masks lays within this area, see Figure 12-7 (9). Click apply.
    c. Now you have a final venous track mask that perfectly fits onto the right heart model, see Figure 12-7 (10).

Depending on the printer’s dimensions, you can cut this mask into parts by duplicating the mask in the object tree and use the trimming tool.

15. Once all final parts are completed, ‘File > Export > STL’. Select the final masks as entities and define the desired path for your Output directory. Set file format to Binary and click ‘Apply’.

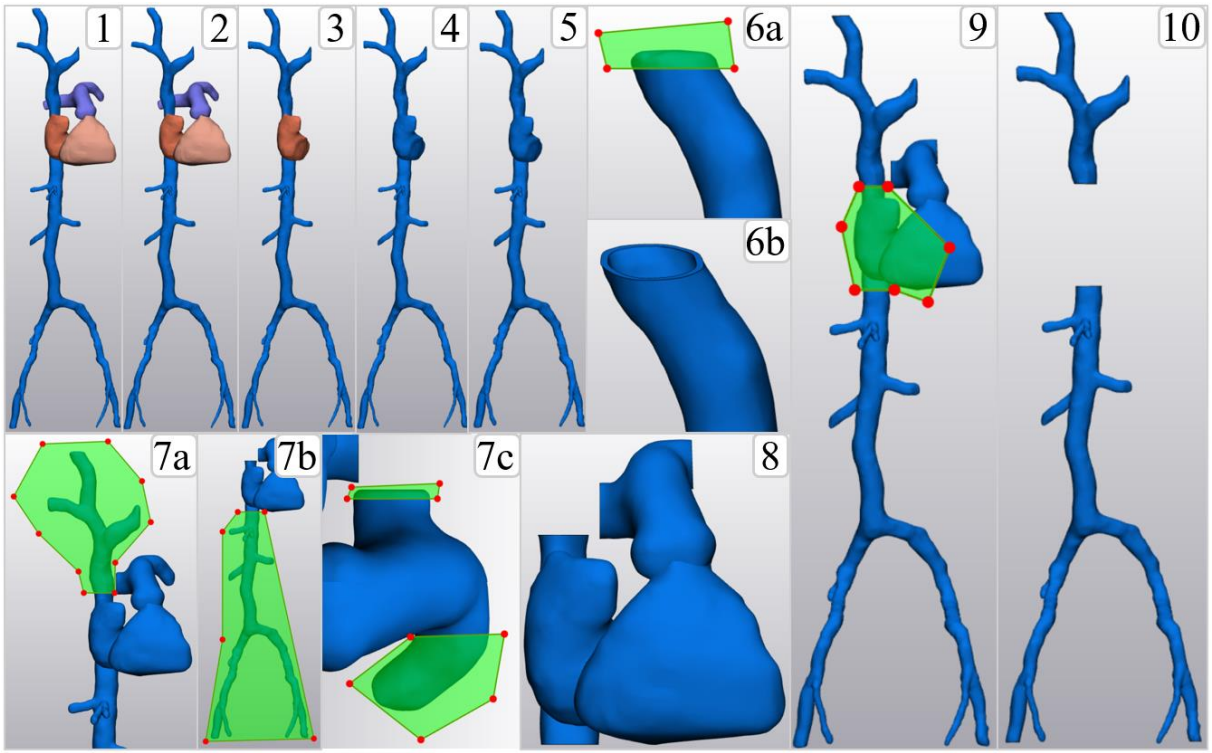


Figure 12-7: Visualization of the process of remodeling the venous model. Images 1 until 6b show the steps done to prepare the venous track (component 3a). Image 7a until 8 show the steps done to finalize the model of the right heart (component 3b). Finally, images 9 and 10 show how the right heart model was used to finalize the model for the venous track.

Adding external parts to the remodelled segmentation model

If you want to add parts to your remodelled, segmented model as done in this thesis regarding the right PA outlet and the valve seating, you can follow the next steps (this example adds a part onto the right PA so it will fit a 3/8-inch connector):

1. File > Import part. Select the desired STL file. (see Figure 12-8 (1)).
2. Align > arc to arc.
    a. Select the edge of the outlet of the right PA of the Right Heart mask as ‘Arc on fixed entity’ (see Figure 12-8 (2 red)),
    b. Select the edge of the outlet of the imported part as ‘Arc on moving entity’ (see Figure 12-8 (2 green)),
    c. Use the Method parameter to align the imported part coincident or coincident face to face.
    d. Click apply. See Figure 12-8 (3) for result.
3. Align > Translate/Rotate.
    a. Select the imported part as Main entity.
    b. Select only Translate.
    c. Move the part approximately 30 mm towards the left (from a frontal view), so it passes the SVC outlet, see Figure 12-8 (4).
4. Design > Loft. This tool will merge the two parts.
    a. Selection:

i. Type: Loft with thickness using surface.
ii. Entity 1: Side surface of the right Heart mask that forms the edge of the outlet of the right PA (same as in step 2).
iii. Entity 2: Side surface of the Imported part (same as in step 2).

b. A red line should appear between the two surfaces. If this is not the case, make sure the elected surfaces are not divided. Otherwise merge these two surfaces by selecting them both, clicking on the right mouse and select ‘merge’.
c. Click ‘Apply. See Figure 12-8 (5) for the result.

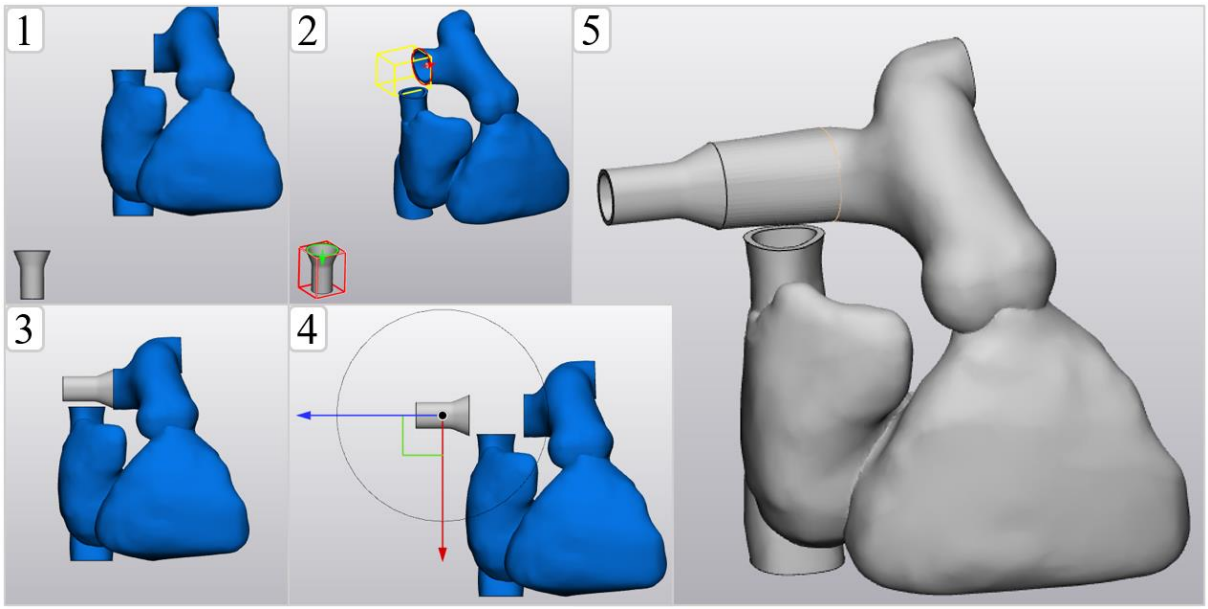


Figure 12-8: Visualization of the process of adding parts to the remodeled venous model. In this example, a 3/8-inch tube is added so the model can easily be connected with a prefabricated connector. Images 1 until 4 show process steps and image 5 shows the final model.

12.2.2.5 Component 3b: Pulmonary Valve seating

The design sprint methodology was used to develop and test the pulmonary valve seating.

Valve seating design

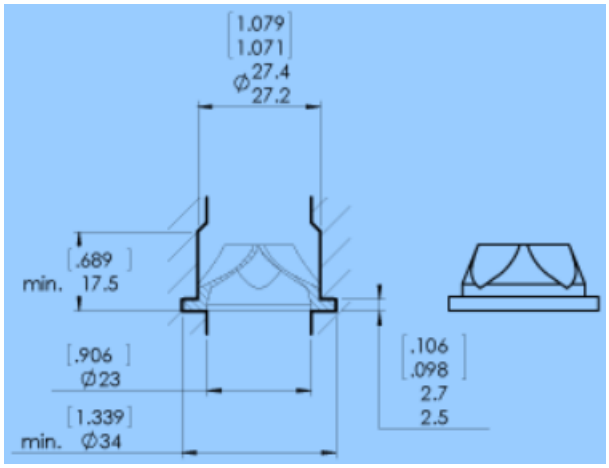


Figure 12-9: Seating suggestion from Minivalve© for the cross-split valve with diameter of 27.0 mm. The seating design is based on these dimensions.

Valve seating testing

The custom-made test part (where the valve seating dimensions were incorporated into) is divided into two parts so inserting the valve for testing would be possible. These two parts are connected through a tread. The endings have 3/8-inch connector diameters for easy fitting of 3/8 tubing. Table 12-8 shows the test results of the valve seating test. Figure 12-10 shows a schematic of the test setup. Tested on maximal pressure of 60 mmHg and a flowrate of 5 L/min.

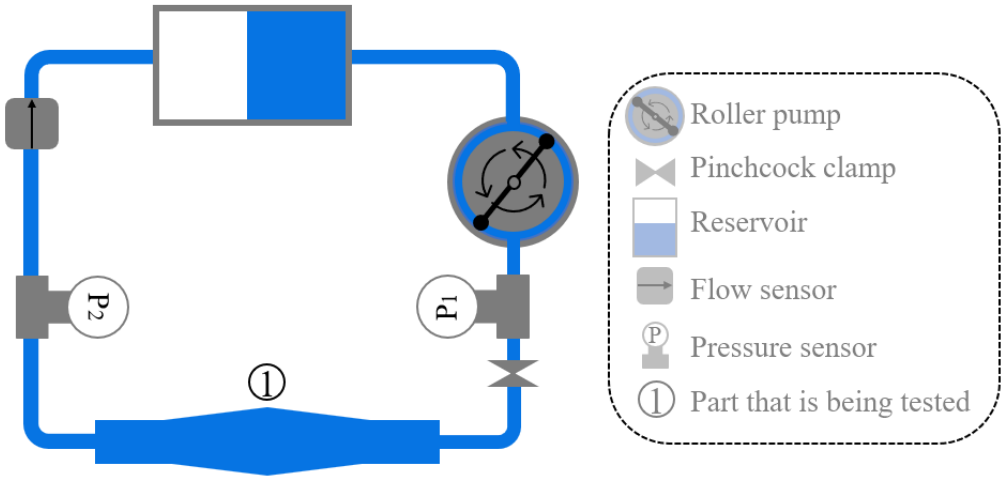


Figure 12-10: Schematic test-setup of parts that are being tested during the development process. (1) Can be different things such as the valve seating, or connection methods.

Table 12-8: Output data of testing the valve seating. Data flowrate (*Q*) in L/min, obtained with a flow sensor. Pressure (*P*) in mmHg is obtained with two pressure sensors.

2023-05-01	***Q* (L/min)**	***P*$_1$ (mmHg)**	***P*$_2$ (mmHg)**
Zeroing pressure sensors			
Open to atmosphere	0	0	0
Closed to atmosphere	0	3	2
Open to set-up	0	25	25
***t* (min)**	*Q* (L/min)	*P*$_1$ (mmHg)	*P*$_2$ (mmHg)
0	0	25	25
1	3.0	25	25
2	4.0	32	25
3	5.0	44	25
4	5.0	57	25
6	5.0	57	25
8	5.0	57	25
10	5.0	63	25

Valve seating placement into the digital model of the cannulation path

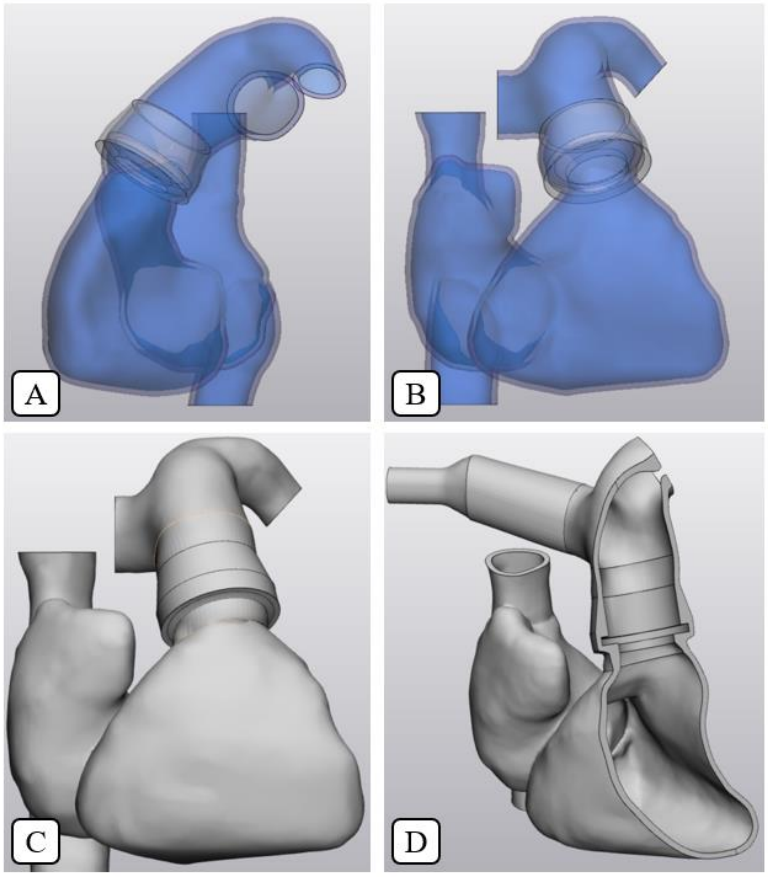


Figure 12-11: (A) & (B): Views of how the valve seating was implemented into the digital model of the cannulation path, using 3-Matic. The right heart's transparency was increased, so the correct position of the seating could easily be seen from each angle. (C) Finalized implementation of the valve seating into the right heart. (D) Cutaway view to check if the valve seat aligned properly with the right heart.

12.2.2.6 Component 3: Process description on cannulation path prototypes

Table 12-9: Test print of the Inferior Vena Cava, printed by 3D medical support using Flex 80A resin.

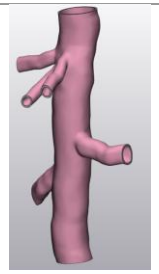
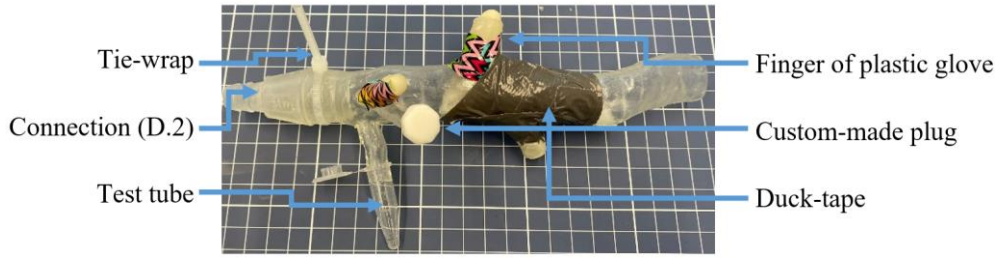
Date	2023-03-30
Description	Test print of the Inferior Vena Cava (IVC)
Images	  
Production	Printed by 3D Medical Support that used the Phrozen© SLA printer (Hsinchu, Taiwan) and a confidential flexible resin. They say it has comparable material properties to Flex 80A resin (FormFutura®, Nijmegen, Netherlands).
Concept details	Wall thickness: 1 mm Length: 20 mm Diameter IVC: 20.7 mm
Purpose/aim	This print was made to test if this production method could produce such complex and large parts of the cannulation path. The print was used to experiment with the compliance of the material, and to analyse the anatomical shape of the print.
Testing	**Compliance of material (qualitative analysis):** The material is quite brittle as it easily tears, see Figure 4-12. **Anatomical shape/feel (qualitative analysis):** For this analysis, the opinion of Dr. F.R. Halfwerk – who is a technical medical doctor in cardiothoracic surgery –, and MSc. L. van de Velde – who is a PhD-candidate at the UT who specializes in simulations of the cardiovascular system –, was asked as they could physically meet. Therefore, they could feel and see the part in real-life. Anatomical shape: Both gave positive feedback on the anatomical shape of the IVC and its branches. Realistic feel: Both gave comparable feedback. The vessel is stiffer than real veins, which would result in less yield during a cannulation. **Fluid tightness:** The material itself is fluid tight, however creating a closed-loop circuit was challenging. As shown in the figure on the right, several methods where tried to close the branches but it continues to leak a bit.
Conclusion	With an improved digital design were branches are closed or their diameter is altered, the assumption was made that this production method could be used for producting the cannulation path.

Table 12-10: Final (four) prints that together form the cannulation path (comp. 3), printed by 3D medical support using Flex 80A resin.

Description	**2023-05-03**			
Concept	Full cannulation path, printed in four parts called: (1) Superior Vena Cava (SVC), (2) Right heart (RH), (3) Inferior Vena Cava (IVC), (4) Iliac veins (IVs)			
Images	 (1) (2) (3) (4)			
Production	Printed by 3D Medical Support that used the Phrozen© SLA printer (Hsinchu, Taiwan) and a confidential flexible resin. They say it has comparable material properties to Flex 80A resin (FormFutura®, Nijmegen, Netherlands).			
Concept details	(1) SVC Wall thickness: 1 mm Length: 150 mm Width: 100 mm Depth: 46 mm	(2) RH Wall thickness: 2 mm Length: 139 mm Width: 146 mm Depth: 99 mm	(3) IVC Wall thickness: 1 mm Length: 200 mm Width: 79 mm Depth: 56 mm	(4) IVs Wall thickness: 1 mm Length: 217 mm Width: 172 mm Depth: 105 mm
Purpose	These parts will together form the final cannulation path. To achieve this, all parts must be connected, and tested on fluid tightness, pressure, and flow. Assembly is described in 4.6, product verification is described in section 4.7, and results are discussed in section 5.			

12.2.2.7 Component 4: Connectors

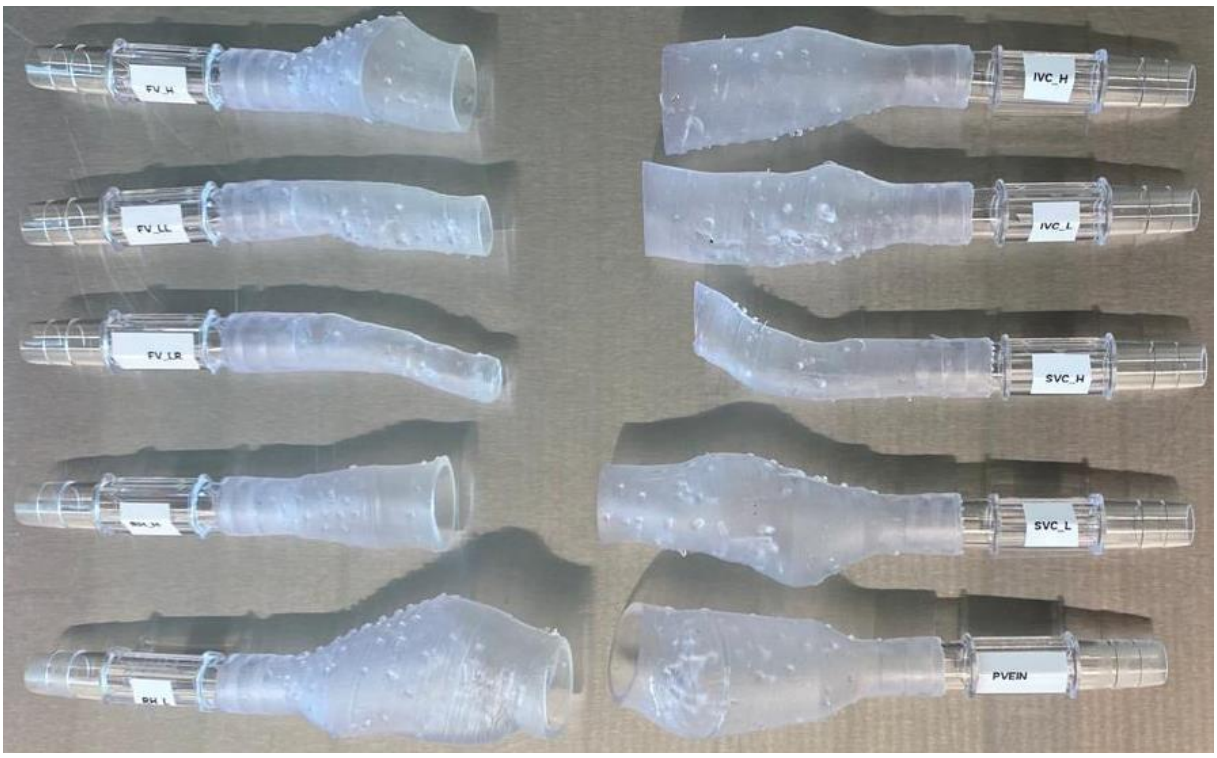
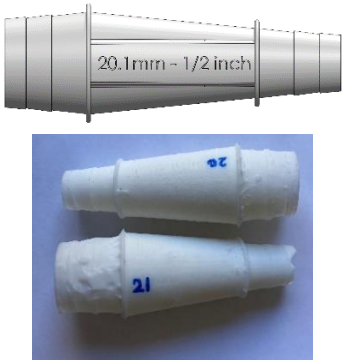
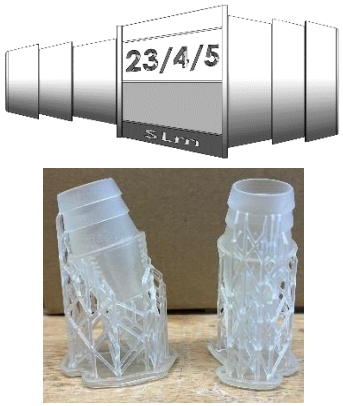
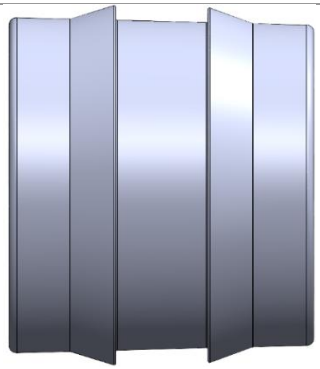


Figure 12-12: Test vessels. Printed with Form 2 SLA printer and Elastic 50A V1 resin. They can be used for testing connectors.

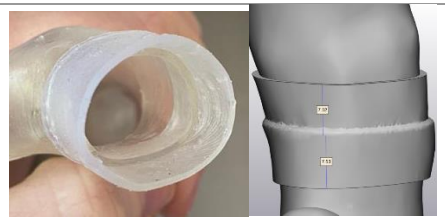
Trial-and-error process of connectors (C.x) and connection methods (D.y/P.y)

Table 12-11: Trial-and-error process of connectors (C.x). ‘x’ indicates the concept. Inlet of a connector is always where it is connected to conduit tubing and the outlet is the connection to the cannulation path. OD is the outer diameter and ID is the internal diameter.

Date	2023-03-31	2023-04-05	2023-05-03	2023-05-10
Concept	**C.1** Concept for comp. 4b	**C.2** Concept for comp. 4b	**C.3** Concept for comp. 4d	**C.4** Concept for comp. 4d
Image				
Development method	Design: Solidworks® Production: FormLabs© Form 2 SLA printer w/ White V4 resin.	Design: Solidworks® Production: FormLabs© Form 2 SLA printer w/ Clear V4 resin.	Design: Solidworks® Production: FormLabs© Form 2 SLA printer w/ Clear V4 resin.	Design: Solidworks® Production: FormLabs© Form 2 SLA printer w/ Clear V4 resin.
Concept details	Connectors endings are placed inside the two tubes its connecting. Thickness: 0 – 1 mm Length: 82 mm OD_inlet: 6.35 mm OD_outlet varies (identical to cannulation path.)	Improvement w.r.t. C.1. Connectors endings are placed inside the two tubes its connecting. Thickness: 1 – 2 mm Length: 62 mm OD_inlet: 5.35 mm OD_outlet varies (identical to cannulation path.)	Entire connector is placed inside the two tubes its connecting. Thickness: 1 – 2 mm Length: 15 mm ODs vary (identical to cannulation path.)	Improvement w.r.t. C.3. Entire connector is placed inside the two tubes its connecting. Thickness: 1 – 2 mm Length: 20 mm ODs vary (identical to cannulation path.)

Pros	· Middle part is strong and thick enough.	· Stronger product. · Clear deviations between parts. · Fits nicely onto comp. 2 & 3. · Text is readable.	· Short.	· Short. · Shape fits nicely onto the comp. 3 parts. · Additional parts can be added.
Cons	· Endings are too thin, causing the prototype to break during production. · Incorrect print angle caused support structures to print onto part. · Text not engraved deep enough, caused not readable. · Too long.	· Too long (Can cause flow disruptions). · Lies internally (Can cause flow disruptions).	· Rigid material. · Shape does not fit nicely onto the comp. 3 parts. (Will cause leakage). · To prevent leakage, an additional strengthened must be added but there is no room for additional parts. · Lies internally (Can cause flow disruptions). · No labelling for identification.	· Rigid material. · Lies internally (Can cause flow disruptions). · No labelling for identification.
Improvements	· Make ‘shark teeth’ shape on endings larger. · Increase overall thickness of endings to < 1 mm. · Reduce length of middle part. · Alter print angle. · Increase depth of engraved text.	· Reduce overall length.	· Alter the shape so additional parts can be added for connection methods.	· Try flexible materials.

Continuation of Table 12-11.

Date	**2023-05-15**	**2023-05-22**	**2023-06-19**
Concept	**C.5** Concept for comp. 4d	**C.6** Concept for comp. 4b	**C.7** Concept for comp. 4b
Image			
Development method	Connector wraps around the connection site (external connection). Design: Materialized© 3-Matic. Production: FormLabs© Form 2 SLA printer w/ Elastic 50A resin.	Connectors endings are placed inside the two tubes its connecting. Design: Solidworks® Production: FormLabs© Form 2 SLA printer w/ Clear V4 resin.	Improvement w.r.t. C.6. Connectors endings are placed inside the two tubes its connecting. Design: Solidworks® Production: FormLabs© Form 2 SLA printer w/ Clear V4 resin.
Concept details	Thickness: 1 mm Length: 15 mm ODs are +1 mm of the vessel that is being connected.	Thickness: 1 mm Length: 20 mm OD_inlet: 5.5 mm OD_outlet varies (identical to cannulation path.)	Thickness: 1 mm Length: 20 mm OD_inlet: 6.35 mm OD_outlet varies (identical to cannulation path.)
Pros	・ Smooth transition between parts of comp. 3. ・ It has identical dimensions to comp. 3 for a perfect fit. (Does not force comp. 3 into a circular shape).	・ Short. ・ Clear labelling for identification. (Arrow-head point into flow direction). ・ IDs are identical to comp. 2 & 3 it is connecting. (No radius deviations that influence the flow.	・ Short. ・ Clear labelling for identification. (Arrow-head point into flow direction). ・ IDs are identical to comp. 2 & 3 it is connecting. (No radius deviations that influence the flow. ・ Grip to detach the connector.

Cons	· Not a strong connection without additional parts/materials to strengthen.	· Slope causes comp. 3 to tear. · No grip to detach the connector. · Lies internally (Can cause flow disruptions).	· Lies internally (Can cause flow disruptions). · Not a strong connection without additional parts/materials to strengthen.
Improvements	N/A		N/A

Continuation of Table 12-11.

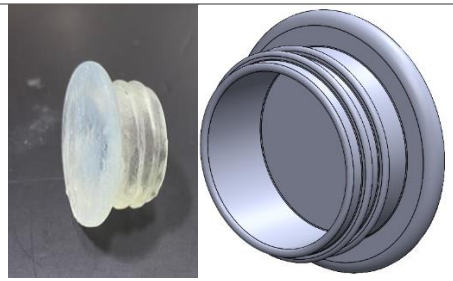
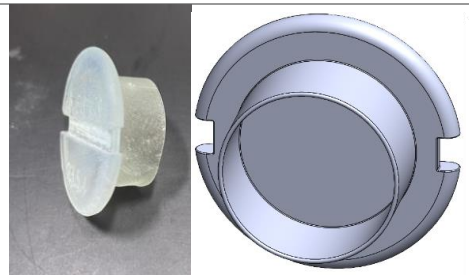
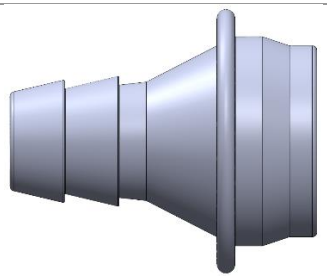
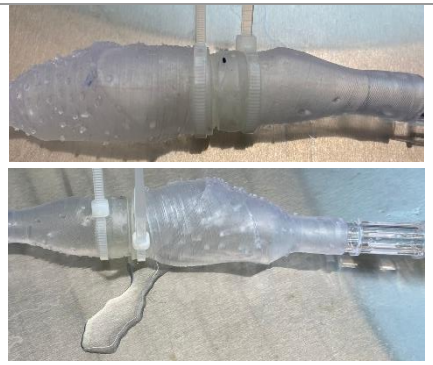
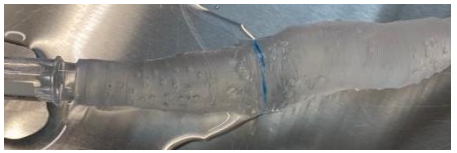
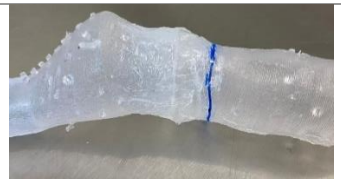
Date	**2023-05-12**	**2023-05-15**	**2023-05-22**
Concept	**C.8** Concept for comp. 4c	**C.9** Concept for comp. 4c	**C.10** Concept for comp. 4c
Image			
Development method	Plugs to close off the left Pulmonary artery. Design: Solidworks® Production: FormLabs© Form 2 SLA printer w/ Clear V4 resin.	Improvement w.r.t. C8. Without ribbed side. Design: Solidworks® Production: FormLabs© Form 2 SLA printer w/ Clear V4 resin.	Makes left Pulmonary artery a second outlet for flow. Design: Solidworks® Production: FormLabs© Form 2 SLA printer w/ Clear V4 resin.
Concept details	Thickness: 1 – 2 mm Length: 13 mm OD: 21 mm	Thickness: 1 mm Length: 13 mm OD: 21 mm	Thickness: 1 mm Length: 34 mm OD: 10.5 mm
Pros	N/A	· Fits into left pulmonary artery opening. · Slot for tie wrap so it can be connected onto component.	· Fits into left pulmonary artery opening. · Allows connection with comp. 2.
Cons	· Does not fit due to ribbed side.	· No flow through left pulmonary artery.	· Needs additional connection method to make fluid tight. · Relatively quick narrowing of diameter, results in increased resistance for flow through left pulmonary artery.
Improvements	· Remove ribbed side.	· Alter design for flow possibility.	N/A

Table 12-12: Trial-and-error process of connection methods (D.y/P.y). ‘D’ indicates a detachable connection method, ‘P’ indicates a permanent connection method, and ‘y’ indicates the concept. For the used connectors is referred to Table 12-11.

Date	2023-04-05	2023-05-01	2023-05-11	2023-05-12
Concept	**D.1** Method for comp. 4b	**D.2** Method for comp. 4b-d	**D.3** Method for comp. 4b-d	**D.4** Method for comp. 4c
Used connector	C.2	C.4	C.4	C.9
Image				
Connection method	Purely the connector and the vessel/tube.	D.1 + tie wrap. · RS© Tie wrap size: 150 x 3.6 mm.	D.2 + vinyl tape. · RS© Tesa 4163 Black PVC Electrical tape, 19 x 33 mm.	D.2 + Rubber ring.
Testing fluid tightness (FU-5)	Leakage at connection w/ comp. 3. Fluid tight at connection w/ comp. 2.	During priming (with a flowrate of 0.3 L/min), the connection detached, and water leaked out.	Tested fluid tight up to > 50 mmHg. See annex B, Table 12-13 for test data.	During priming (with a flowrate of 0.3 L/min), the connection leaked.
Pros	· Simple connection method. · Works for comp. 2.	· Tie wrap strengthens the connection. · Simple connection method.	· Simple connection method. · Fluid tight.	· Simple connection method.
Cons	· Leakage at comp. 3 connection site.	· Comp. 3 is prone to tearing and a tie wrap can ‘cut’ into the material.	· Not a ‘pretty’ seal method. · Tape is not reusable.	· Not fluid tight. · Blocks flow.

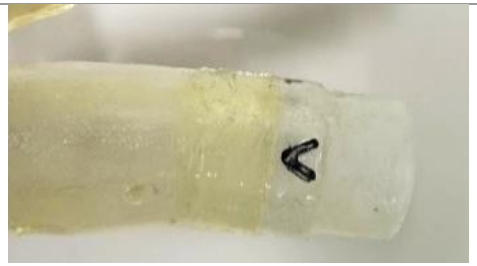
		· Not fluid tight because tie wrap could not be tightened all the way because of the tearing. · Forces comp. 3 into a circular shape.	· Forces comp. 3 into a circular shape.	
Improvements	· Add additional part to strengthen connection.	· Add additional part to reduce change of tearing and strengthen connection.	· Try method where comp. 3 is not forced into different shape.	· Allow flow.

Continuation of Table 12-12.

Date	**2023-05-11**	**2023-05-11**	**2023-05-11**	**2023-05-12**
Concept	**P.1** Method for comp. 4d	**P.2** Method for comp. 4d	**P.3** Method for comp. 4d	**P.4** Method for comp. 4d
Used connector	C.4	N/A	N/A	C.5
Image		 		 
Connection method	D.1 + Interfacing paper ・ HEMA© Interfacing paper. For adhesion, heat is applied onto the paper.	Two vessels are ‘glued’ against each other with SRC. ・ RS© Silicone Rubber Compound (RS 555-588).	Two vessels have an overlap of ± 5 mm and are ‘glued’ together with SRC. ・ RS© Silicone Rubber Compound (RS 555-588).	Two vessels are ‘glued’ together with SRC and for more surface area, C.5 is wrapped around the connection site. ・ RS© Silicone Rubber Compound (RS 555-588).
Testing fluid tightness (FU-5)	Did not adhere to the vessel, so not fluid tight.	During priming the set up (with a flowrate of 0.3 L/min), the connection broke and water leaked out.	Tested fluid tight up to > 60 mmHg. See Annex B, Table 12-13 for test data.	Not individually tested as it is a similar connection method to P.3.
Pros	N/A	・ Minimal use of additional parts/materials to connect vessels.	・ Fluid tight. ・ Strong. ・ Connection site stays flexible. ・ Shape of comp. 3 is not altered.	・ Smooth transition between parts of comp. 3. ・ Strong. ・ Connection site stays flexible.

				· Shape of comp. 3 is not altered.
Cons	· Not fluid tight. · Weak connection. ·	· Not strong enough to withstand pressures. · Prone to leakages.	· Not all connection sites can overlap each other. · No smooth transition from the two vessels internally.	· Use of additional parts/materials to connect vessels (makes the connection site a little stiffer).
Improvements	· N/A (not suitable concept for further exploration)	· Add additional material so there is an overlapping area.	· Find a way to connect without needing overlapping comp. 3.	N/A

Continuation of Table 12-12.

Date	**2023-05-23**	**2023-05-23**	**2023-06-19**
Concept	**P.5**		
	Method for comp. 4c	Method for comp. 4c	Method for comp. 4b
Used connector	C.10	3/8-inch luer-lock connector (Maquet© Cardiopulmonary/Getinge, Hechingen, Germany)	C.7
Image			
Connection method	Comp. 3 is ‘glued’ onto the used connector using Silicone Rubber Compound (SRC). · RS© Silicone Rubber Compound (RS 555-588).		
Testing fluid tightness (FU-5)	This concept arose during product assembly (section 4.6.) and was tested during the quantitative measurements, see section 5.		
Pros	· Fluid tight. · Strong. · Other side of the connector can still be used for detachable connection methods.		
Cons	· Internal, rigid connector on the cannulation path of when a cannula is inserted. This is only applicable for the combination of P.5-C.7 (right image). · Forces comp. 3 into circular shape.		
Improvements	N/A	N/A	N/A

Test details during ‘trial-and-error’ phase of component 4

Table 12-13: Output data of test D.3 and P.3. Data flowrate (Q) in L/min, obtained with a flow sensor. Pressure (P) in mmHg is obtained with two pressure sensors. See Figure 12-10 for the test set up and where each sensor was located.

2023-05-10	**Q (L/min)**	**P_1 (mmHg)**	**P_2 (mmHg)**		
Zeroing pressure sensors					
Open to atmosphere	0	0	0		
Closed to atmosphere	0	8	2		
Open to set-up	0	27	27		
		Test with D.3 (See Table 12-11)		Test with P.3 (See Table 12-11)	
t (min)	Q (L/min)	P_1 (mmHg)	P_2 (mmHg)	P_1 (mmHg)	P_2 (mmHg)
0	0	27	27	27	29
1	0.8	25	26	25	26
2	0.8	36	26	31	26
3	0.8	44	26	31	26
4	0.8	53	26	65	26
6	0.8	53	26	65	26
8	0.8	53	26	65	26
10	0.8	55	26	66	26

12.2.2.8 Component 6: Protocol preparing 40 % glycerol-water mixture

This Protocol describes the materials and method to make 100 ml of a 40 % glycerol-water mixture, with a dynamic viscosity of 0.046 g/cm · s and density of 1.1 g/ml at a temperature of 21 °C. With this mixture has a comparable viscosity with blood. For different concentrations or temperatures, the online 'Density and viscosity of glycerol/water mixtures' calculator can be used, made by A. Volk et al. [39].

Materials

- 40 ml 100 % Glycerol solution
- 60 ml distilled water (H_2O)
- 1 droplet of Hydra Dragon Red Liquid Dye (Hydra International Ltd, Milton Keynes, UK)

- 10 ml and/or 100 ml pipette.
- 100 ml volume measuring cup OR empty bottle OR volumetric flask.
- Stirring rod
- Temperature meter
- Optionally: oven

Method

1. Measure out 40 ml of Glycerol using the 10 ml or 100 ml pipette.
2. Measure out 100 ml of distilled water using the 100 ml pipette.
3. Add the liquid red dye to the water and stir till mixed properly.
4. Add the measured glycerol and the coloured water into the empty bottle or volumetric flask.
5. Use the stirring rod to mix the content until its properly mixed (and no clumps are visible if using powder).
6. Before use:
    a. Check the temperature with the temperature meter and if necessary, adjust it to 21 °C. This can be done by placing it in the oven at °C for 20 – 30 min (depending on the temperature difference prior to checking).
    b. Stir the mixture with the stirring rod.
    c. Check the temperature again.
7. Storage:
    a. Store in a sealed container.
    b. Location of storage should be a dry and dark (away from sunlight) place at room temperature.
    c. As both glycerol and distilled water can be kept indefinitely, if both properly sealed and uncontaminated, there is no specific storage time. Before using, always check the mixture if there are any changes in consistency, smell, or colour. Otherwise, prepare new mixture.

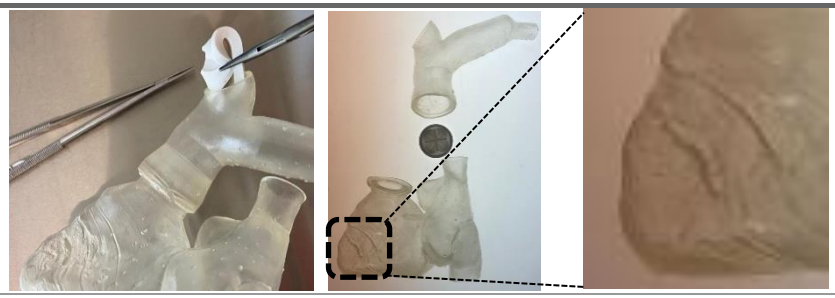
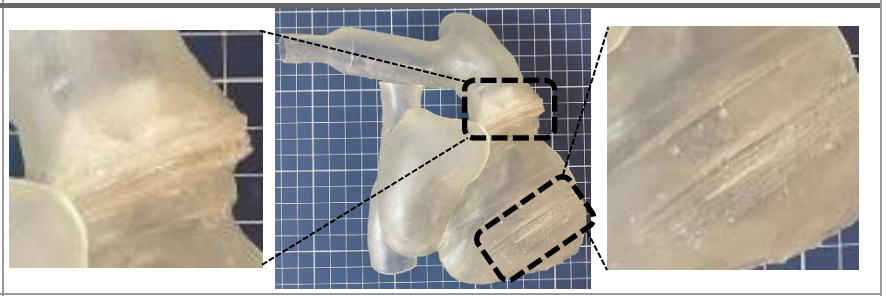
12.2.3 Survey

See document attached for the survey questions, raw results, and combined results of all participants (and selective groups).

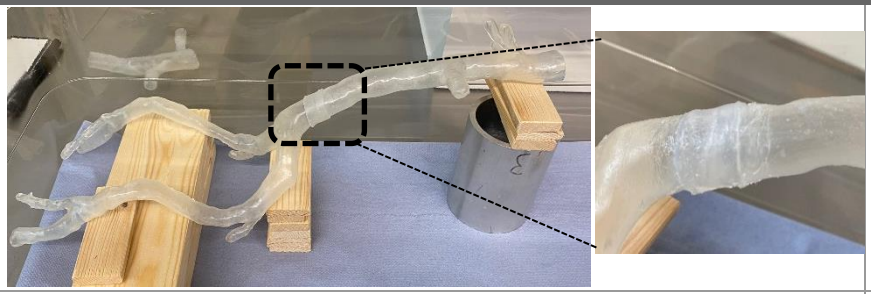
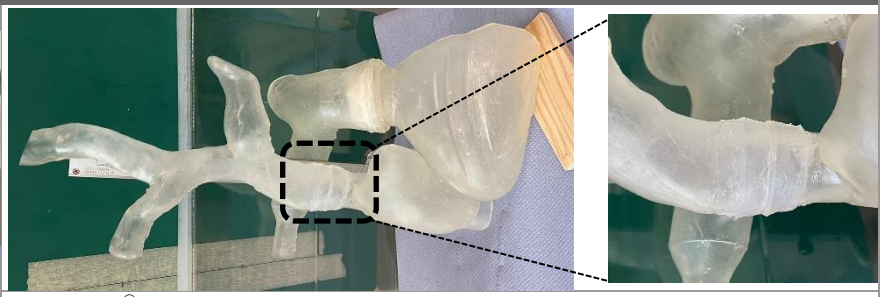
Document name: ES0303_REC_Survey_Rev01_20230702SLm.pdf

12.2.4 Logbook on product assembly

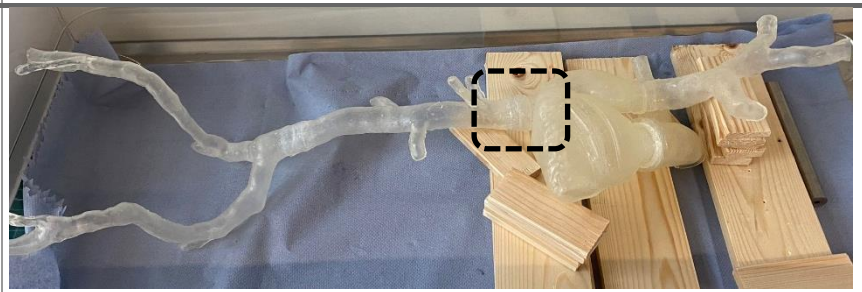
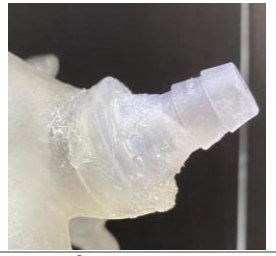
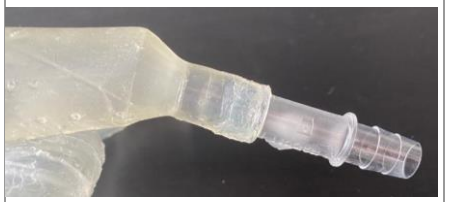
Table 12-14: Logbook on the final product assembly. For abbreviation explanation, see section 0.

Title/date	**Placing cross-split valve into seating though left pulmonary artery (2023-05-08)**	**Strengthen weak points of right heart model w/ Silicone rubber compound (SRC) (2023-05-11)**
Images		
Product details	Cannulation path part: 3D Medical Support (3D-MS) SLA printed with confidential flexible resin, comparable to Flex 82A resin. Cross-split valve: from MiniValve© (Oldenzaal, Netherlands). Material is Silicone; Diameter of 27.0 mm.	Cannulation path part: 3D Medical Support (3D-MS) SLA printed with confidential flexible resin, comparable to Flex 82A resin. Cross-split valve: from MiniValve© (Oldenzaal, Netherlands). Material is Silicone; Diameter of 27.0 mm. SRC: RS© Silicone Rubber Compound (RS 555-588)
Notes	The valve was placed into its seal through the 20.0 mm left pulmonary artery opening. Placing went well. Unfortunately, after several minutes, the right heart model tear at the seating. This resulted in a full detachment of the pulmonary arteries. During printing the heart model, something went wrong, resulting in a gap in the ventricle (see left image). 3D-MS repaired this but gave the sidenote that this section could be fragile/weak.	The heart model was prepared at 3D-MS with correctly placed valve. To test the flexibility of the product, the model was bent to apply torsion. This resulted in a tear on the frontal surface of the ventricle. To repair and strengthen, SRC was applied with glove protected fingers between the gap and over the frontal surface of the ventricle. Because the repaired valve seating was a weak point of the model, SRC was applied as well.
Curing time	Right heart, pulmonary arteries and cross-split valve were brought back to 3D-MS. They repaired the heart model. The valve was placed into the seating before repairing. This was done with resin and UV light.	In my experience, SRC needs at least 12 hours to dry. Full curing takes 7 days according to RS©.
# attempts	1 attempt.	1 attempt.

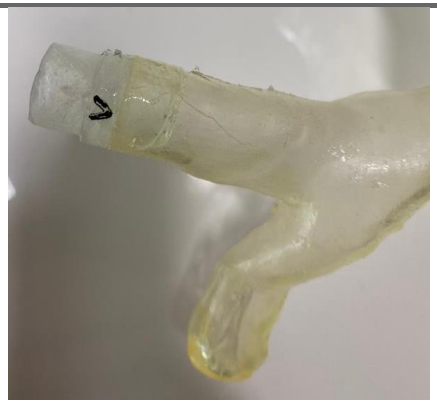
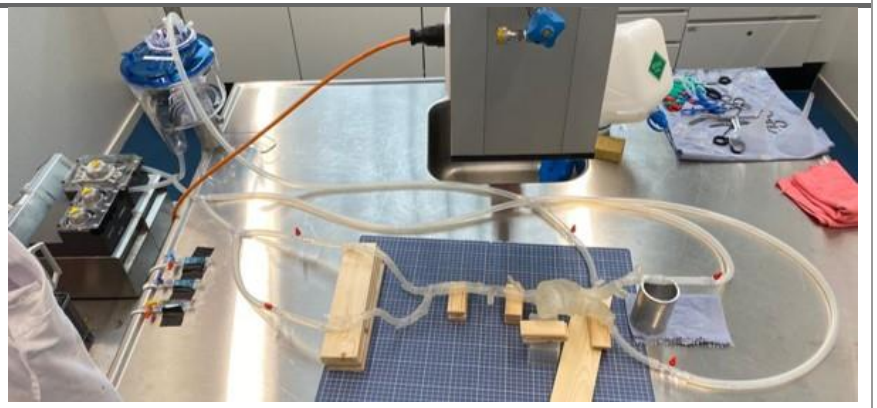
Continuation of Table 12-14.

Title/date	**Attach C.5 onto IVC and IVs w/ P.4 (2023-05-16)**	**Attach C.5 onto SVC and RH w/ P.4 (2023-05-16)**
Images		
Product details	SRC: RS© Silicone Rubber Compound (RS 555-588) Cannulation path parts: 3D-MS SLA printed with confidential flexible resin, comparable to Flex 82A resin. Connector C.5: 15 cm connection surface. Formlabs© Form 2 3D SLA printed with elastic 50A resin.	SRC: RS© Silicone Rubber Compound (RS 555-588) Cannulation path parts: 3D-MS SLA printed with confidential flexible resin, comparable to Flex 82A resin. Connector C.5: 15 cm connection surface. Formlabs© Form 2 3D SLA printed with elastic 50A resin.
Notes	These parts were connected using connector C.5 and connection method P.4. Still wet, the SRC acts as a lubricant. This caused the parts to slide of each other. Therefore, each time, the correct angle had to be determined first. This was realised with wooden parts. After > 4 hours, a second layer was applied on the outer side.	These parts were connected using connector C.5 and connection method P.4. Still wet, the SRC acts as a lubricant. This caused the parts to slide of each other. Therefore, each time, the correct angle had to be determined first. This was realised with wooden parts. After > 4 hours, a second layer was applied on the outer side.
Curing time	In my experience, SRC needs at least 12 hours to dry. Full curing takes 7 days according to RS©.	In my experience, SRC needs at least 12 hours to dry. Full curing takes 7 days according to RS©.
# attempts	1 attempt.	2 attempts; The SVC fell during curing time. Parts had to be cleaned and connected again.

Continuation of Table 12-14.

Title/date	**Attach C.5 onto IVC (& IVs) and RH (& SVC) w/ P.4 (2023-05-17)**	**Attach C.10 and prefabricated connector onto outlets w/ P.5 (2023-05-23)**
Images		Left pulmonary artery (PA) outlet  Right PA outlet 
Product details	SRC: RS© Silicone Rubber Compound (RS 555-588) Cannulation path parts: 3D-MS SLA printed with confidential flexible resin, comparable to Flex 82A resin. Connector C.5: 15 cm connection surface. Designed in 3-Matic and printed with Formlabs© Form 2 3D SLA printer in elastic 50A resin.	SRC: RS© Silicone Rubber Compound (RS 555-588) Cannulation path parts: 3D-MS SLA printed with confidential flexible resin, comparable to Flex 82A resin. Connector C.10 for the right PA: Design made with Solidworks® and Formlabs© Form 2 3D SLA printed with clear resin V4. Prefabricated connector for the left PA: 3/8-inch luer-lock connector from Maquet© (Cardiopulmonary/Getinge, Hechingen, Germany)
Notes	These parts were connected using connector C.5 and connection method P.4. Still wet, the SRC acts as a lubricant. This caused the parts to slide of each other. Therefore, each time, the correct angle had to be determined first. This was realised with wooden parts. After > 4 hours, a second layer was applied on the outer side.	These parts were connected using connector C.10 and a prefabricated connector, and connection method P.5.
Curing time	In my experience, SRC needs at least 12 hours to dry. Full curing takes 7 days according to RS©.	In my experience, SRC needs at least 12 hours to dry. Full curing takes 7 days according to RS©.
# attempts	1 attempt.	1 attempt.

Continuation of Table 12-14.

Title/date	**Attach C.7 onto inlets of cannulation path w/ P.5 (2023-05-23)**	**Full product assembly (2023-05-24)**
Images		
Product details	SRC: RS© Silicone Rubber Compound (RS 555-588) Cannulation path: 3D-MS SLA printed with confidential flexible resin, comparable to Flex 82A resin. Connector C.7: Design made with Solidworks® and Formlabs© Form 2 3D SLA printed with clear resin V4.	Final product: Product details of all components are listed in Table 4-3. The cannulation path is supported with pieces of wood to maintain shape during testing.
Notes	These parts were connected using connector C.7 and connection method P.5. Connection went well.	After comp. 3 was fully assembled with accompanying connectors, the full product assembly was done easily. Due to the weight of comp. 3 once primed, support was added.
Curing time	In my experience, SRC needs at least 12 hours to dry. Full curing takes 7 days according to RS©.	Connecting all components takes approximately 15 min (n = 5).
# attempts	1 attempt.	1 attempt.

12.2.5 Specification on test requirements

12.2.5.1 Literature research on desired flow/pressure values

Table 12-15 summarizes the literature research that was done to define the desired values of flow and pressure. The desired values were found by taking the average of the collective research. During tests, these desired values are tried to be met.

Table 12-15: Literature research overview of parameter values in the native vessels of component 3.

Parameter	**Range**	**Mean**	**Specification**	**Ref.**
Flow, [*Q*] (L/min)	4 – 5	4.5 ± 0.5	Regarding the systemic circulation.	**[13]**
Pressure in venous track (comp. 3a), [*P*] (mmHg)	15 – 3	9 ± 6	Mean pressure range in large veins of systemic circulation. Value decreases when approaching the heart.	**[13]**
Pressure in venous track (comp. 3a), [*P*] (mmHg)	20 – 3	11.5 ± 8.5	Mean pressure range in large veins of systemic circulation of healthy adults. Value decreases when approaching the heart.	**[23]**
Mean right arterial pressure (RAP), [*P*] (mmHg) (n = 60)	1 – 15	8 ± 7	The RAP is considered the central venous pressure. From this study can be concluded that the pressure difference throughout the cannulation track (comp. 3a) are nil.	**[53]**
Mean pressure difference between SVC and RAP, [Δ*P*] (mmHg)	N/A	0.08		
Mean pressure difference between IVC and RAP, [Δ*P*] (mmHg)	N/A	0.23		
Mean pressure difference between FV and RAP, [Δ*P*] (mmHg)	N/A	0.87		
Pressure in pulmonary artery (part of comp. 3b), [*P*] (mmHg)	15 – 5	10 ± 5	Value decreases when leaving the heart.	**[13]**
Desired flowrate (Q) for tests: 4.5 ± 0.5 L/min				
Desired Pressure (*P*) in comp. 3a for tests: 10 ± 10 mmHg				
Desired Pressure (*P*) in comp. 3b for tests: 10 ± 5 mmHg				

12.2.5.2 VV-ECMO cannulas specifications

Since cannulas have to fit through the cannulation path for simulations, sizes of cannulas that are used for VV-ECMO were compared. Section 1.1 is used to define the type of cannulas considered. In Table 12-16, diameter ranges of cannulas are listed, based on literature and what is commercially available. This is needed prior to testing.

Table 12-16: Overview of (commercially available) cannulas used for VV-ECMO.

Name cannula/vendor	**Size range (Fr.)** *	**Ref.**
Single lumen cannulas – Insertion: Femoral vein		
Medtronic, Minneapolis, USA.	19 – 29	[7]
Maquet Cardiopulmonary/Getinge, Hechingen, Germany.	19 – 29	[7]
Edwards Lifesciences Corp., Irvine, USA.	18 – 28	[7]
N/A (Average of used cannulas in patients at the Alfred Hospital in Melbourne, Australia).	19 – 25	[54]
Dual lumen cannulas – Insertion: Internal jugular vein		
Avalon Elite (Maquet Cardiopulmonary/Getinge, Hechingen, Germany).	20 – 31	[7] [55]
Nova-Port (Fresenius Medical Care, Waltham, USA).	18 – 24	[7]
OriGen (OriGen, Austin, USA).	23 – 32	[7] [55]
Crescent (Medtronic, Minneapolis, USA).	30 – 34	[55]
PROTEKDuo (LivaNova PLC, London, UK).	29 – 31	[9]
* (Fr.): French		

Concluding from Table 12-16, for cannulation through the right iliac vein (with insertion vein being the femoral vein), the product should comply with a cannulas ≥ 18 French (Fr.). For cannulation through the right internal jugular vein, the product should comply with a cannulas ≥ 29 Fr., as the ProtekDuo cannula must fit. For other dual lumen cannulations, the product should comply with a cannulas ≥ 18 Fr.

12.3 Annex C: Additional to final product

12.3.1 Product testing – set-up protocol

This protocol describes steps needed to assemble, prime, and prepare the product for any test with flow. Figure 12-13 gives a schematic overview of all components. All conduit tubing has been labeled (B1 – B9). An overview of the final setup and all components is shown in Figure 12-14.

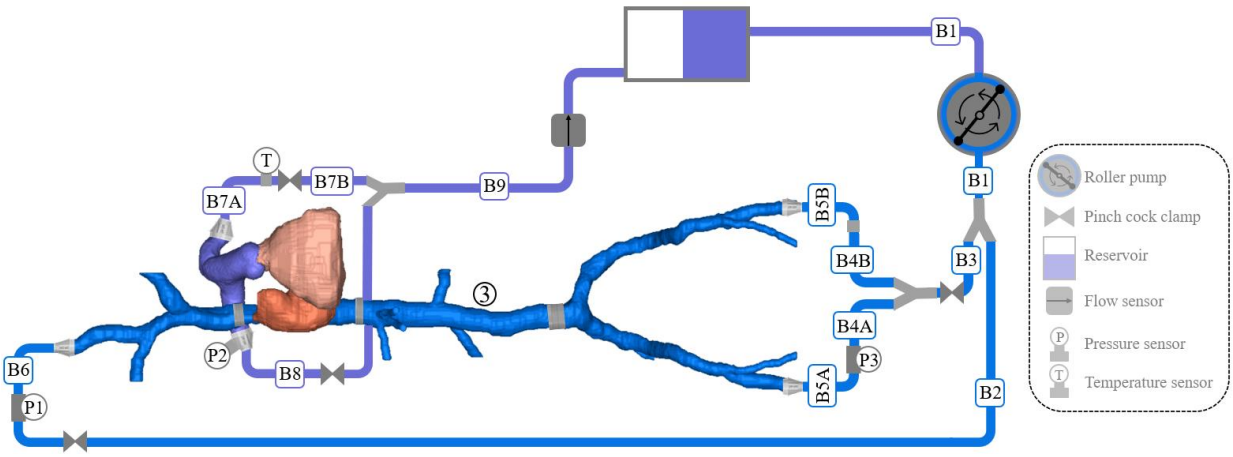


Figure 12-13: Schematic of product setup. All conduit tubing has been labeled (B1 - B9). (3) Cannulation path component. Other icons are identified in the legend.

Priming the cannulation path

The cannulation path (comp. 3) is primed individually because priming requires rotating/tilting the component, and this is experienced more easily without all conduit tubing already connected to it.

1. Connect tubes B5A, B5B, B6, B7A & B8 with comp. 3.
    a. This is done so clamps can be placed on these tubes after priming.
2. Close tubes B5A, B5B & B7A using clamp scissors.
    a. Always place clamp scissors as close to the extremity of tubes, so as much air as possible is removed.
3. Place the extremity of tube B8 in a sink or container. (This tube is relatively long).
4. Connect tube B6 with the faucet using connectors (4a connectors).
5. Open the faucet and let comp. 3 fill itself up while air escapes through tube B8.
6. Close the faucet, close tubes B6 & B8 with clamp scissors.
7. With the help of a colleague, carefully rotate/tilt the component so all air moves towards one ending. Carefully tapping the tubes with the back of a clamp scissor can help to create vibrations in the component that help transport air.
    a. In my experience, air moves the easiest towards tube B8.
8. Once all air is collected at one outlet (B8), remove the clamp scissors from tube B6 & B8. Open the faucet slowly so air is pushed out.
9. Once the component is completely primed, close the faucet and close tube B8 and B6 with clamp scissors.

Assembling and priming setup

1. Lay out the components as shown in Figure 12-13, without incorporating the cannulation path (comp. 3).

2. Connect B1 with the reservoir, guide it through the roller pump and connect is with B2 and B3 using a Y-connector.
    a. Adjust the rollers of the pump so the tube is completely pressed together. You can test this by filling the reservoir with some water. If no water passes the roller, it is tight enough.
3. Connect tube B3 with B4A and B4B using a Y-connector.
4. Fill the reservoir with > 2 L of the desired fluid.
5. Place the extremities of tubes B2, B4A & B4B in a sink or container.
6. Slowly start the pump. (Flow of 0.5 L/min is fine).
7. Tap the tubes with the back of a clamp scissor to create vibrations in the component. This helps to remove air.
8. Once all air is removed, stop the pump and close tubes B2, B4A & B4B using clamp scissors.
    a. Place clamp scissors as close to the extremity of tubes, so as much air as possible is removed.
9. Insert comp. 3 into the setup by using connectors to connect:
    a. B4A with B5A
    b. B4B with B5B
    c. B2 with B6
    d. B7A with B7B
10. For these connections, use a luer-lock connector, so pressure sensors can be placed around the cannulation site.
11. Connect B7B and B8 with B9 using a Y-connector and connect B9 with the reservoir.
12. Connect pressure sensors to the luer-locks on desired locations.
    a. In this thesis, three pressure sensors were available and placed on connectors between:
        i. Pressure sensor 1: B4A with B5A
        ii. Pressure sensor 2: Connector 4b, outlet of right pulmonary artery is a luer-lock connector.
        iii. Pressure sensor 3: B2 with B6
13. Remove the clamp scissors from tubes B2, B4A, B4B, B5A, B5B & B6.
14. Start the pump with a flowrate < 0.5 L/min, and once flow starts, quickly remove clamps scissors from tubes B7A & B8.
15. Any air bubbles should be removed using previous listed methods.
16. Once all air is removed, stop the pump. If necessary, place a clamp scissor on tube B9 to prevent air traveling back into the setup.
17. Place a flowmeter on tube B9.
    a. Make sure to use lubricant before placing the flowmeter.
18. Place pinch cock clamps as desired. For an example were to place them, see Figure 12-13.
19. Now, the product is ready to be used and should look comparable to Figure 12-14.

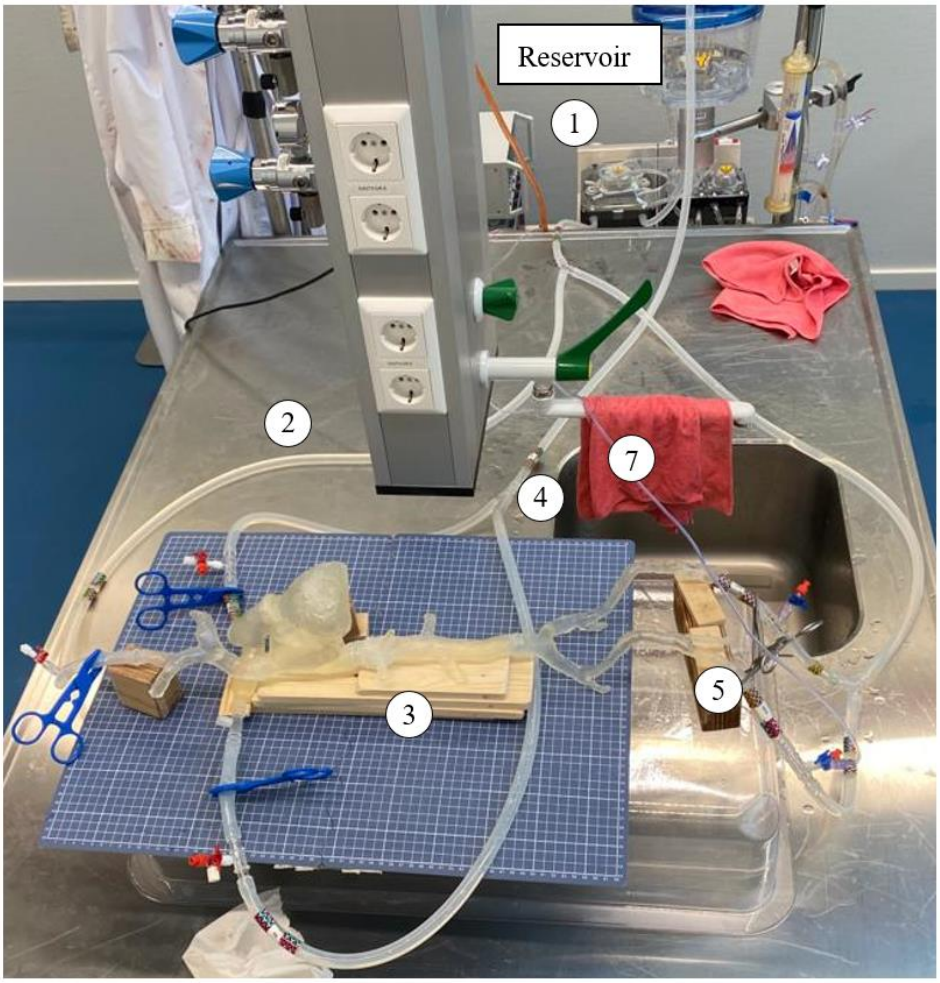


Figure 12-14: Visualization of fully assembled and primed product setup. (1) Pump, (2) Tubing, (3) Cannulation path, (4) Connectors, (5) Resistor, (7) Pressure sensor.

12.3.2 Product testing – Test results

12.3.2.1 Test 1 & 2

As described in section 5 and shown in Figure 5-1, the cannulation path ruptured in the posterior surface of the ventricle and the cannulation path broke apart during test 1 and 2.

To repair the rupture that arose during test 1, a variant of connection method P.2 was used were Silicone rubber compound (SRC) was applied in, between, and over the crack. Because it was such a big rupture, it allowed applying SRC from the inside out. The ventricle was kept in position manually for 10 minutes. The next day, a second layer of SRC was applied to strengthen the repair.

To connect the broken cannulation path that occurred during test 2, a variant of connection method P.4 was used. As shown in Figure 12-15 (A), the cannulation path was missing a part where it broke in half. Also, the location of breaking was unfortunate because of the hepatic vein branches. Therefore, a customized sleeve was designed in 3-Matic and printed with elastic 50A resin using the 3D SLA Form 2 printer, see Figure 12-15 (B – C). The design was not printed as desired. It had multiple holes and support structures could not be removed from the branches. Therefore, this print was altered using scissors cutting of parts. This resulted in a sleeve that connected the cannulation path once again.

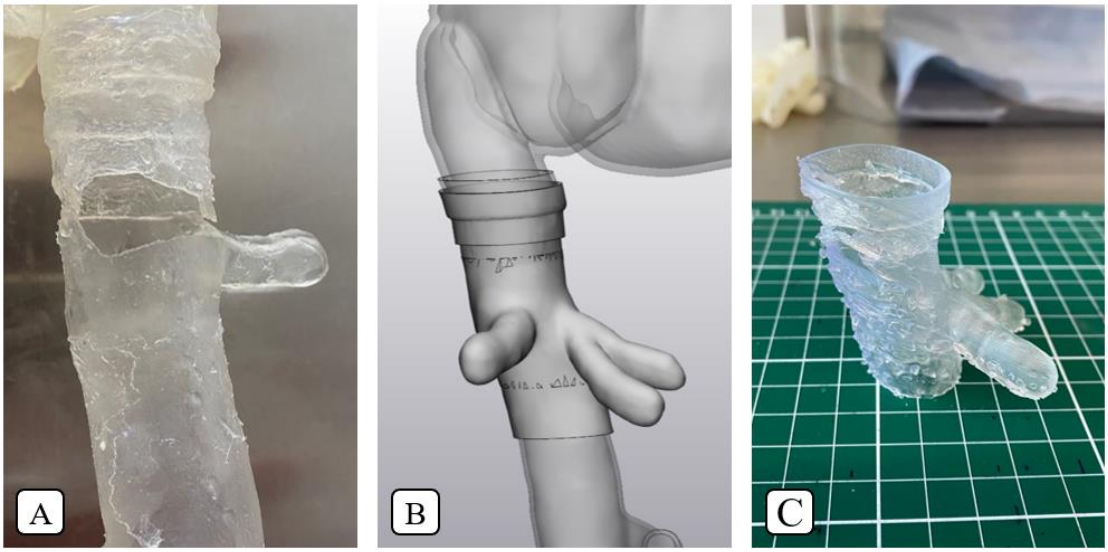


Figure 12-15: Images of how the broken comp. 3 was repaired.
(A) Comp. 3 broken and missing a piece of the Inferior Vena Cava. (B) Custom-made sleeve design for repair. Made in Materialized© 3-matic software. (C) Sleeve printed using FormLabs© Form 2 printer with elastic 50A resin.

12.3.2.2 Test 3

Test 3 focused on satisfying Req. 1 till 5. As previous tests failed during priming, a different method was tried were priming of the cannulation path was done separately of other components. With the support of a colleague, comp. 3 was primed successfully.

Table 12-17: Output data of final product test 3. Flowrate (Q) in L/min, obtained with a flow sensor. See Figure 12-13 for schematic test set up, and where all components are located.

Test 3 (2023-05-31)			
Goal: maintain fluid tight, closed-loop circuit whilst flow is increased to 5 L/min.			
t (min)	**Q (L/min)**	**t (min)**	**Q (L/min)**
0.0	0.0	7	4.0
1.0	1.0	7.5	4.5
2.0	1.4	8	5.0
3.0	2.2	9	1.9
4.7	2.8	10	3.0
5.0	3.0	14	3.1
6.5	4.0	15.5	4.0
Notes: The first 8 minutes, the flow was increased until 5 L/min. At t = 9, connection of the left iliac vein detached. To repair, the flow was increased. Once repaired, the flow was again increased. At t = 15.5 min, a small rupture in the frontal surface of the ventricle emerged. End of test.			

12.3.2.3 Test 4

Table 12-18: Output data of final product testing 4.1: testing flowrate and fluid tightness. Data flowrate (Q) in L/min, obtained with a flow sensor. See Figure 12-13 for schematic test set up, and where all components are located.

Test 4.1 (2023-06-05)
Goal: maintain fluid tight, closed-loop circuit w/ flow of 3.5 L/min for > 15 min.

t (min)	Q (L/min)	t (min)	Q (L/min)
0	0.6	10	3.0
1	0.6	15	3.5
2.5	1.0	19	3.5
3	2.0	24	3.5
6	2.0	25	3.5
6.5	2.0	30	3.5
7	2.5		
Notes: During testing, the product remained a fluid tight, closed-loop circuit.			

Table 12-19: Output data of final product testing 4.2: testing flowrate, pressure, and fluid tightness. Data flowrate (Q) in L/min, obtained with a flow sensor. Pressures (P_1, P_2, P_3) in mmHg are obtained with three pressure sensors in three different locations. See Figure 12-13 for schematic test set up, and where all components are located.

Test 4.2 (2023-06-05)

Goal: Try to mimic native pressures in the cannulation path whilst maintain fluid tight, closed-loop circuit w/ flowrate of 3 L/min.

Sensor P_1 is located at inlet right femoral vein, (see Figure 12-13).

Sensor P_2 is located at outlet right pulmonary artery, (see Figure 12-13).

Sensor P_3 is located at inlet internal jugular vein, (see Figure 12-13).

Zeroing pressure sensors	Q (L/min)	P_1 (mmHg)	P_2 (mmHg)	P_3 (mmHg)
Open to atmosphere	0	0	0	0
Closed to atmosphere	0	2	3	2
Open to set-up	0	17	31	17
t (min)	**Q (L/min)**	**P_1 (mmHg)**	**P_2 (mmHg)**	**P_3 (mmHg)**
0	0	45	44	31
1	2	54	54	31
1.5	2	54	54	36
2	3	53	56	36
5	3	53	56	36
7	3	53	53	36
9	3	35	41	36
14	3	35	41	36
Notes: During testing, the product remained a fluid tight, closed-loop circuit. Desired pressures were not realized due to limited time in testing lab. Used flowrate was increased to 3 L/min to focus on achieving desired pressure rates.				

12.4 Annex D: Initial work for future research

12.4.1 Testing alternatives for the cannulation path material

One of the main outcomes of the test results (section 5) was that the material used for the cannulation path (Flex 82A Resin) appeared not to be suitable for simulation-based training applications as desired for the venous model. This conclusion can be drawn since several ruptures emerged during testing and/or when connecting connectors. As for the survey, more emphasis should have been on the compliance of the vein. A material is needed with a lower Ultimate Tensile strength and higher Elongation at break value compared to the Flex 82A Resin.

The test vessels made for testing connectors and connection methods of component 4 (made with Elastic 50A resin and the FormLabs© Form 2 SLA printer, see Figure 12-12) showed strength and compliance during tests. Therefore, an attempt was done to print a part of the cannulation path with this production method. The results are described in Table 12-20. Unfortunately, this attempt failed during production because of several reasons but mainly due to the weight of the vessel and the amount of support structures it needed. In order to use this printer and resin, the cannulation path has to be divided into more than four parts for production. This is not desired since connections are generally weak points in a product and increases the production time.

The research group RAM of the UT (Enschede, Netherlands) was contacted a second time to see if their Stratasys© Object 280 printer was no longer malfunctioning, and this time, collaboration was possible. This 3D printing methods can produce products with IORA Model Flex 30A resin, which has a lower Ultimate Tensile strength and higher Elongation at break value compared to the Flex 82A Resin. For support structures, a water dissolvent resin is used (in combination with IORA resin they use Support706™). Both the main and support resin are produced by isquared© (Lengwil, Switzerland). This way, removing support structures inside the cannulation path and closed branches is no longer a hurdle. An initial test was done to see if this production method and accompanying resin is a suitable alternative for producing the cannulation path. A total of three STL-files were sent to RAM for production, that together form the Inferior Vena Cava (hereinafter: the IORA prototype), see Table 12-21. All three parts of the IORA prototype had a wall thickness of 1 mm. This production method had difficulty with the thin wall thickness. This led to small holes in the IORA prototype after production was finished. However, a qualitative analysis could still be performed. Figure 12-16 shows the behaviour of the IORA prototype under different conditions. The IORA prototype:

- Appears to be, when fully relaxed, flat, see Figure 12-16 (A) and (C). This is comparable behaviour to a VC when fully relaxed, see section 3.1.5, Figure 3-5 (A),
- Its relative volume increased quickly into a fully expanded vessel when flow was applied, see Figure 12-16 (D). This shows again comparable behaviour to a VC when fully expanded, see section 3.1.5, Figure 3-5 (A), and
- Exhibits flexible behaviour when little force is applied, see Figure 12-16 (B).

Based on this, the IORA material seems to mimic the behaviour of large veins more realistically than the current cannulation path in flexibility and compliance. Furthermore, connection method P.4 and D.2 were verified compatible with this material. Based on this, a hypothesis regarding the production method

with accompanying material was formed. This and future recommendations are further discussed in sections 6 and 7.

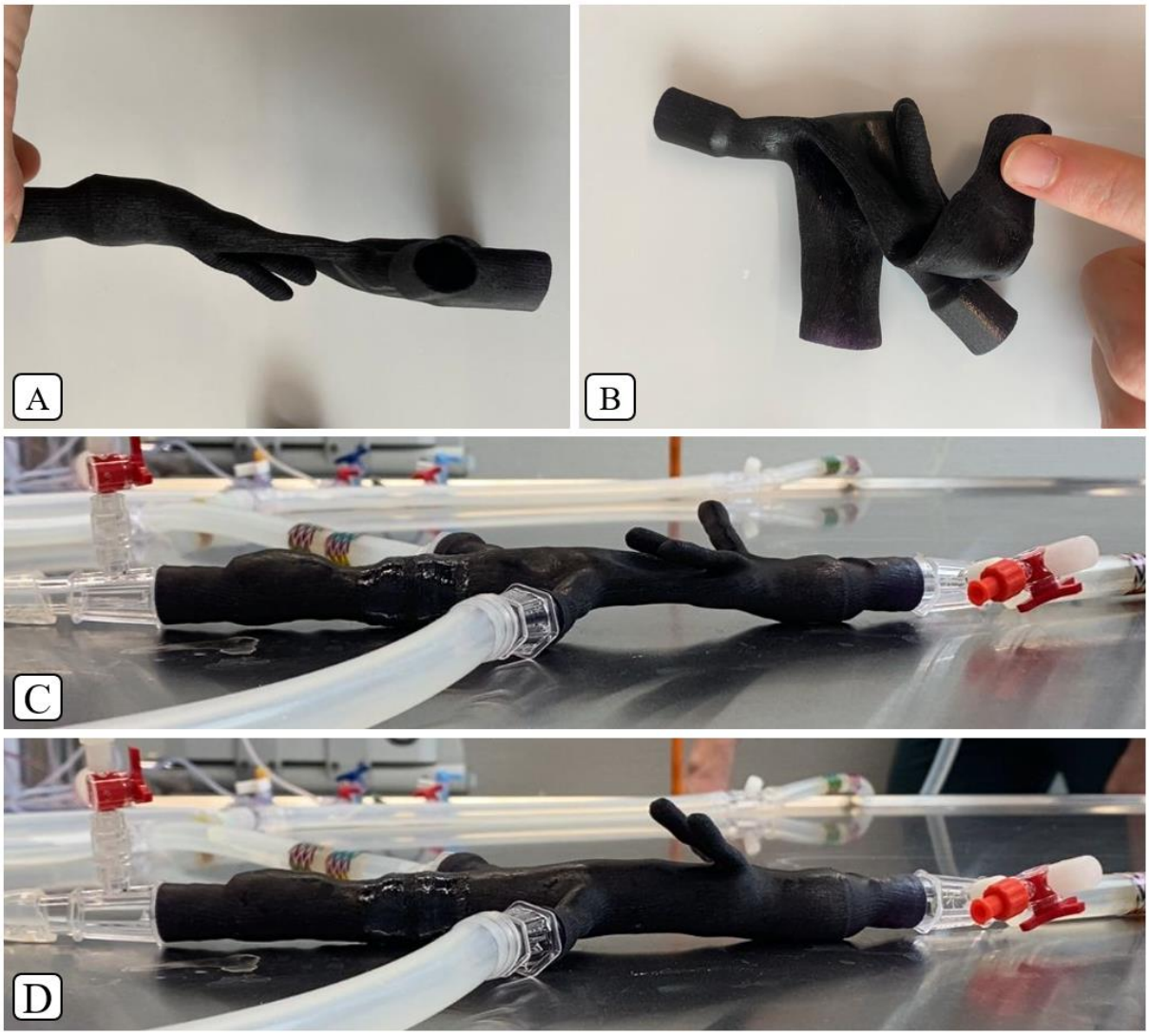


Figure 12-16: Images taken of the IORA prototype during tests. Image (C) – (D) were taken when the prototype was connected to a closed-loop circuit to test its behaviour when fluid would flow through it.
(A) The IORA prototype appears to be, when fully relaxed, flat. This is comparable behaviour to a VC when fully relaxed, see section 3.1.5, Figure 3-5 (A).
(B) The IORA prototype exhibits flexible behaviour when forced into different shapes.
(C) Before priming. The prototype shows similar behaviour as in image (A).
(D) Once primed. The prototype's relative volume increased until it was fully expanded. Again, this is comparable behaviour to a VC when fully expanded, see section 3.1.5, Figure 3-5 (A).

Table 12-20: Test print of the Inferior Vena Cava (IVC), printed with Formlabs© Form 2 SLA printer using Elastic 50A resin.

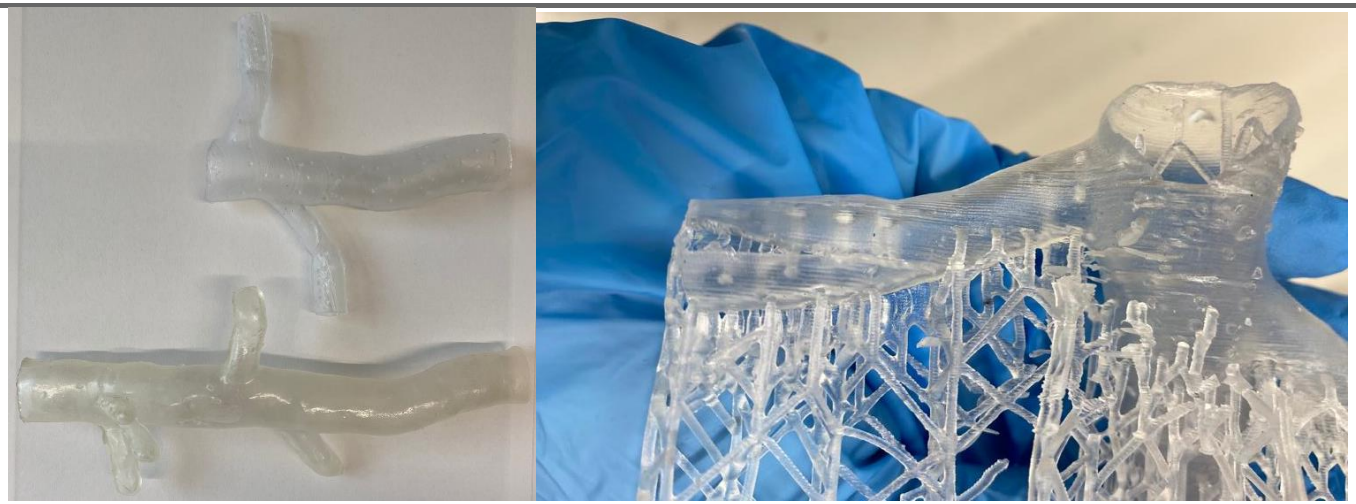
Date	**2023-05-16**
Images	
Production	FormLabs© Form 2 3D SLA printer with Elastic 50A resin at the Rapid prototyping lab of the UT (Enschede, Netherlands).
Design details	Comparable to the IVC part in Table 12-10, however now branches of the hepatic veins are included into design. These branches have a diameter of 3/8-inch. This was done so internal support would be easier to remove. Wall thickness: 1 mm Length: 200 mm Width: 79 mm Depth: 56 mm
Purpose/aim	Test to see if this production method and accompanying material is more suitable for the production of the cannulation path.
Observations	The left image shows the comparison of the test print (made from Elastic 50A resin) with the IVC printed by 3D Medical Support (made from Flex 80 A resin). The right image shows holes in the hepatic vein branches and that the upper part of the IVC broke off during printing.
Conclusion	Printing such complex and large parts is not feasable. It is optional that this production method would work is smaller parts are printed, however this is only hypothasized.

Table 12-21: Product details on, and the assembly of the IORA prototype.

Date	**2023-06-21**		
Description	Parts received from research group RAM that together form the IORA prototype		
Images			
Image description	Left image (f.l.t.r.): · (1) A part of the Inferior Vena Cava (IVC), starting just below the Right Atrium until the renal veins are passed. The branches of the renal veins were opened, and their diameters were adjusted to 3/8-inch for easy connection with prefabricated connectors of ECM Europe BV© (Gemert, Netherlands). · (2) A part of the IVC that is the continuing of the previous part towards the iliac veins. · (3) The part to test connector C.5 and connection method P.4. Right image: The three parts were connected using connection method P.4.		
Production method	Printed by research group RAM (Enschede, Netherlands) using Stratasys© Object 280 printer and IORA Model Flex 30A black resin.		
Design details	(1) Large part of IVC Wall thickness: 1.0 mm Length: 160.9 mm Width: 105.3 mm Depth: 52.3 mm	(2) Connector C.5 Wall thickness: 1.0 mm Length: 15.0 mm Width: 22.8 mm Depth: 22.6 mm	(3) Small part of IVC Wall thickness: 1.0 mm Length: 74.1 mm Width: 28.0 mm Depth: 23.8 mm
Purpose/aim	Test to see if this production method and accompanying material is more suitable for the production of the cannulation path.		
Observations	· RAM reported they had difficulty printing the IORA prototype due to the thin wall thickness. They tried to repair the prototype as much as possible but warned for possible small, not visible holes in the wall. · Connecting the parts of the IORA prototype with P.4 went successful.		

12.4.2 Pre-concept for implementing Tricuspid Valve

This pre-concept was made with the intention of implementing it in a later phase of this thesis. It was therefore created with the idea that the cannulation path was already produced and assembled. Due to time, this was not achieved. Figure 12-17 is self-explanatory.

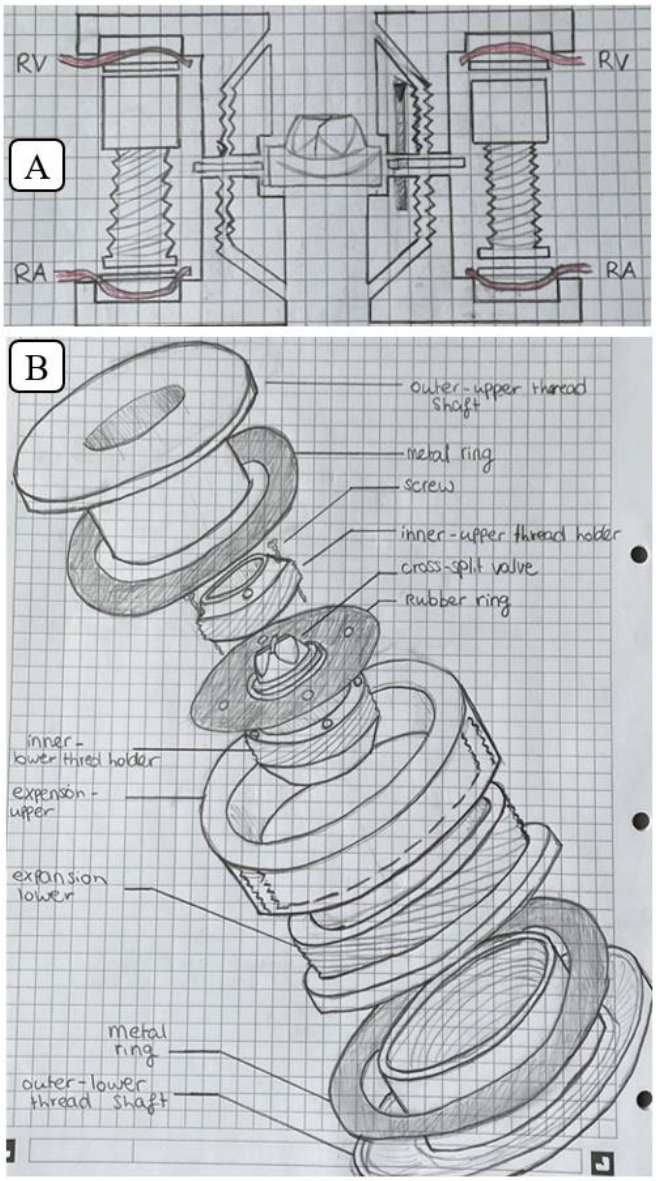


Figure 12-17: Pre-concept of implementing the valve into the Tricuspid Valve hole. (A) a cutaway view, and (B) an exploded view of the pre-concept. RV is the Right Ventricle; RA is the Right Atrium.
Description step-by-step: 1) The cross-split valve representing the Tricuspid Valve is placed between two parts of an inner-thread shaft that are screwed together with a rubber ring between them for fluid tightness. This is called the inner thread unit. 2) The cannulation path is cut open at the Tricuspid Valve hole. 3) the two parts of the outer thread shaft are placed inside the RV and RA, with the shaft protruding. 4) A metal ring is placed around both protruding shafts, now laying on the surface of the RV and RA. 5) The expansion unit is placed around one of the shafts. 6) the inner threat unit (step 1) is screwed into the two parts of the outer shaft. Now, the valve is placed on the correct position. 7) Finally, to ensure fluid tightness, the expansion unit is screwed open. This causes the unit to expand and forcing itself against the metal rings. Due to the opposite forces of the expansion unit and the inner/outer threat unit, the valve seated steady.

12.4.3 Initial research on contracting movement of the Right Ventricle

A first literature review of the state of the art was done regarding a contracting Right Ventricle component (obstacle of the right heart (comp. 3b)). With this component, the function of the myocardium is mimicked that lets the RV contract. This contraction results in a pressure-driven flow that lets blood exit the RV through the Pulmonary Valve into the pulmonary artery. In this section, methods – substantiated by literature – that could be used as a starting point for future development and incorporation of this component are briefly described.

To realize the contracting movement, a type of soft actuator is needed. Commonly used soft actuators are artificial muscles. These are soft robotic devices that are designed with the architecture of native cardiac muscle fibres as reference [56]. There are varieties of artificial muscles such as flat pleated pneumatic artificial muscles (fPPAMs), fluid-driven origami-inspired artificial muscles (FOAMs), McKibben PAMs, hydraulic artificial muscles (HAMs) [57], and vacuum-actuated muscle-inspired pneumatic structures (VAMPs) [56, 58]. The most highly developed and studied type of PAMs are McKibben PAMs, according to Roche et al. [59]. Figure 12-18 visualizes the working of a McKibben PAM. When no pressure is applied (relaxed) the PAM is stretched. When pressure is applied, the PAM contracts linear [Δl] and expands radial [Δr].

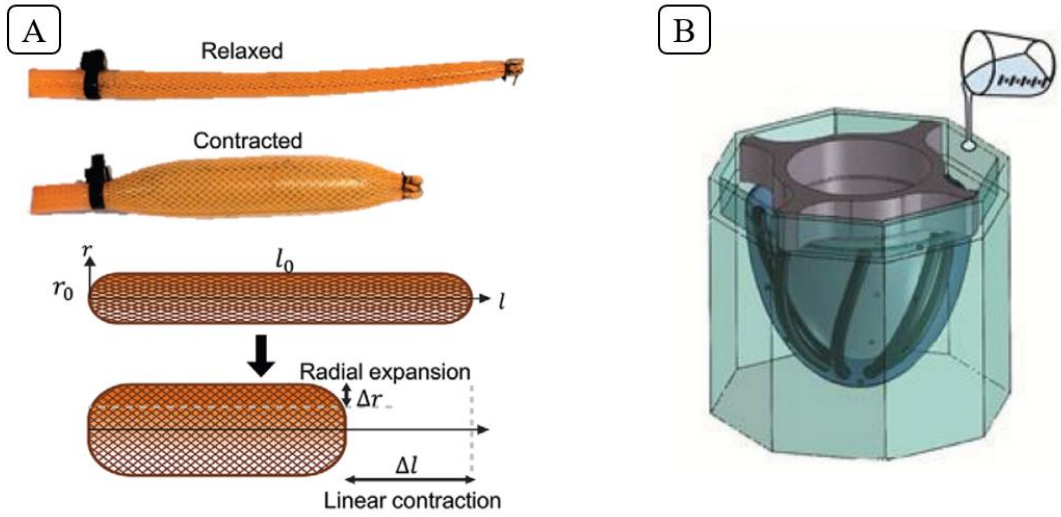


Figure 12-18: (A) Explanation on how McKibben PAMs work. When no pressure is applied (relaxed) the PAM is stretched. When pressure is applied, the PAM contracts linear [Δl] and expands radial [Δr] [56]. (B) Vizualisation of how PAMs are alligned in a bioinspired 3D mould. A resin is added to the mould and cured to form a full artificial muscle [59].

PAMs in combination with an elastic housing can be used to create a (selective) contracting component that could potentially be implemented into the venous model. In 2013, Roche et al. [59], created a method to create Bioinspired soft actuated materials. Based on the fibre orientation of the selected muscle, PAMs were aligned accordingly in a 3D mould that was shaped as the selected muscle. Then, Ecoflex 00-30 was poured into the mould as this material can generate large strains, and the structure was cured. With this, complex biological motions were mimicked successfully. In 2022, Park et al. [56], created a computational framework for defining and optimizing the ideal alignment of the PAMs in artificial soft actuated materials. They studied the fibre muscle alignment of the myocardium and computed several experiments with different combinations of PAMs aligned a certain way. Through this, an optimized design of aligned PAMs was realized and validated.

Additionally, as discussed in section 6, contact was made with AdjuCor (munich, Germany) regarding implementing their reBEAT® product to realize the contracting component.

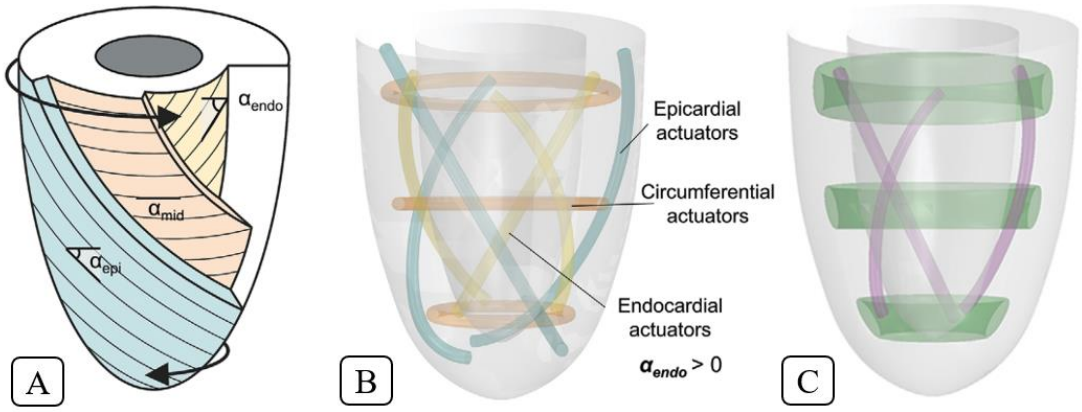


Figure 12-19: (A) Schematic of fiber alignments of muscle layers of the myocardium. (B) PAMs aligned accordingly to the muscle layers of the myocardium. (C) Optimized design of PAMs and their alignment for creating a contracting movement. [56]

12.4.4 Pulsatile component for VA-ECMO application

A big difference between the arterial and venous system is that there is a high-pressure range in the arteries and a low-pressure range in the veins, as shown in Figure 3-1 (B). The high-pressure is caused by the cardiac output of the Left Ventricle. In order for arteries to withstand such pressure, compliance is introduced. This is a mechanism of the vessel to capture systolic pressure temporarily in the vessel walls as kinetic energy. Once the pressure drops, during the diastole, this energy is used to ensure a continue blood flow by contracting back to the original shape of the vessel. In a pressurized compartment, compliance [*C*] can be measured with the volume difference [ΔV] against the pressure difference [ΔP] in the compartment. For a cylindric compartment such as blood vessels, this definition can be simplified by replacing ΔV with the change in diameter [ΔD] and multiplying [ΔP] with the diameter at rest [D_0] [60].

A method widely used in studies to model arterial compliance is the Windkessel model [27, 45, 51, 61, 62]. This model is used to model the arterial system. The model is comprised of elements, with one-element being a simplified model, and four-elements being a highly complex model. In 2009, Westerhof et al. [61] found that a three-element Windkessel model can best be used to describe the hemodynamics of the arterial system. The three elements represent the peripheral resistance, compliance, and impedance. Impedance defines the pulsatile flow in arterial systems due to pressure. In 2010, Kung et al. [27] developed a physical module based on the three-element Windkessel model that could be used to execute *in vitro* cardiovascular studies.

When it is desired to incorporate the pulsatile behaviour of arteries into the eduECMO, studies like listed above (regarding the Windkessel model), can be used for conceptualizing a pulsatile component. A compliance chamber is a commonly used component to realize change of compliance in cardiovascular simulators [51]. This usually works with air being trapped in a reservoir that is part of the circuit (thus containing a fluid as well) By using e.g. a pressurizing cylinder, the air expresses pressure onto the fluid in the reservoir.

Figure 12-20 shows a pre-concept of how this could be used to create a pulsatile flow while using a continuum pump. Flow enters through a passive valve into the compliance chamber. At the outlet of the

compliance chamber a mechanical valve is placed. When this valve is closed, pressure builds up inside the compliance chamber. Once opened, the fluid is released with a driving force caused by the pressure build-up.

Figure 12-20: Pre-concept of pulsatile component in a circuit with a continuum pump. Fluid moves from right to left. Flow enters through a passive valve into the compliance chamber. At the outlet of the compliance chamber a mechanical valve is placed. When this valve is closed, pressure builds up inside the compliance chamber. Once opened, the fluid is released with a driving force caused by the pressure build-up.

12.5 Annex E: Accompanying document

Identification of URS & DRS-ID's

All requirements should be quantitative, otherwise it is hard to assess concepts and products. If certain hard data is not yet available (e.g., how strong a device should be if the load that will act on it is still unknown), estimation should be made.

In order to create a complete list of requirements, the template from the EOST-group was used for a 'User Requirements Specification' (URS) document and a 'Design Requirement Specification' (DRS) document, which can be found at the end of this Annex.

The URS covers a complete list of requirements for deliveries and services, from the user's perspective. Each requirement has an ID assigned to it, structured as followed: URS-ID: 1.1-010. The value before the hyphen is the (sub)chapter and after the hyphen there are three additional digits, where individual requirements are assigned in intervals of 010.

The DRS contains the implementation specifications and describes these. In the DRS, the requirements from the URS are translated into concrete and testable requirements for the design to be developed. Each requirement has an ID assigned to it, which consists of the URS-ID it comes from and extended by three digits: DRS-ID: 1.1-010.000. If the URS requirement stays unchanged, the extension is .000. If the URS requirement results into one or more DRS requirements, the extensions are .010, .020, etc. Countermeasures that arise from the Risk analysis (RIA) must be incorporated into the DRS. Their DRS-ID can be identified as 'R.X-000.000', where 'X' represents type of the countermeasure (e.g., A for Application), '000' works the same as before. If a large number of requirements arise from the same origin, an interval of .001 is used.

Note that (sub-) chapters that are not applicable for this thesis are not deleted but the content of that chapter is replaced with 'N/A'. This ensures for a fixed numbering which is key when working with ID's and makes it clear that these chapters are considered.

12.5.1 Risk Analysis

See document attached for the Risk Analysis which was performed through Failure Modes and Effects Analysis (FMEA).

Document name: ES0303_RIX_RiskAnalysis_Rev06_20230702SLm.pfd

12.5.2 User Requirement specifications

See document attached for the User Requirement Specifications.

Document name: ES0303_URS_Rev05_20230702SLm.pfd

12.5.3 Design Requirement specifications

See document attached for the Design Requirement Specifications

Document name: ES0303_DRS_Rev05_20230702SLm.pfd