# Prolonged Ex vivo Preservation

Creating a Normothermic Machine Perfusion Setup

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## Summary

Transplantation waiting lists are too long. In the Netherlands alone, 1711 patients were added to the waiting list in 2017 and sadly 136 patients died before they had the much-needed surgery. To prevent deaths, Expanded Criteria Donor organs of a lesser quality are being used more often in clinical setting. Literature indicates the regenerative ability of the organs might be able to restore the organ to full functionality in vivo over time. Interestingly, it might be possible to start the restoration progress ex vivo by preserving the organs under controlled healthy circumstances.

This study fits into a larger project of Erasmus Medical Center of which the goal is: *"The development of an organ incubator with the possibility to mimic the physiological conditions of the kidney after procurement to stabilize, optimize and monitor the organ function for multiple days."*

For long term kidney stabilization, optimization and monitoring an organ incubator is preferable. However, it is unclear which available parts would work best in synergy. The goal of this study is to lay a foundation for the research of Erasmus Medical Center by creating a potential NMP setup with which pro-longed preservation could be achieved. Within the field of kidney transplantation, this study focuses on ex vivo Normothermic Machine Perfusion (NMP) for Donation after Cardiac Death organ preservation and regeneration.

In this study an experimental setup to conduct research into kidney preservation will be built. The weak points identified in the physical NMP setup, along with the points of improvement that follow from the mathematical model should be used as starting point for the development of an experimental setup that can be used for academic research.

The design choices and the theoretical and mechanical methods used to further develop an NMP setup are discussed. In the end the author was able to do some preliminary experiments with the NMP setup build. The literature review showed whole blood to be optimal for prolonged preservation. However, due to its scarcity porcine blood could only be used in one experiment. In other experiments, water was used. The final physical setup was not fully operational. One of the functions missing was the capability to damp pulsations created by the pump. The elasticity of the aorta functions as a damper to the pulsating pressure profile created by heart contractions, this is also known as a Windkessel effect. In the current setup there is no adjustment for this effect. A mathematical model of a Windkessel was developed to study the necessity of a physical Windkessel.

The next step would be to control the volume of blood in the Windkessel. The outwards flow may never drain the volume of blood from the Windkessel as this would introduce air into the blood stream which could have dire consequences for the organ. If the volume of the Windkessel drops significantly the pump should pump fluid more rapidly to increase the flow into the Windkessel before this happens.

In the experiment using blood the pressure was extremely low. It is of vital importance to keep the pressure at around $75[mmHg]$. The pressures measured would most likely damage the blood during prolonged exposure to such extreme peaks. Both the low pressure and these peaks have contributed to the degradation of the blood. The peak in pressure and temperature that can be seen around 12 hours is due to the coagulation of blood. Furthermore, there is a clear lack of oxygen measured in the experiment and the sodium and lactate values rose steadily indicating extreme degradation of the blood.

The results collected with a theoretical mathematical model were highly promising. The extreme peaks of the pulsatile pressure profile were damped correctly. Although the smallest usable volume for the Windkessel was chosen, it is still quite large. The volume of air is now dependent on the compliance and pressure. However, if the air pressure in the Windkessel could be controlled with the help of an

electronic pressure regulator and if the noise on the pressure profile is minimal this could mean the full Windkessel effect could be taken over by an electronic air pressure regulator. A much smaller volume would then be needed to regulate the air pressure. If the mathematical Windkessel model is physically constructed and the air pressure system works as predicted, it is advised to calculate the minimal volume in a follow-up study.

In the mathematical model the flow into and the flow out of the Windkessel are stable over time. The volume of the blood in the Windkessel is also stable over time. In the mathematical model a small margin of a few milliliters is enough to deal with the fluctuations in volume and no further action is needed to maintain a stable volume. When translating the mathematical model to a physical model it is advised to implement a precautionary feedback loop as a safety measure. If the blood volume falls below a certain threshold the feedback system should accelerate the pump to refill the Windkessel with blood.

Several improvements need to be made before the setup can be used as a fully functioning NMP setup for kidneys. These include the the addition of a sterile container, a Windkessel, a dialyzer and a Masterflex L/S pump system.

It was possible for the equipment to work in synergy. The current NMP setup is an adequate initial perfusion setup and can be used for simple studies using water. It might also be able to be used for studies using porcine blood. It might not be able to support a kidney, but this study should be regarded as a great start and research should be continued to improve the workings of the initial setup.

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# Nomenclature

| | |
|---|---|
| $\eta$ | viscosity |
| C | Compliance |
| $cK_+$ | Concentration of Potassium |
| $cm$ | centimeter |
| $cNa_+$ | Concentration of Sodium |
| DCD | Donation after Cardiac Death |
| DGF | Delayed Graft Function |
| ECD | Expanded Criteria Donor |
| EMC | Erasmus Medical Center |
| IRI | Ischemia Reperfusion Injury |
| $L$ | Liter |
| L | Length of a tube |
| mA | milliampere |
| $min$ | minutes |
| $ml$ | milliliters |
| $mmHg$ | millimeter of mercury |
| NMP | Normothermic Machine Perfusion |
| $pCO_2$ | partial pressure of carbondioxide |
| $pO_2$ | partial pressure of oxygen |
| $r$ | radius |
| $R_1$ | Resistance of the tube |
| $R_2$ | Resistance of the peripheral system |
| RPM | Rotations Per Minutes |
| $s$ | seconds |
| $sO_2$ | saturation |
| t | time |
| $V$ | Voltage |

# Part I

# Article

# Prolonged Ex Vivo Preservation: Creating a Normothermic Machine Perfusion Setup

Ian Max Ernst Brouwer, BSc

## 1 Abstract

Expanded Criteria Donor (ECD) organs are being used more often in clinical setting. The regenerative ability of the organs might be able to restore the organ to full functionality ex vivo. For long term kidney stabilization, optimization and monitoring an organ incubator is preferable. However, it is unclear which available parts would work best in synergy. A Normothermic Machine Perfusion (NMP) setup and a Mathematical Windkessel Model were created as a first step in a larger project of prolonged preservation of ECD organs. While the current NMP setup was found adequate for academic research, it can only be used for simple studies using water. Several fundamental improvements need to be made before the setup can be used as a fully functioning NMP setup for kidneys. Key improvements would be the addition of a Windkessel and a different cardiac pump.

## 2 Introduction

There are numerous people currently on the waiting lists for new organs. And there is a greater demand for healthy organs than there is a supply. In the Netherlands alone, 1711 patients were added to the waiting list in 2017 and sadly 136 patients died before they had the much-needed surgery.[1], [2] To prevent deaths, organs of a lesser quality are being used more often in clinical setting. The lesser quality organs are referred to as Expanded Criteria Donor (ECD) organs in the literature. These are often organs obtained from Donation after Cardiac Death (DCD) and from elderly donors (50+).[3] DCD organs are damaged by the stop of the flow of blood (ischemia) and the re-perfusion of the blood flow after obtaining the organ. This phenomenon is also known as Ischemia Reperfusion Injury (IRI). There is a strong correlation between IRI & Delayed Graft Function (DGF) and the rejection of the organ.[4]–[6] Literature indicates the regenerative ability of the organs might be able to restore the organ to full functionality in vivo over time. Interestingly, it might be possible to start the restoration progress ex vivo by preserving the organs under controlled healthy circumstances. Over the last couple of years the amount of research about this topic has increased rapidly.[7], [8] In addition, there is a growing number of start-ups and scale-ups focused on the development of perfusion setups. Standardized, sustainable, and functional organ systems will potentially allow clinical residents to keep an organ under physiological healthy conditions for days while they dynamically analyze its metabolic function, homeostatic abilities and evaluate distress. Ultimately, it might be feasible to pro-actively manipulate the metabolism with the aid of advanced computational algorithms. A literature review performed prior to this article concluded that Normothermic Machine Perfusion (NMP) using whole blood would provide the best chances of success for pro-longed preservation.[9]

### Problem definition

This study fits into a larger project of Erasmus Medical Center (EMC) of which the goal is: *"The development of an organ incubator with the possibility to mimic the physiological conditions of the kidney after procurement to stabilize, optimize and monitor the organ function for multiple days."*

The problems identified can be clustered in three levels of problem analyses.

First, kidney disease itself and the possibility of complications during transplantation was analyzed. This was also done to create better understanding of the physiology of kidneys and complications during surgery. However, the information gained did not create insights in the development of an organ incubator that are not already easily available (e.g. medical books and scientific papers).

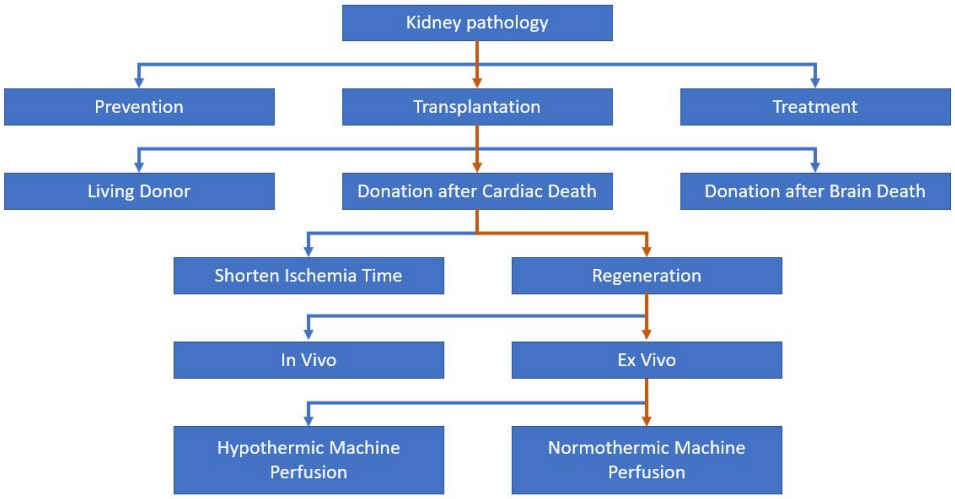


Figure 1: Problem definition from Kidney pathology to Normothermic Machine Perfusion

Secondly, options for long-term kidney preservation were gathered. This gave better insight into the choice to develop an organ incubator by EMC, but did not create further insights in how to develop an organ incubator. This information is elaborately explored in the prior literature review.[9]

Thirdly, information on the different physiological needs of a kidney during preservation and the potential technical solutions was gathered. This turned out to be an interesting topic as different parties all claim to have the best incubator or incubator parts and different studies suggest a variety of combinations as well. This information is greatly needed in the pursuit of the development of an organ incubator.

Combining this information resulted in the flowchart found in Figure 1. Within the field of kidney transplantation, this study focuses on ex vivo NMP for DCD organ preservation and regeneration. To create an organ incubator capable of this, a literature review was conducted to determine the physiological needs of a kidney to be stabilized, optimized and monitored. The machinery used by others in the literature was the first foundation to create an NMP setup as will further be discussed in the Methods section. The physiological features to be considered are: *flow, pressure, pulsatile profile, oxygen, temperature, nutrients and medicine.* To stabilize and monitor these physiological features, different incubator parts are needed. The incubator parts to be considered are: *pump, heating unit, oxygenator, temperature sensors, pressure sensors, outer shell, container, tubing, perfusion fluid/ oxygen carrier, medicine and nutrient administration, dialyzer.*

**Problem statement** For long term kidney stabilization, optimization and monitoring an organ incubator is preferable. However, it is unclear which available parts would work best in synergy.

The goal of this study was to lay a foundation for EMC by creating a potential NMP setup with which pro-longed preservation could be achieved. This article is a report on the steps taken and the advisable steps to be taken.

## Scope

This article is the report of work performed as a start of a larger project. The design choices and the theoretical and mechanical methods used to further develop an NMP setup are discussed. In the end the author was able to do some preliminary experiments with the NMP setup build, however the final setup was not fully operational. One of the functions missing was the capability to damp pulsations created by the pump. This deficiency in the physical model was supplemented with a mathematical model of a Windkessel to show the necessity of a physical Windkessel. The following two sections (3: Methods & 4: Results) are separated in two subsections: Normothermic Machine Perfusion Setup & Mathematical Windkessel Model. This choice was made as both parts of the project have had their own full process.

**Kalenski et al. 2016**

**Porcine kidney Blood**

1. Pulsatile roller pump (ISMATEC MPC standard, IDEX Health & Science GmbH)
2. Gas flow control
3. Oxygenator (Hilite 2400 LT, Medos)
4. Temperature control
5. Arterial sample port
6. Bubble trap
7. Pressure sensor (MLT844, AD Instruments GmbH)
8. Flow sensor ((ME2PXL1072, TS410 flow meter module, Transonic Systems Inc.)
9. Urine sample port
10. Venous sample port
11. Data acquisition system (PowerLab 8/30, AD Instruments GmbH)

Figure 2: Machinery itemization of Kalenski et. al [10]

Readers looking for more information are referred to the Literature Review and Appendices attached to this work.

# 3 Methods

To reach the goal of laying a foundation for the EMC project a physical setup and an additional mathematical model were created. The physical setup created is discussed in subsection: Normothermic Machine Perfusion Setup. The mathematical additions are discussed in subsection: Mathematical Windkessel Model.

## Normothermic Machine Perfusion Setup

The physical setup was created as an initial research setup. The goal was to create a sufficiently working setup which could function as a foundation for further research.

### Machinery needed

The literature showed several examples of possible setup configurations. For example, Kalenski et. al [10] has a very detailed description of all used machines and parts for their NMP setup as can be seen in Figure 2. The other item lists found in the literature can be found in Appendix C: Literature Itemization. The machinery needed consisted of (but was not limited to): *pump, heating unit, oxygenator, temperature sensors, pressure sensors, outer shell, container, tubing, perfusion fluid/ oxygen carrier, medicine and nutrient administration.* Collecting and comparing the machinery and parts used in the literature enabled a simplified vision of the NMP setup as depicted in Figure 3.

### Available machinery

Limited funds were available for the first proof of concept and it was imperative to use as much of the machinery available at hand at Erasmus MC. The following pieces of equipment were gathered and bought for this setup. A picture is shown in Figure 4.

1. Pulsatile blood pump (Verder 2006.A, 0.07:14.6[L/min])
2. Oxygenator (Organ Assist, Kidney Assist Transport part)
3. Disposable circulatory sets (LifePort & Organ Assist Transporter)

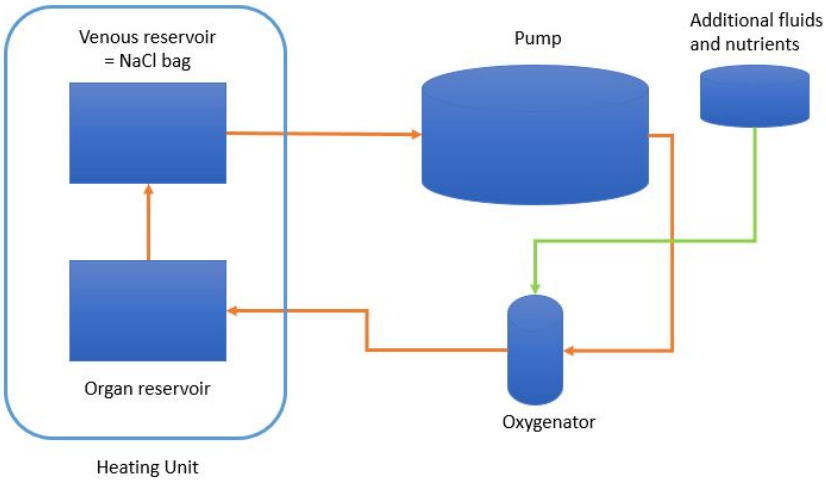


Figure 3: Simplified schematic of the current Normothermic Machine Perfusion setup

4. Disposable pressure sensor (Merit Medical Safedraw PMSET 1 DT-XX 1 Safedraw Transducer Blood Sampling Set)
5. Heating unit (brand & product line unknown)
6. Injection pump (Alaris CC)
7. Porcine blood (Experiment number: TCD10, Earnumber: 5758; 97$[kg]$; Anticoagulation: daily Ascal (300$[mg]$), Plavix (150$[mg]$) and Heparine ($0,72[ml]; 25.000[IE/ml]$) & right before blood sampling: Heparine (25.000$[IE/ml]$))
8. Tubing (inner radius 4 mm)
9. Bloodgas Analyzer (Radiometer ABL825 Flex)
10. Thermocouple type T (Labfacility XF-1095-FAR)

The choice was made to use LabVIEW for collecting and processing the data gathered real time. Both the thermocouple and the disposable pressure sensor needed to be connected to the computer on which the LabVIEW executable was able to run to collect the data. This is compatible with National Instrument USB connectors as LabVIEW is National Instruments software. A NI-USB 6211 was connected to read the pressure sensor and a NI-USB 9162 was used for the thermocouples.

The Verder 2006.A pulsatile blood pump can be controlled manually, but also with an analog signal. However, it needs a $4-20[mA]$ signal whereas the NI-USB 6211 can have an output of $0-10[V]$ at $\pm 2[mA]$ making the two devices incompatible. Therefore a Power Supply (ES 030-5, Delta Elektronika [0-30V 0-5A]), an amplifier (Scaime, CPJ-RAIL) and an operational amplifier (Texas Instruments, LM741CN/NOPB) were connected to enable automated control.

Optimally the pump would be a self-controlling, pressure driven pump as flow driven pumps will potentially put more strain on the organ with abnormally high or low pressures. However, the currently used pump uses a manual input (or analog signal from another source) to determine a rotation speed with a specific flow. Because the flow is controlled by the pump, it is not possible to also control the pressure with the same pump.

To get the preferred initial pressure of $75[mmHg]$, the choice was made to add more perfusion fluid and read out the pressure before the pump was turned on.

Regular tap water was used to quickly test the current NMP setup for structural integrity and pressure stability. The literature review showed whole blood to be optimal for prolonged preservation. However, due to its scarcity porcine blood could only be used in one experiment. During this experiment with blood, the blood gas analyzer was used at $t = 0, 150, 290, 1270, 1440$ $[min]$ to measure the acidity ($pH$), partial pressure of oxygen and dioxide ($pO_2$ and $pCO_2$), oxygen saturation ($sO_2$) and sodium & potassium concentrations ($cNa_+$ and $cK_+$) among other values.

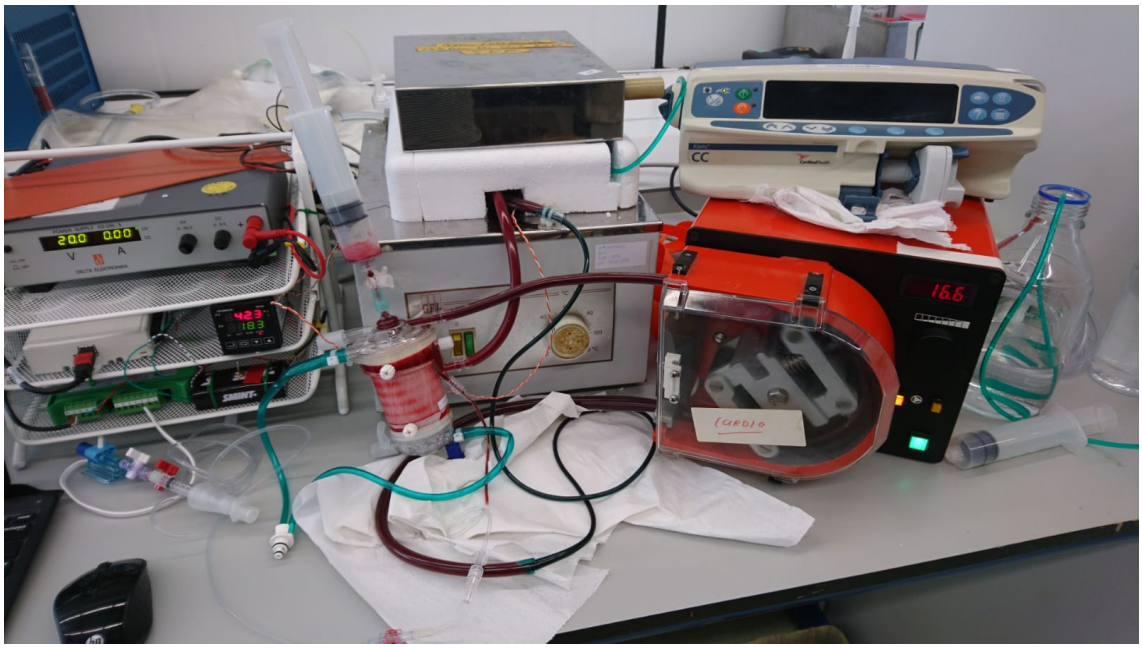


Figure 4: Picture of the NMP setup at the lab during an experiment using whole blood from a porcine model

| Physical quantity | Value | Unit of measurement |
|---|---|---|
| Temperature | 39 | $[C^o]$ |
| Flow | 550 | [ml/min] |
| pH | 7.46 +- 0.06 | |
| Sodium concentration | 137.1 +- 3.8 | [mmol/L] |
| Potassium concentration | 3.85 +- 0.46 | [mmol/L] |
| Pressure | 75 | [mmHg] |

Table 1: Physiological condition of porcine kidneys

### Physiological condition

The initial research goal was use the setup to study porcine kidneys as a model for human kidneys. To determine the desirable conditions for the NMP setup to create a healthy environment, the physiological conditions of a porcine kidney need to be used. A porcine kidney is fairly similar in size and shape to a human kidney, however it should be noted that the exact physiological conditions are somewhat different from a human kidney. Luckily this information was readily available in the literature and summarized in Table 1.[11], [12]

### Verification

To verify the usability of the setup created, Matlab was used to read the data files created by LabVIEW after each experiment. It is also possible to show near real time data by processing the newest file in Matlab, because the file is rewritten every second by the LabVIEW executable during the experiment. This will allow the researcher to identify possible errors and trends during the experiment, thus allowing the researcher to intervene.

The choice was made to calculate the partial averages and the overall mean to find trends. Each partial average is calculated by collecting the data of the 1.000 pressure samples (10.000 for temperature due to higher sample rate) that went before a sample and calculating its average. This gives insight into the trend of the signal and still shows the general shape of the data. In addition, the `mean` is calculated and plotted. This does not give insight in quick changes but it does show global trends which can help identify problems such as a drop in pressure over a longer period of time. If pressure does not decline and

if on top of that the pulsations are similar to that of a regular heart beat the setup is considered to be sufficiently functional. A healthy pressure profile could not be realized with the current NMP setup, as will be further discussed in section 5: Discussion. A mathematical model of a Windkessel was developed to study the necessity of a physical Windkessel to enable a subtler pressure profile.

## Mathematical Windkessel Model

In addition to the physical setup a mathematical model was created to provide empirical feedback on the pressure profile obtained with the current NMP setup and to identify possible areas of improvement.

The elasticity of the aorta functions as a damper to the pulsating pressure profile created by heart contractions. In the current setup there is no adjustment for this effect by the rigid tubes used. Literature suggest the use of a Windkessel to model the aortic elasticity in a perfusion system. A Windkessel is a chamber filled with air that will dampen pressure fluctuations of a fluid flowing through the chamber by compressing the air. The name Windkessel was first introduced by Otto Frank[13], this is a derivative of the German words: "wind" and "kessel", which can be roughly translated as "air" and "chamber".[14] A mathematical model was created to explain and provide proof for the necessity of a Windkessel in the current setup. In addition, the option to change the air chamber with a preferred pressure profile is explained and a fail safe option is explored.

To verify the mathematical model of the Windkessel model we first need a model of a pulsatile profile `[I(t)]` with a high peak followed by zero pressure each cycle. This can be accomplished by adding a couple of zeroes behind half a sine wave. This sine wave can be constructed using the rotations per minute (RPM) of the pump and the volume per pulsation. Furthermore, the pressure `[P]`, the compliance `[C]` and the resistances `[R1&R2]` are used in the mathematical model of the Windkessel in the form of a differential equation. Equation 1 shows the differential equation which is the mathematical model of the 3-Element Windkessel model. Equation 2 shows the line of code representing this differential equation. Here time and pressure are used as variables.

$$(1 + \frac{R_1}{R_2})I(t) + CR_1\frac{dI(t)}{dt} = \frac{P(t)}{R_2} + C\frac{dP(t)}{dt} \tag{1}$$

$$@(t, pres), \quad (-pres/(R2 * C) + I(t) * (R2 + R1)/(R2 * C) + R1) \tag{2}$$

Solving this equation will provide us with the new damped pressure profile. `2000` samples per cycle are used as it was quick and accurate as tested per trial and error.

### Input values

First the RPM need to be calculated based on the flow needed. By computationally extracting the RPM for different input values a formula was created which can be found as Equation 3.

$$RPM \approx 1.691x + 1.207 \tag{3}$$

Here x is the input value on the pump used which has a range of `[0:100]`. A number of cycles needs to be chosen. After a few cycles the pulsations will be stable and thus it is advisable to choose a number of cycles of 8 or more. Compliance `[C]` in ml/mmHg is the ratio of (air) volume to pressure. A higher compliance will result in more damping and thus lower peaks. The resistance of the tube between the pump and the Windkessel `[R1]` was calculated using an adapted form of the Hagen–Poiseuille equation, Equation 4. Here `[L]` is the length of the tube in cm, `[r]` is the radius of the tube in cm and `[`$\eta$`]` is the dynamic viscosity in mmHg*s.

$$R_1 = \frac{8L\eta}{\pi r^4} = \frac{8 * 25[cm] * 1.9725 * 10^{-05}[mmHg * s]}{0.24[cm]^4 * \pi} \approx 0.38[mmHg * s/ml] \tag{4}$$

The initial pressure inside the setup and for the mathematical model is set at $75[mmHg]$ as this is the value found in the literature, see Table 1. Literature shows the pressure behind the kidney to be $5[mmHg]$. The resistance of the rest of the system (including the kidney) `[R2]` is calculated using the pressure difference between the mean of the pressure in the Windkessel and a healthy flow of $550[ml/min]$ as shown in Equation 5.

$$R_2 = \frac{\Delta P}{Q} \approx \frac{75 - 5[mmHg]}{9.17[ml/s]} \approx 7.64[mmHg * s/ml] \tag{5}$$

**Change the pressure profile**

The pressure profile should not only be damped, but also be converted to a healthy pressure profile. The damped pressure profile will protect the blood and kidney from unhealthy low and high pressure peaks. However, an aorta is not a perfect damper so a fluctuating pressure between $60 - 90[mmHg]$ is considered healthy for a kidney. To change the pressure profile, the pressure needs to be measured and the pressure of the air in the Windkessel needs to be adjusted. The adjustment will not only zero out the leftover pulses of the Windkessel, but should also add the preferred pulsatile pressure profile. The pulsatile profile can be adjusted into the preferred profile by adjusting the pressure in the chamber. In the physical setup this would require very accurate and fast pressure sensors and the ability to change the pressure quickly and reliably within the Windkessel with an air pump. The assumption is made that there will be a slight time delay $0.01[s]$ before the pressure is perceived by the computer and a second larger time delay $0.1[s]$ is assumed in the control of the air pump connected to the Windkessel.

Without an intervention the output of the Windkessel would be too damped and without a healthy pulsatile profile. With an intervention it would be possible to approximate a healthy pressure profile. First, the choice is made to simply deduct the pressure from $75[mmHg]$. Here the first time delay is taken into account. This would lead to a constant output pressure of $75[mmHg]$. In addition, the preferred pressure profile needs to be added to construct a fluctuating pressure between $60 - 90[mmHg]$. Here the second time delay is also taken into account.

**Volume Control**

The next step would be to control the volume of blood in the Windkessel. The flow into the Windkessel is equal to the output flow of the pump. And the flow out of the Windkessel is equal to the difference in pressure divided by the peripheral resistance `[R2]`. The outwards flow may never drain the volume of blood from the Windkessel as this would introduce air into the blood stream which could have dire consequences for the organ. In a closed system the only way to drain the volume of blood from the Windkessel is if the pressure in the Windkessel becomes too high. If the volume of the Windkessel drops significantly the pump should pump fluid more rapidly to increase the flow into the Windkessel before this happens.

# 4 Results

## Normothermic Machine Perfusion Setup

During initial testing the pressure could not be maintained. An example of this pressure drop can be found in Figure 5. The problem was most likely caused by the elasticity of the initial reservoir. It was possible to maintain a steady pressure in follow-up experiments. In a test to measure the differences in pressure profiles per speed input this can be seen clearly. The pressure measurement is shown in Figure 6. Here the time axis is deliberately chosen to only show $t = 0[s]$ to $t = 32[s]$ as speeds above the second speed input of 20% resulted in unrealistically high pressure peaks. In Figure 7 an even smaller time sample is depicted of $t = 22[s]$ to $t = 32[s]$. Here the peaks are more clearly displayed and it also becomes very clear the peaks are very intense. The green line represents the mean and indicates if the pressure stays stable.

One of two the key experiments for testing the setup is an experiment for a period of 8 hours using water. The graphs of the pressure and temperature of the experiment using water can be found in Figure

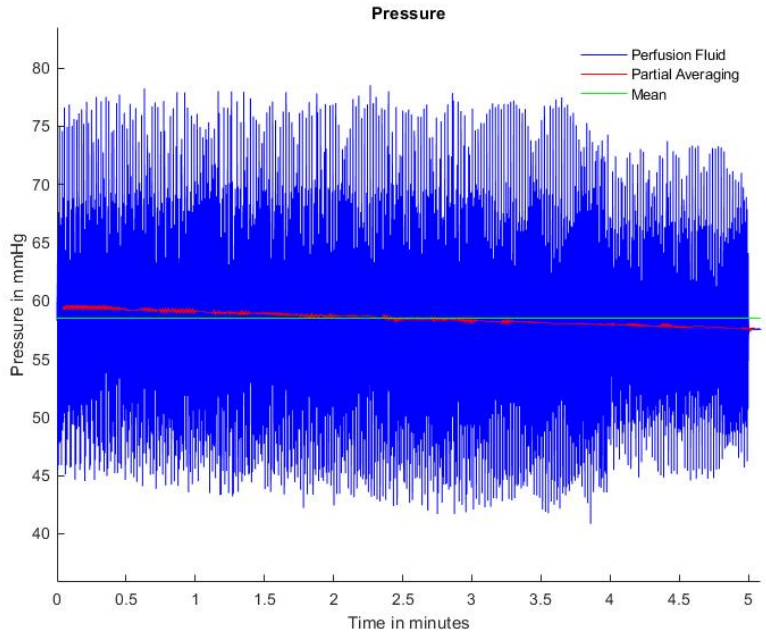


Figure 5: Pressure drop at time $t = 0 : 5.1[min]$ with a sampling frequency of $20[samples/s]$; the pressure profile drops below the mean at the end

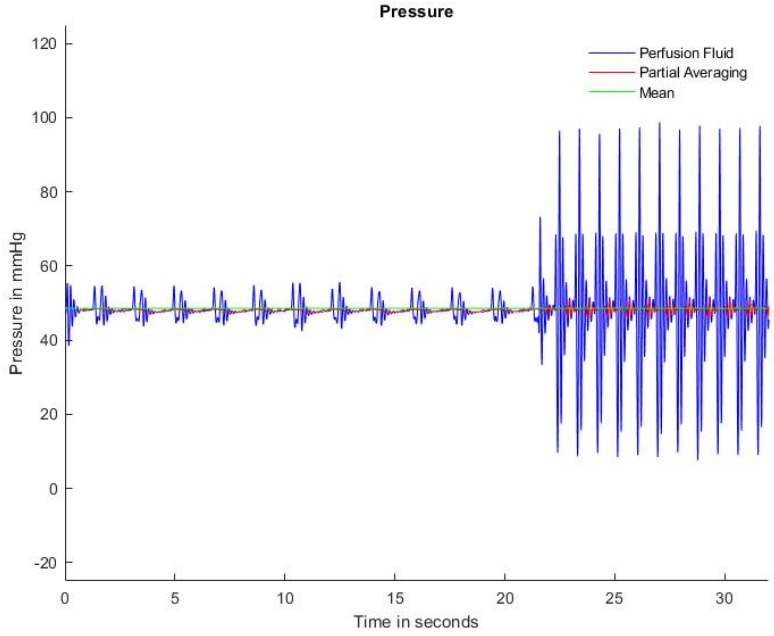


Figure 6: Stable pressure profile of around $65[mmHg]$ at time $t = 2 : 4.3[min]$ with a sampling frequency of $20[samples/s]$

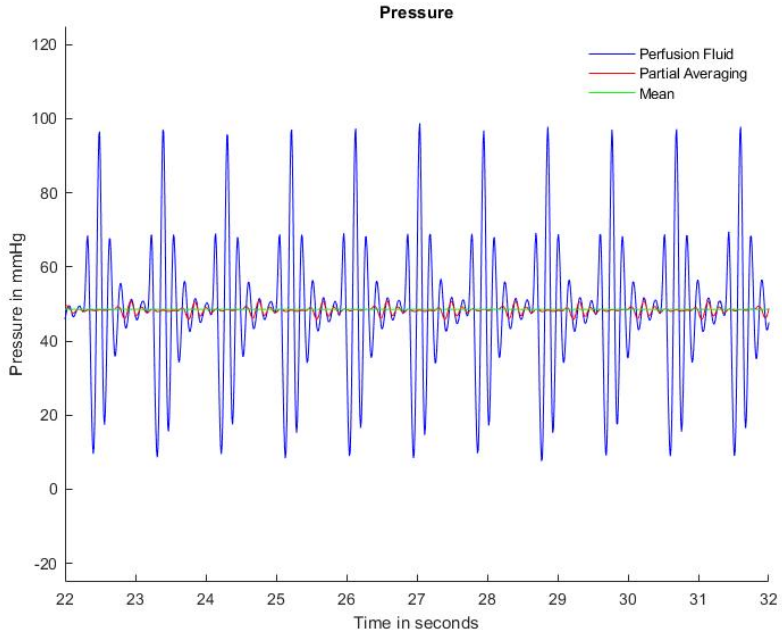


Figure 7: Stable pressure profile of around 65$[mmHg]$ at time $t = 120 : 130[s]$ with a sampling frequency of 20$[samples/s]$

8 & 9 respectively. This experiment was done to study the setup over a longer period of time. The second key experiment was held for 24 hours using porcine blood. The graphs of the pressure and temperature of the experiment using blood can be found in Figure 10 & 11 respectively. In the temperature graph as well as in the pressure graph there is a peak that can be seen around 12 hours. From the experiment it can be seen that the mean pressure was extremely low. A blood gas analysis was performed throughout the experiment. This data is shown in Figure 12. It is clear $pH$, $pO_2$ and $sO_2$ drop and $pCO_2$, $cK_+$ and Lactate concentration increase which all indicates a degradation of the blood. Hemoglobin levels ($ctHb$) and red blood cell count ($Hctc$) remain quite constant. The outlier of the third red blood cell count and hemoglobin levels measurement are neglected. This peak is discussed with an expert on cell oxygen consumption and it is predicted this outlier measurement was the result of an uncommon red blood cell concentration at the sample port caused by coagulation. The saturation could not be measured at $t = 0$ due to a technical error which was fixed between the first and second measurement.

## Mathematical Windkessel Model

Using the mathematical model created it is possible to graph the pulses. In Figure 13 different values of `C` [0.5 1 1.5 2 2.5]$[ml/mmHg]$ are used to calculate the damped pressure profile. Here the relation between the compliance and damping can clearly be seen: A higher compliance correlates to more damping and lower peaks, which was expected.

The air volume needed inside the Windkessel can now easily be calculated by multiplying the compliance with the mean pressure: $\pm$[40 80 110 150 190]$[ml]$. Ideally the blood volume should be as low as possible, but the pressure range should also be relatively small. For the rest of the modeling a compliance of 1$[ml/mmHg]$ with a corresponding volume of 80$[ml]$ was chosen. This pulsation has a range of less than 3.58$[mmHg]$ and is a very stable and has low pulsation.

### Change the pressure profile

In Figure 14 the preferred pulsatile pressure profile, the theoretical pressure without intervention and the theoretical pressure with intervention can be found. Changing the pulsatile pressure profile with such

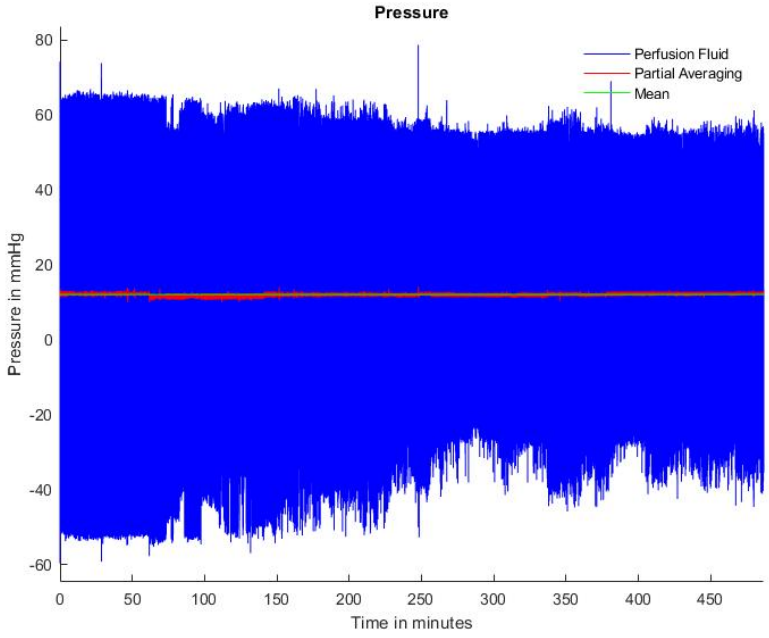


Figure 8: Pressure during the experiment using water for 8 hours with a sampling frequency of 20[$samples/min$]

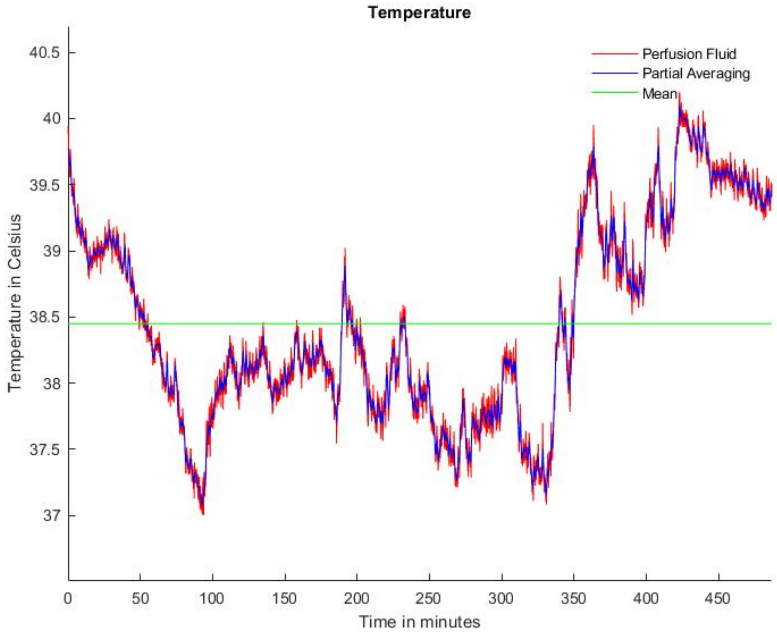


Figure 9: Temperature during the experiment using water for 8 hours with a sampling frequency of 20[$samples/min$]

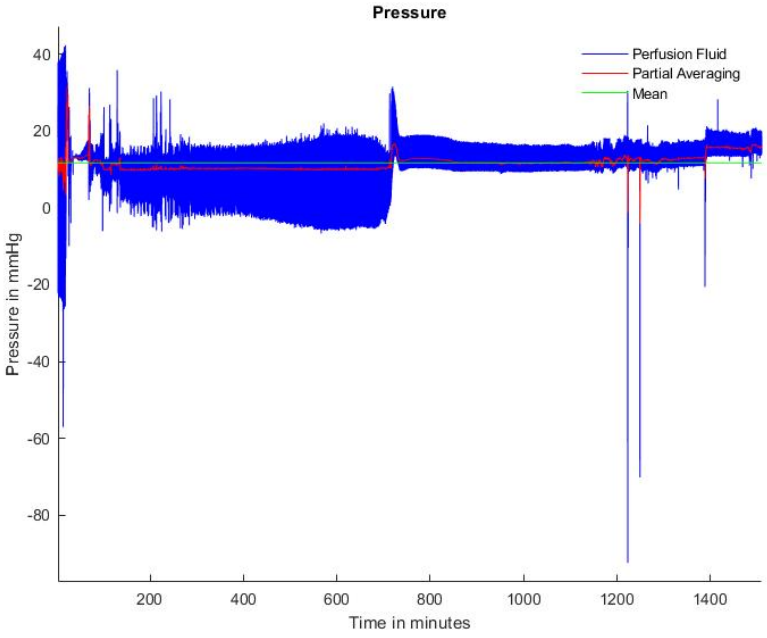


Figure 10: Pressure during the experiment using blood for 24 hours with a sampling frequency of 5[*samples*/*min*]

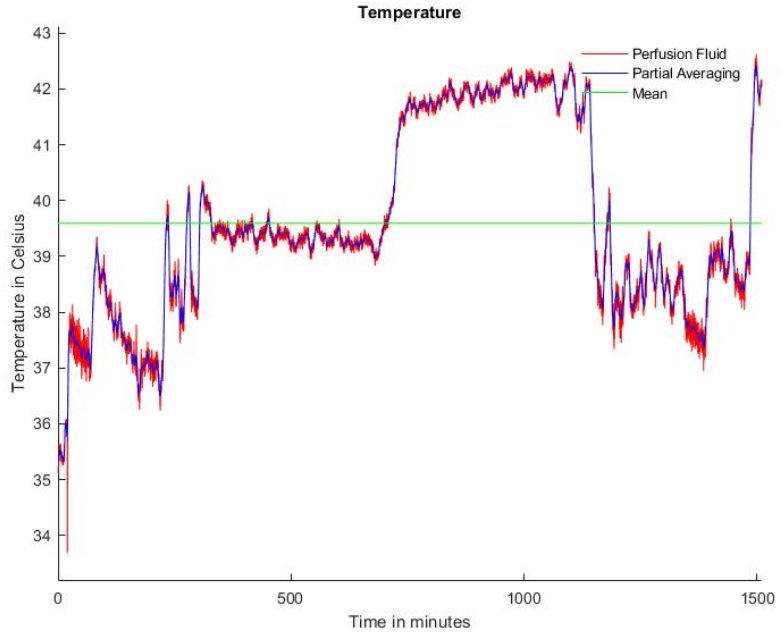


Figure 11: Temperature during the experiment using blood for 24 hours with a sampling frequency of 5[*samples*/*min*]

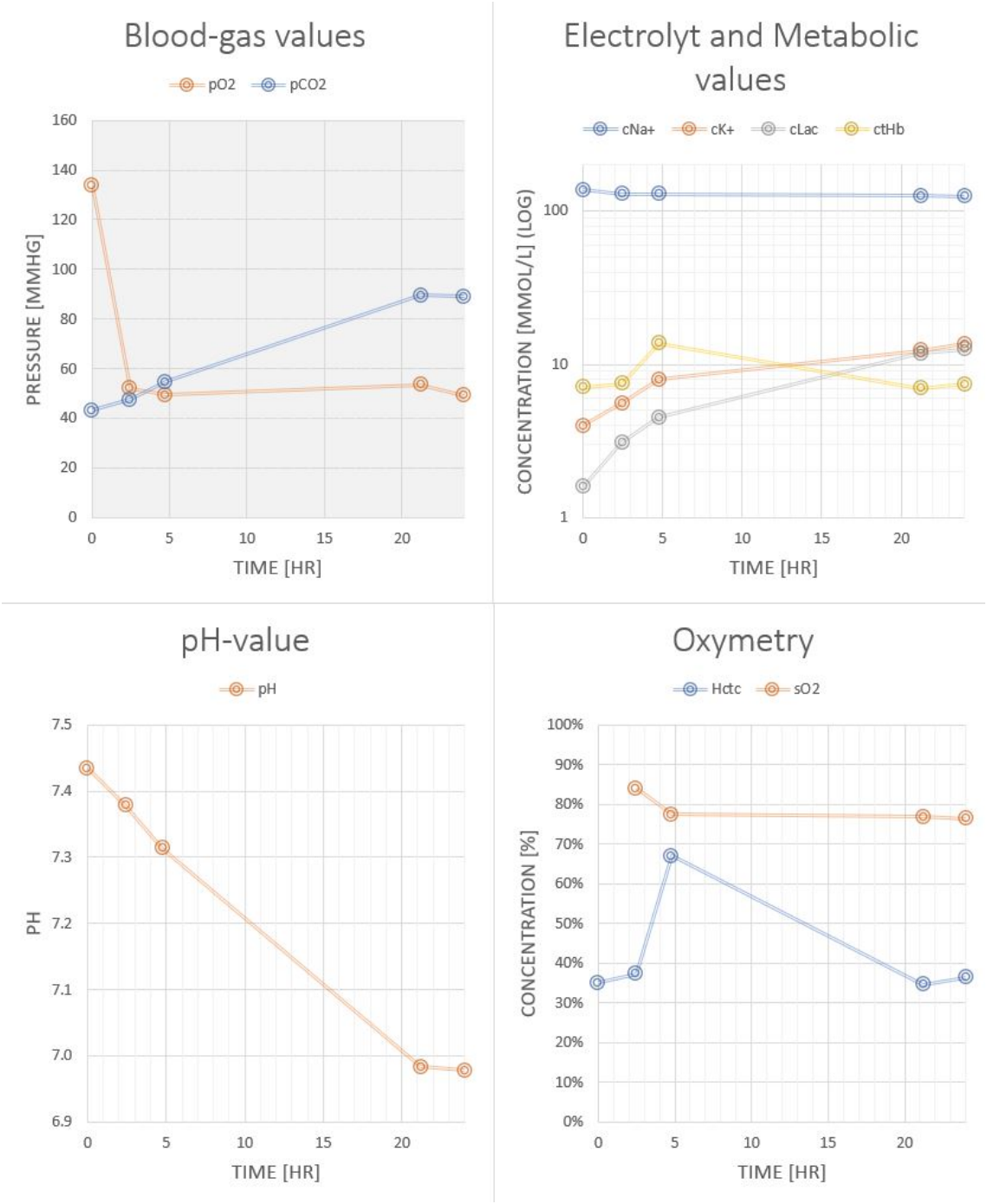


Figure 12: Blood gas analysis of the experiment using blood over 24 hours with a sample taken at t = 0, 2.5, 4.8, 21.2, 24 [hours] ; a. Partial pressure of Oxygen and Carbon-dioxide in [mmHg]; b. Concentration of Sodium ($cNa_+$), Potassium ($cK_+$), Lactate ($cLac$) & Hemoglobin ($ctHb$) in [mmol/L]; c. pH level; d. Concentration of Red Blood Cell count ($Hctc$) & Saturation ($sO_2$) in percentages

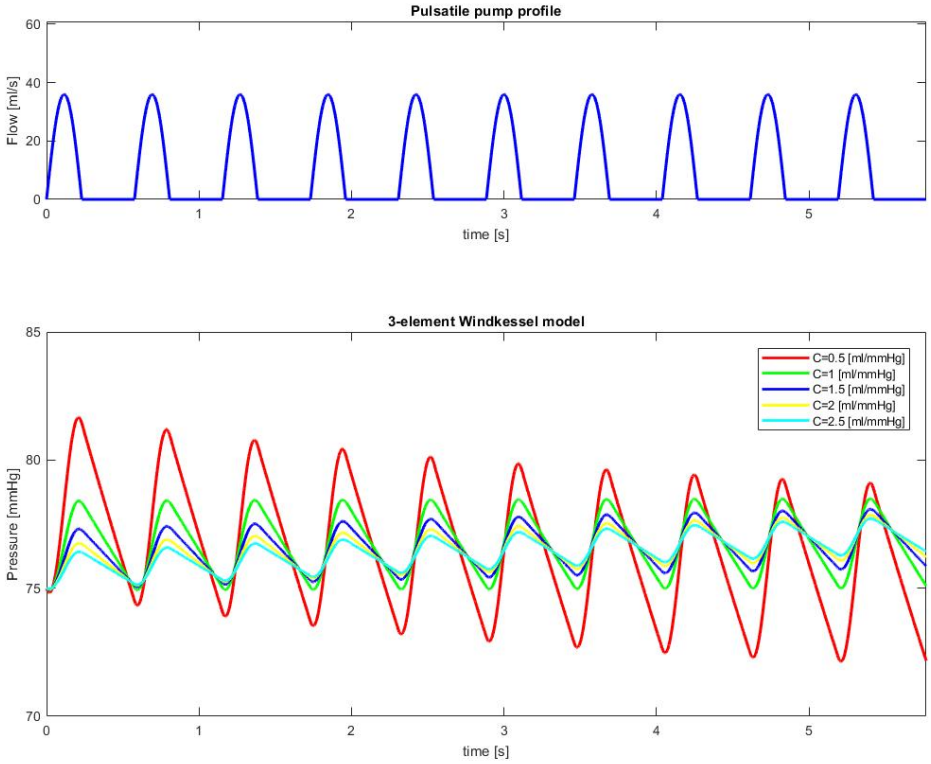


Figure 13: Pulsatile pump profile & 3-Element Windkessel model of 10 cycles at 52 cycles per minute and a sampling frequency of 2000[$samples/s$] with compliance: C= 0.5, 1, 1.5, 2, 2.5 [ml/mmHg]

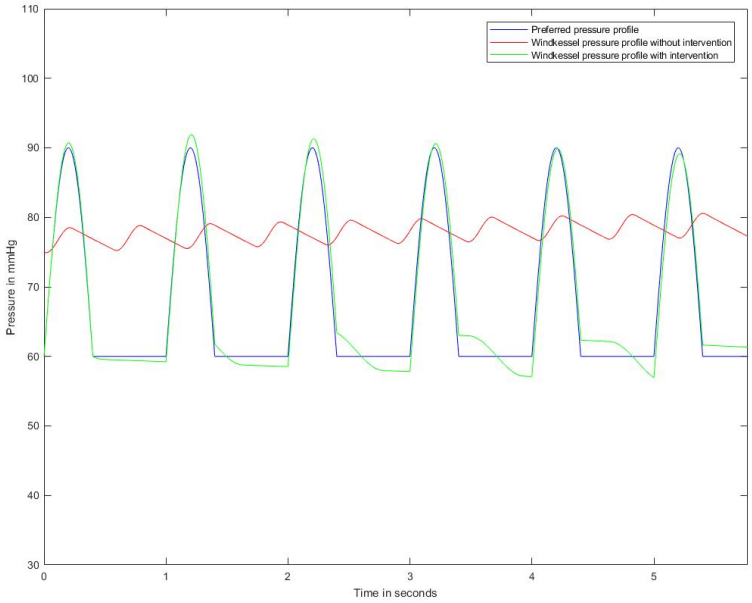


Figure 14: Pressure profile during 6 cycles with a frequency of 60 cycles per minute: a. Preferred pulsatile pressure profile [blue]; b. Windkessel pressure profile without intervention [red]; c. Windkessel pressure profile with intervention [green]

an intervention would make the physical situation, as opposed to a mathematical situation, a lot more complex. The complexity will mostly come from the addition of pressure regulators and automated air pump.

### Volume Control

In Figure 15 the blood flow into and out of the Windkessel is shown. While there are changes in volume, the volume of the fluid is shown to be stable over time. The size of the chamber is directly influenced by the biggest differences between flow in and out. Smaller peaks of flow into the Windkessel will result in smaller Windkessel size needed. If the RPM of the pump remains relatively low, these peaks will also remain relatively low.

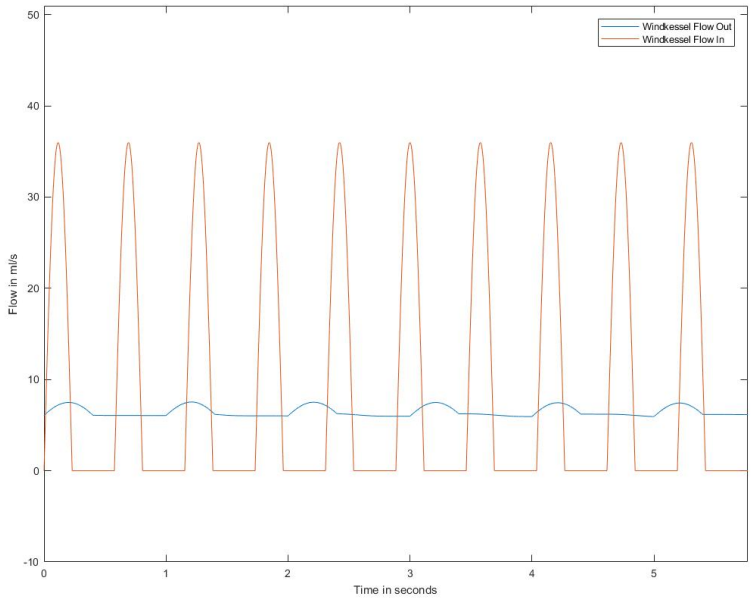


Figure 15: Inwards and outwards flow in ml/s of the Windkessel

# 5 Discussion

This study provides insight into the way an experimental setup to conduct research into kidney preservation should be set up. The weak points identified in the current NMP setup, along with the points of improvement that follow from the mathematical model should be used as starting point for the development of an experimental setup that can be used for academic research.

## Interpretation

In the literature review performed before this study ([9]) it became apparent that pro-longed preservation is possible, but it is still in a relative early stage and more research is clearly needed.[7], [8] Moreover, using NMP for preservation is complex and it might be inadvisable to use a research setup without consulting a medical technician.

**Normothermic Machine Perfusion Setup;** In the experiment using blood the pressure was extremely low. It is of vital importance to keep the pressure at around 75$[mmHg]$. The pressures measured would most likely damage the blood during prolonged exposure to such extreme peaks. Both the low pressure and these peaks have contributed to the degradation of the blood. The peak in pressure and temperature that can be seen around 12 hours is due to the coagulation of the blood. Blood flow halted and the temperature rose in the heating unit where the temperature was measured. Without the flow of blood going through the cold pump and tubing outside the heating unit it remained at an unhealthy high temperature. Furthermore, there is a clear lack of oxygen measured in the experiment and the sodium and lactate values rose steadily indicating extreme degradation of the blood. Moreover, a glucose measurement was done at the end of the experiment and the glucose concentration was too low for the device to even measure its concentration. The gas connected to the oxygenator was regular air. Changing this to (95%) oxygen could make great differences in maintaining the partial pressure of oxygen and saturation at desired levels. However, this was not available during the experiment. A healthy kidney should maintain potassium and pH levels. Otherwise, sodium bicarbonate could be added in intervals to better maintain the pH and potassium levels. During the experiment, no additional nutrients were available. No full coagulation was measured for 12 hours and the concentration of hemoglobin was steady (even over 24 hours) indicating it might be possible to maintain relatively healthy blood by connecting

oxygen to the oxygenator and by adding nutrients.

**Mathematical Windkessel Model;** The results collected with a theoretical mathematical model were highly promising. The extreme peaks of the pulsatile pressure profile were damped correctly. The pressure profile of the Windkessel pressure with intervention is a bit less smooth than the preferred pressure. This difference can be explained by the combination of both time delays discussed in section 3: Methods. Although the smallest usable volume for the Windkessel was chosen, it is still quite large. The compliance is directly correlated to the volume and thus a smaller compliance is preferable. The volume of air is now dependent on the compliance and pressure. However, if the air pressure in the Windkessel could be controlled with the help of an electronic pressure regulator and if the noise on the pressure profile is minimal this could mean the full Windkessel effect could be taken over by an electronic air pressure regulator. A much smaller volume would then be needed to regulate the air pressure. If the mathematical Windkessel model is physically constructed and the air pressure system works as predicted, it is advised to calculate the minimal volume in a follow-up study.

**Volume Control;** In the mathematical model the flow into and the flow out of the Windkessel are stable over time. The volume of the blood in the Windkessel is also stable over time. In the mathematical model a small margin of a few milliliters is enough to deal with the fluctuations in volume and no further action is needed to maintain a stable volume. If the volume of blood in the physical Windkessel drains, air will enter the system and the kidney will fail. This is unacceptable and when translating the mathematical model to a physical model it is advised to implement a precautionary feedback loop as a safety measure. The height of the blood inside the Windkessel should be measured to determine the blood volume. If this volume falls below a certain threshold the feedback system should accelerate the pump to refill the Windkessel with blood.

## Points of improvement

To enable the NMP setup to support a kidney a few alterations and improvements are needed. These parts need to be included to increase the chance of pro-longed preservation of the porcine kidneys in research setting:

**Container**
If this project is continued and kidneys are used a sterile container is needed. The kidney would most likely not be able to survive the harsh circumstances of the current reservoir. One solution would be to re-use an Organ Assist container which has been rinsed and cleaned after being used in clinical setting. However, this equipment is hard to come by as a procedure using the Organ Assist is not performed often.

**Windkessel**
The need for a Windkessel is elaborately discussed in the previous sections. Without damping the pressure peaks caused by the pulsatile pump it is unwise to let organic material in the system. If the pressure becomes to low or high this could heavily damage the cells. A Windkessel of $\pm 0.08$ liter would be sufficient as this would enable a compliance of $1[ml/mmHg]$ with a pressure of $75[mmHg]$.

**Dialyzer**
In the early stages the assumption was made through literature that a dialyzer could help make the NMP setup a more stable and healthy environment for a kidney. This piece of equipment could not be acquired for this project and since the current NMP setup was unable to sustain a kidney the choice was made not to put any more effort into acquiring a dialyzer. However, it is still advised to add a dialyzer.

**Pump**
It is advised to continue with another pump. The Verder 2006.A is a relatively old cardiac pump and to enable it to work in synergy with other newer equipment is needlessly hard to do. Furthermore, the pressure profile can be made more stable using more than two rollers and having a differently shaped release system that will help release the fluids more gradually. At the experimental transplantation and intestinal surgery lab at Erasmus MC they use a Masterflex L/S system which meets these requirements. It is advised to invest in such a device for the follow-up of this study.

## Possible biases

As much of this study was based on the work of other scientists it is vulnerable to bias. This is not only the result of the tendency to publish more relevant papers and to withhold negative results, which has a great influence on the initial boundaries set to this study, but also of the secondary interpretation of their data by the author of this article. Moreover, the author could have been influenced by his prior knowledge in the pursuit of this information and only used search terms that would further prove his train of thought. More than a hundred data sets were gathered throughout the project. Most of these were small tests and some were started as full experiments but were ended prematurely. When errors presented themselves during or at the end of a test these tests were not useful and the choice was made not to present them here. This selection of data could influence the readers perspective on the usability of this NMP setup in another way than the author's intention.

## Conclusion

It was possible for the equipment to work in synergy. The current NMP setup is a decent perfusion setup and can be used for simple studies using water. It might also be usable for studies using porcine blood with some improvements as discussed earlier. It might not be able to support a kidney, but this study should be regarded as a great start and research should be continued to improve the workings of the setup. Several improvements need to be made before the setup can be used as a fully functioning NMP setup for kidneys. These improvements include the addition of a sterile container, a Windkessel, a dialyzer and a Masterflex L/S system. The most important improvement would be the addition of a physical Windkessel as this would greatly improve the circumstances under which the kidney is preserved. Enhancing the pressure to create a healthy pressure profile and to minimize the Windkessel air volume is achievable. However, this would require an investment in an accurate and fast, digitally controlled air pump and several accurate air pressure sensors. This report contains valuable information for the researchers at EMC and will enable further research into prolonged ex vivo preservation with NMP.

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# Part II

# Appendix

Part II of this thesis report is the appendix of the article. It includes appendices referred to in the article and also a lot of peripheral information. The goal of this part is to explore the steps taken and by doing so create an effective basis for a knowledge transfer.

# A Project background information

## A.1 Project proposal

Erasmus MC is one of the best medical centres in Europe and one of the lead innovators in developing new techniques to care for patients. They would like to further develop steps into the long-term preservation of organs for pre-operation restoration. They have research teams working on these developments and one of their teams saw an opportunity in further investigating the possibility of creating an NMP setup to restore an organ pre-operative ex vivo. The choice was made to let a Biomedical Engineering student further investigate the possibilities by building a technical solution. The end goal of this multiple year project is to develop an NMP setup for kidneys and livers in clinical setting, however this thesis solely focused on the development for a testing setup for porcine kidneys.

## A.2 Literature Review

Before the start of the project the author was asked to provide a theoretical basis in the form of a literature review [9]. This work focused on the different preservation techniques and preservation fluids commonly used in both clinical and research setting. One of the key steps in gathering information was the development of the criteria for pro-longed preservation under healthy circumstances. Keeping in mind the end goal of transplant surgery of a healthy organ, metabolic support and monitoring of the organ during preservation are of the utmost importance. The literature review concluded that NMP with whole blood is predicatively the best combination for pro-longed preservation. It is advisable to the reader to read the full article as it provides more in depth explanation of some of the earlier choices made.

## A.3 Additional theory

In addition to the literature review other resources were used to further develop an idea of the needs of the organ preservation setup. An online course in Transplantation Surgery was followed to better understand the working circumstances of the clinical residents working with donor organs. Also a transplantation procedure of a living donor transplantation was witnessed.


Figure 16: Image of a 240 deg 5-pin DIN connector[15]. Pins counted 1:5 from left bottom to right bottom.

# B Current Normothermic Machine Perfusion Setup

## B.1 Current machinery

1. Pump

   The pump used is a Verder 2006.A pulsatile pump which can be controlled with an analog signal through a 240 deg 5-pin DIN connector as depicted in Figure 16. With the connector of this specific pump, the speed can be controlled by signaling between pin 2 and 3. Pin 1 and 5 can be used to switch the pump on and off. Other specifications can be found in Figure18: Verder 2006.A specification sheet (Dutch). A resistor of 471.5Ω within the main circuit card is directly connect to this connector. The complete circuit of the pump is shown in Figure 17 and the purpose of each wire explained in Table 2. The 4-20[mA] can be controlled with a voltage range of which can be calculated with $I * R = U$:

   $$[4 : 20] * 471.5 = [1.886 : 9.430] \tag{6}$$

   The "back" Printed Circuit Board (PCB) perceives the intensity of the power needed and is able to switch between Manual input and Analog input. The intensity will be shown through the Display.

   The "bottom" PCB receives all information and influences the path between the pump and motor. It receives information of the On/Off switch, the direction of the pump, the intensity (through the display) and the safety switch.

2. Operational amplifier

   An amplifier and an additional operational amplifier (opamp) needed to be included in the system to be able to amplify the pressure sensor's signal to the computer and the computer's signal to the pump. This opamp was connected without negative feedback (a comparator). A circuit schematic of such a comparator can be seen in Figure 19.

3. Thermocouples

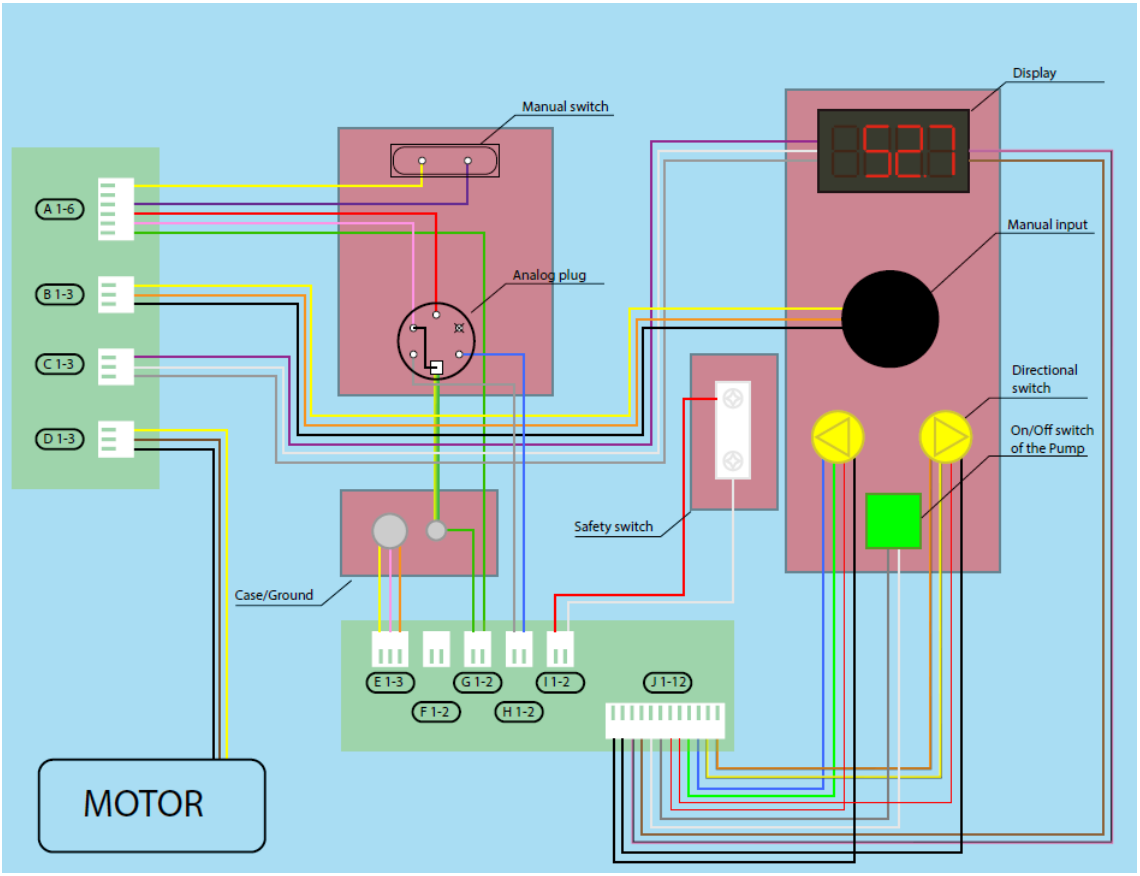



Figure 17: Pump circuit; left green rectangle, back printed circuit board; left red rectangle, back of the pump; right red rectangle, front of the pump; bottom green rectangle, bottom printed circuit board

| PCB | Gate | Wire | Purpose |
|---|---|---|---|
| Back PCB | A | 1 & 3 | Receive information from the Manual switch by close circuit |
| | | 4 & 5 | Receive information from the Analog plug |
| | | 6 | Power source or ground |
| | B | 1 – 3 | Receive information from the Manual Input |
| | C | 1 – 3 | Offer information on the current pump power to the Display |
| | D | 1 – 3 | Drive the Motor |
| Bottom PCB | E | 1 – 3 | Ground |
| | F | 1 & 2 | Connecting the two PCBs |
| | G | 1 & 2 | Power source or ground |
| | H | 1 & 2 | Receive information from the Analog plug |
| | I | 1 & 2 | Safety Switch |
| | J | 1, 7, 9 & 10 | Receive information from the Left Directional Switch |
| | | 2, 8, 11 & 12 | Receive information from the Right Directional Switch |
| | | 3 & 4 | Receive information of the Display |
| | | 5 & 6 | On/Off switch of the Pump |

Table 2: Pump circuit information table

VERDER

# TECHNICUM SLANGENPOMPEN

## Capaciteit van 0,07 - 14,6 l/min.

**Model 2006 regelbaar**

De Verder 2006 slangenpomp is een robuuste en betrouwbare slangenpomp, die geschikt is voor alle doseer-, transport- en monstername toepassingen. Een krachtige gelijkstroommotor met een maximaal toerental van 165 omw/min verzorgt de aandrijving. Veelvuldig in- en uitschakelen is probleemloos te realiseren. De pompkop is voorzien van verende rollen, waardoor een extreem slangvriendelijke pompwerking wordt bereikt. Eenvoudig is het inleggen en uitnemen van de slang. Slangen met wanddikten van 1,6-3,2 mm en binnendiameters van 1,6-19 mm zorgen voor een optimale aanpassing aan een breed scala van doseeropgaven.

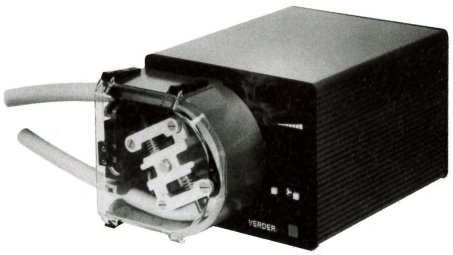
Het toerental is in een verhouding van 1:20 traploos door middel van een potentiometer en digitale display instelbaar. De potentiometer wordt door een O-ring beschermd tegen vuil en spatwater. De centrale hoofdschakelaar schakelt de pomp en via richtingskeuze toetsen kan de pomprichting worden omgekeerd. De beschermkap over de pompkop is voorzien van een veiligheidsschakelaar die de pomp uitschakelt wanneer de kap wordt geopend. De motor is beveiligd tegen overbelasting door een stroomschakelaar.

**Model 2006.A regel- en aanstuurbaar**

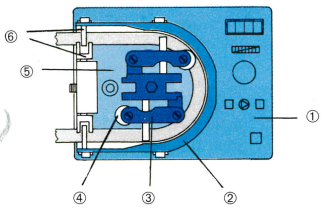
Het model 2006.A is in principe gelijk aan model 2006. Het verschil bestaat uit de mogelijkheid het model 2006.A middels een analoog signaal (4-20 mA) extern aan te sturen.

**Toepassingen**

Toepassingen zijn o.a. monstername van procesvloeistoffen en afvalwater en transport van voedingsmiddelen en pharmaceutische produkten.



## Uitvoering




| | Deel | Materiaal |
|---|---|---|
| 1 | Kast | gemoffeld aluminium |
| 2 | Slangbedding | gemoffeld aluminium |
| 3 | Rotor | geanodiseerd aluminium |
| 4 | Rollen | Nylatron |
| 5 | Beschermkap | Plexiglas |
| 6 | Slangklemmen | geanodiseerd aluminium |

Figure 18: Verder 2006.A specification sheet (Dutch)

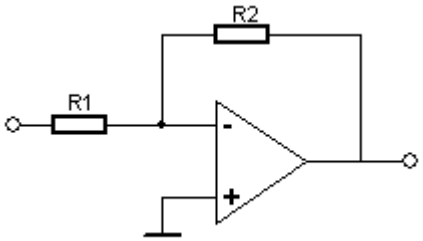



Figure 19: Operational amplifier

The choice was made to use type-T Thermocouples. These are affordable and have a relatively small temperature of -100$C^o$ to 400$C^o$.

## B.2 Assembly

1. Required machinery

   This equipment is required to keep in order for the current setup to work. This list is followed by a second list of all the equipment which is needed, however other brands and or product lines may be used too.

   (a) Pulsatile blood pump, Verder 2006.A, 0.07:14.6[L/min]
   (b) Thermocouple type T, Labfacility XF-1095-FAR
   (c) Heating unit (brand & product line unknown)
   (d) NI-USB 6211
   (e) NI-USB 9162
   (f) Amplifier, Scaime CPJ-RAIL

   (a) Tubing
   (b) Disposable circulatory sets
   (c) Oxygenator
   (d) Disposable pressure sensor
   (e) Injection pump
   (f) Power Supply, [0-30V 0-5A]
   (g) Bloodgas Analyzer
   (h) Porcine blood

# C Literature itemization

The first step in building a preservation system is figuring out which devices and parts are essential. The literature studied for the literature review [[9]] of pro-longed preservation techniques was a great source of technical information. Often, the information of these papers was not limited to the results of their studies but elaborate methodology was provided and technical details of these devices were shared.

## Vogel et al. 2017

**Porcine Liver Blood** [16]

- Tubing components from cardiopulmonary bypass suppliers
- Centrifugal pump drive (Medtronic)
- Hollow fibre membrane oxygenator (D905 EOS, Sorin, Italy)
- Soft-shell reservoir (Capiox 1500, Terumo)
- Medical grade silicon tubing (Raumedic AG, Germany)

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## Imber et al. 2002

**Porcine Liver Blood & UW** [17]

1. Centrifugal pump (BP50 Centrifugal pump, Medtronic)
2. Oxygenator (1500 ECMO Oxygenator, Medtronic, UK)
3. Heat exchanger (Ecmotherm II HE, Medtronic)
4. Reservoir (Venous reservoir bag 800 mL, Medtronic)
5. Tubing (PVC 1/4 and 3/16 inch internal diameter, Medtronic)
6. 1500 mL blood

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## Jamieson et al. 2011

**Porcine Liver Blood** [18]

1. Centrifugal pump (BP50 Centrifugal pump, Medtronic)
2. Oxygenator (Jostra Quadrox HMO 2000 Oxygenator, Maquet Cardiopulmonary, UK)
3. Soft-shell reservoir (MVR 800, Medtronic)
4. Intestinal bag (Vi-Drape, MCD)
5. Tubing (PVC 1/4 and 3/8 inch internal diameter with polycarbonate connectors, Medtronic)
6. A gate clamp (EW-0683310, Cole Palmer)
7. Flow probes (DP 38P, Medtronics)
8. Heat exchanger (Biomedicus, Medtronics)
9. 1500 mL blood

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## Liu et al. 2016

**Porcine Liver Blood** [19]

1. Centrifugal pump
2. Leukocyte filter
3. Oxygenator
4. Heat exchanger
5. Sampling port
6. Roller pump
7. Flowmeter
8. Pressure monitor
9. Reservoir
10. Protacyclin infusion
11. Nutrition and supplements

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## Bessems et al. 2005

**Rat Liver MP solution** [20]

1. Roller pump (Ismatec, Glattburg, Switzerland)
2. Glass oxygenator
   Carbogen (95% O2/ 5% CO2, 1L/min, Hoekloos Medical, Netherlands)
   Bubbletrap
3. Heat exchanger (HMT-200, Heto, NL)
4. Flow meter (HT-207, Transonic Systems Inc., NL)
5. Temperature probe (Lameris, NL)
6. Reservoir
7. Organ Chamber
8. Tubing

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## Worner et al. 2014

**Rabbit Kidney MP solution** [21]

1. Roller pump (BP-3A, Gambro Instruments AB, Lund, Sweden)
2. Pulsatile pump
   Pillow valve (Comef S.p.A., Italy)
3. Hollow fiber dialyzer (Fresenius F3, Germany)

4. Bubble oxygenator
   95% O2/ 5% CO2
5. Venous reservoir
6. Pressure transducer
7. Windkessel device (20ml syringe)
8. Waming plate
9. Kidney chamber
10. Urine collection flask
11. Tubing

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## Hosgood et al. 2013

**Porcine kidney Blood** [22]

1. Pediatric cardiopulmonary bypass technology (Bioconsole 550, Medtronic)
2. White cell filter (LeukoGuard RS, Pall Medical)
3. 95% O2 & 5% CO2 at 0.5 L per min
4. Soft Silastic catheters (Pennine Healthcare)
5. Blood gas analysis (Rapidlab 248 blood gas analyzer)

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## Patel et al. 2014

**Porcine kidney MP solution** [12]

1. Organ perfusion system (Medtronic)

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## Kalenski et al. 2016

**Porcine kidney Blood** [10]

1. Pulsatile roller pump (ISMATEC MPC standard, IDEX Health & Science GmbH)
2. Gas flow control
3. Oxygenator (Hilite 2400 LT, Medos)
4. Temperature control
5. Arterial sample port
6. Bubble trap
7. Pressure sensor (MLT844, AD Instruments GmbH)
8. Flow sensor ((ME2PXL1072, TS410 flow meter module, Transonic Systems Inc.)
9. Urine sample port
10. Venous sample port
11. Data acquisition system (PowerLab 8/30, AD Instruments GmbH)

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## Kaths et al. 2017

**Porcine kidney MP solution** [23]

1. S3 heart-lung machine
2. Neonatal cardiopulmonary bypass equipment
3. Data Management System (DMS, LivaNova PLC)

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# D Criteria

To find the criteria for a kidney preservation system the choice was made to do a Function Analysis of the kidney in vivo. The focus of the Function Analysis were the required physical conditions for a kidney in terms of criteria. Furthermore, by using a Process Tree the required steps in handling the kidney and the system were collected.

The choice was made to include the criteria gathered from the previous two techniques in the list created with the help from Pugh's Checklist. Pugh's Checklist helps organize the different criteria and wishes for your design into 22 different categories (e.g. Performance, Maintenance, Safety).

## Performance

1. Measure physiological condition
   - Pressure
   - Temperature
   - pH
   - pO2
   - pCO2
   - sO2
   - Na concentration
   - K concentration
2. Save measured data in a safe digital environment
3. Produce graphs and visualizations of the collected data
4. Keep temperature controlled at 39 C (for porcine models)
5. Control blood pressure at 75 mm Hg
6. Provide nutrients and oxygen
   - Glucose
   - Sodium bicarbonate
7. Room for 1 porcine kidney per use
8. Possibility to use blood as a perfusion fluid

## Environment

9. The setup should stay stable
   - Bumping against the table/platform should not negatively influence the setup
   - Each individual instrument should remain rigid in place
10. Small shifts in pressure outside the system should be overcome
11. Shifts in temperature outside the system should be overcome
12. Humidity must be kept in mind
13. Radiation heating should be prevented
14. Toxicity should be prevented
    - Overdose in blood
    - In gas/air

### Life in Service

15. Tubing and fluid are usable only once
16. At least 5 days per use (120 hours)
17. Other parts should maintain useful for over 20 uses (2400 hours)

### Maintenance

18. Maintenance should be done after each use
19. Check every part before use

    Thorough cleaning per use is vital!

### Target production cost

20. Comparable to other similar equipment

### Transportation

21. Fluid transporter is needed
22. Organ transporter is needed
23. Instruments must be transportable per piece in a clean and safe way
24. Setup scheme is needed to copy setup in new settings

### Packaging

N/A

### Quantity

25. Designed for a single setup

### Manufacturing Facilities

26. Design must not force new manufacturing techniques
27. All parts should be purchasable or build-able through prototyping means

### Size and Weight

28. Size is constrained by labspace
29. Weight is constrained by labspace

### Aesthetic, Appearance & Finish

30. Look and feel professional
31. Cleanable surface
32. Use-cues for instant adjustment

    Also when using a digital interface

33. Interface
    - Clear visuals
    - Simple warnings
    - Easy and logical to operate by target group based on their experience with medical interfaces

## Materials

34. Medical grade materials
35. Cleanable

## Product Life Span

36. One time use

## Standards

37. EMC standards
38. Lab standards

## Ergonomics

39. Operate from a chair
40. Build on standard height ( 72 cm) for optimal height in placement
41. Interface should be user friendly
    - Use-cues
    - Clear labels
    - All “buttons” within range of normal use

## Quality & Reliability

42. Same initial values should generate same outcome
43. Failure during use is not acceptable
    - Should be detected during check up
44. Repair and maintenance is optional
    - Never during use!
45. Extreme failure examples
    - Unwanted and unpredicted flow rate changes
    - Unwanted and unpredicted pressure changes
    - Unwanted and unpredicted temperature changes
    - Unwanted and unpredicted nutrients and oxygen changes
    - Collapsing parts
    - Breaking piece
    - Leakage
    - Organ injury
    - Interface outage
    - Warning negligence caused by the machine

### Storage

46. Initial storage material should be saved to increase the possibility of re-using the instruments

### Safety

47. Avoid sharp edges
48. Avoid heavy parts
49. Avoid hazardous fluids/materials
50. Safety clothing to avoid decontamination (both for the system as for the user)
    Gloves
    Lab coat

### Social and Political Implications

51. Could help people understand the complexity

### Product liability

52. During the period of his employment, all responsibility lies on Max Brouwer
    This employment is the responsibility of the TU Delft

### Installation & Operation

53. Primary installation has no real time constraints
    Secondary installation should be below 5 hours
54. Operation time is constrained
    Initial learning should be less than 45 min
    Initial use (after placing the organ and attaching all parts) should be less than 5 min
    Secondary use should be less than 1 min

### Re-use, Recycling, Disposal

55. The parts are recycled for next uses
56. Possible disposal of tubing and tubing parts
57. Disposal of fluid and organ transporter parts (e.g. bag)

# E Wishes

## Performance

1. Measure values
2. Indicate deterioration of the organ through data collection
3. Enable intervention without
4. Room for 2 or more porcine kidneys per use
5. Possibility to use another perfusion fluid
6. Track and time the initial values and information available
   Time between obtaining organ up to Placing in system
   Temp and other initial values of organ and system

## Life in Service

7. At least 10 days per use (240 hours)
8. Other parts should maintain useful for over 50 uses (12.000 hours)

## Maintenance

9. A cleaning set to quickly clean all instruments used after a use

## Transportation

10. Possibility to transport all parts simultaneously as a show case model

## Packaging

11. A combined package to transport all instrument simultaneously

## Quantity

12. The option of reproducibility needs to be explored

## Size and Weight

13. Size can be constrained by combined size for combined packaging
    Combined size should be similar to the size of a roller suitcase
14. Weight can be constrained by combined weight for combined packaging
    Combined weight should be below 25 kg

## Social and Political Implications

15. Reaching out to Donorweek or other organization to increase publicity

## Installation & Operation

16. Primary installation time constraints

    Secondary installation should be below 2 hours

17. Operation time constraints

    Initial learning should be less than 15 min

    Initial use (after placing the organ and attaching all parts) should be less than 1 min

    Secondary use should be less than 10 sec

## Re-use, Recycling, Disposal

18. Re-use components for other research