

# **A Mock Circulatory System Incorporating a Compliant 3D-printed Anatomical Model to Investigate Pulmonary Haemodynamics**

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Conception and design of the work: PGMK, GB, ADH, SS, RT; experimental setup, data acquisition and analysis: PGMK, GB, LX; interpretation of the data: PGMK, GB, ADH, KHP, RT; drafting the manuscript: PGMK, GB, RT; all authors critically revised the manuscript, read and approved the final manuscript.

## Abstract

A realistic mock circulatory system (MCS) could be a valuable in-vitro testbed to study human circulatory haemodynamics. The objective of this study was to design a MCS replicating the pulmonary arterial circulation, incorporating an anatomically representative arterial model suitable for testing clinically relevant scenarios. A second objective of the study was to ensure the system's compatibility with magnetic resonance imaging (MRI) for additional measurements.

A latex pulmonary arterial model with two generations of bifurcations was manufactured starting from a 3D-printed mould reconstructed from patient data. The model was incorporated into a MCS for in-vitro hydrodynamic measurements. The setup was tested under physiological pulsatile flow conditions and results were evaluated using wave intensity analysis (WIA) to investigate waves travelling in the arterial system. Increased pulmonary vascular resistance (IPVR) was simulated as an example of one pathological scenario.

Flow split between right and left pulmonary artery was found to be realistic (54% and 46% respectively). No substantial difference in pressure waveform was observed throughout the various generations of bifurcations. Based on WIA, three main waves were identified in the main pulmonary artery (MPA), i.e. forward compression wave (FCW), backward compression wave (BCW), and forward expansion wave (FEW). For IPVR, a rise in mean pressure was recorded in the MPA, within the clinical range of pulmonary arterial hypertension. The feasibility of using the MCS in the MRI scanner was demonstrated with the MCS running 2 hours consecutively while acquiring preliminary MRI data.

This study shows the development and verification of a pulmonary MCS, including an anatomically correct, compliant latex phantom. The setup can be useful to explore a wide range of haemodynamic questions, including the development of patient- and pathology-specific

models, considering the ease and low cost of producing rapid prototyping moulds, and the versatility of the setup for invasive and non-invasive (i.e. MRI) measurements.

## 1. Introduction

Mock circulatory systems (MCS) are widely used to gather hydrodynamic data in vitro. They allow investigation of the cardiovascular system in both healthy and pathological scenarios, with the possibility of testing devices, e.g. the intra-aortic balloon pump (1), centrifugal and axial pumps (2), stents (3), and heart valves (4). The pulmonary circulation in these MCS is often lumped and modelled with capillary tubes for resistance and air chambers for compliance, acting as a 2- or 3-element Windkessel (2,5,6).

Rigid or flexible anatomical phantoms can be incorporated in MCS for more realistic simulations. Different materials are available for manufacturing rigid models (4,7), typically for the purpose of carrying out visualisation studies, e.g. particle image velocimetry (PIV) (8). However, rigid models do not replicate the compliant properties of the vasculature. Flexible elastomer arterial models with varying wall thickness have been used for investigating haemodynamics of the aortic circulation (9,10), but a realistic compliant model of the pulmonary arteries has not been presented. In this study, we describe the manufacturing of a compliant pulmonary arterial model based on patient anatomy created with rapid prototyping. This can be used within a MCS for in vitro testing of the haemodynamics associated with various (patho)physiologies and cardiovascular devices. Examples of pathologies of interest in this context are pulmonary arterial hypertension (PAH) (11), unilateral stenosis in the pulmonary artery (12), unusual flow split following repair of transposition of the great arteries (TGA) (13), and Eisenmenger's syndrome (14). In order to demonstrate the feasibility and realistic nature of the model, time-dependent flow velocity and pressure were measured under pulsatile conditions and verified, as the main objective of the study. Data were processed using wave intensity analysis (WIA), in order to gather additional insight into system haemodynamics and demonstrate the suitability of the in vitro data for this analytical approach. WIA indeed provides a convenient, time domain wave-

to-wave alternative to Fourier or impedance analysis (15), and it has been widely utilised to study wave propagation in animals and humans (16-20). As a secondary aim of the study, the system was tested for compatibility within the magnetic resonance imaging (MRI) setting, to demonstrate the versatility of the MCS and its suitability for imaging studies.

## 2. Materials and Methods

### 2.1 Pulmonary arterial model

An anatomically correct latex pulmonary arterial model was fabricated for in vitro studies of the adult pulmonary circulation. The model comprises one inlet and seven outlets. The inlet is defined as the cross-section just above the pulmonary valve on the main pulmonary artery (MPA). The outlets are defined on the downstream branches, of which five are on the right pulmonary artery (RPA) side and two are on the left pulmonary artery (LPA) side.

Figure 1 depicts the six steps to obtain the latex pulmonary arterial model representing the patient anatomy; these steps are:

1. CT images of a 72-year-old male with no known pulmonary disease were segmented for the pulmonary vessel tree and the lumen surface model was reconstructed using commercial image-processing software (Mimics, Materialise NV, Leuven, Belgium). The model was exported in IGES format and imported in computer aided design software Autodesk Fusion 360 (Autodesk, Inc., San Rafael, CA, USA) for further elaboration as in the following 2 steps.
2. Arteries smaller than 5 mm were removed and surfaces irregularities were patched and smoothed.
3. The inlet and the seven outlets were extruded (30 mm length) and flanges (20 mm diameter, 3 mm thickness) were built in order to facilitate connections to the MCS. Outlets 1 and 2 are on the RPA side and 3—7 on the LPA side. This modified 3D model was sectioned to obtain a modular structure of 11 parts such that they can be disassembled and removed from the compliant model without damaging it.

4. The parts were 3D-printed in polylactic acid (PLA) using an Ultimaker 2 (Ultimaker, Geldermalsen, The Netherlands) and were used as a mould for latex brushing.
5. 10 layers of liquid latex (Trylon Ltd, Hingham Ferrers, UK) produced a waterproof and durable latex model. After curing the latex overnight, the mould parts were removed and thus a hollow latex pulmonary arterial model was obtained. The Young's modulus was verified with a uniaxial tensile test (Zwick Roell, Ulm, Germany) and the wall thickness with a calliper.
6. An acrylic box was designed to contain the model, which was anchored to the box using the flanges. The placement of the model in the acrylic box was completed with custom made 3D-printed PLA connectors to provide leak-free snug connections between the latex model and external tubing.

## 2.2 Pump

A Harvard Apparatus Pulsatile Blood Pump Series 1400 (Harvard Apparatus UK, Cambridge, UK) was connected to the inlet of the model, and provided pulsatile flow with adjustable stroke volume (SV), heart rate (HR), and diastolic time fraction (DTF). For all experiments, the following settings were used: SV = 50 ml, HR = 60 bpm, DTF = 50%. The 'trigger signal' extracted from the pump, i.e. square wave of input voltage indicating the pump action, was recorded and monitored, and it helped visualised the 50/50 systole/diastole ratio.

## 2.3 Downstream flow circuit

Resistance was implemented using needle-pinch valves (Sigma-Aldrich Company Ltd, Gillingham, Dorset, UK) at common outlets 1-2, 3-4, and 5-7. The valves are metered such that the parameters are easily reproducible.

Compliance was implemented by the distensible latex model and additional proximal compliance was implemented using a custom-made acrylic air chamber. The diameter and

height of the chamber were 8.5 cm and 30 cm, and the level of water was set at 7 cm. Compliance (C) was calculated by dividing the air volume ( $V_{air}$ ) by the atmospheric ( $P_{atm}$ ) and mean pulmonary pressure (mPAP) (20,21). Given a mPAP of 15 mmHg, this resulted in (Equation 1):

$$C = \frac{V_{air}}{P_{atm} + mPAP} = \frac{1300 \text{ [ml]}}{760 + 15 \text{ [mmHg]}} = 1.68 \text{ ml/mmHg} \quad (1)$$

## 2.4 Assembly of the mock circulatory system

All the above components were connected as shown schematically in Figure 2. Flexible but relatively non-compliant Tygon tubing with an inner diameter of 9.5 mm and outer diameter of 13 mm was used for connections. The outlets of the pulmonary arterial model were connected to an 'atrial' reservoir providing head pressure of about 15 mmHg. The reservoir was connected back to the Harvard pump. Water at room temperature (22°C) was used as the flowing medium.

## 2.5 Data acquisition

A Transonic 9PXL perivascular ultrasound probe (Transonic Systems Inc., Ithaca, NY, USA) was used for flow measurements. The flow probe was calibrated ("timed collection" method) over a range of flows (0 – 6 l/min). The flow probe was connected to a Transonic TS410 tubing flow meter (Transonic Systems Inc., Ithaca, NY, USA). A high-fidelity fibre optic pressure wire (Opsens, Quebec, Quebec, Canada) was used for pressure measurements. The pressure transducer was calibrated ("column of water" method) over a range of static pressures (0 – 120 mmHg). The pressure wire was inserted through a 9F catheter sheath into the pulmonary model via one of the outlets. Its position in the pulmonary model was adjusted by the "pull back" method. The pressure wire was connected to a fibre optic sensor module (Opsens, Quebec, Quebec, Canada). Pressure and flow tracings and the trigger signal from the pump were recorded at 250 Hz with a data acquisition device (Biopac MP150, Biopac Systems Inc., Goleta, CA, USA). A laptop was



used for data acquisition and real-time display during the measurements (AcqKnowledge Software, Biopac Systems Inc., Goleta, CA, USA).

Pressure and flow were measured for two scenarios: healthy and pathological. The former investigated flows in the MCS set up as described above – “*healthy scenario*” – and the latter investigated flows with the same MCS setting but increased pulmonary vascular resistance – “*IPVR scenario*”. Pulmonary vascular resistance (PVR) was calculated as follows (Equation 2):

$$PVR = \frac{mPAP - mPWP}{CO} \quad (2)$$

where mean pulmonary wedge pressure (mPWP) equalled the reservoir pressure head, and cardiac output (CO) equalled SV multiplied by HR.

For the IPVR scenario, the needle-pinch valves at the outlet tubing were tightened to increase downstream resistance. All other settings were identical to the healthy scenario. For comparison purposes, measurements were performed on the same day and under the same conditions for both scenarios.

Flow was measured at the inlet, each outlet, and the common outlets, to investigate flow distribution in the model. Pressure was measured in each generation of vessels to observe pressure at different locations in the pulmonary model, inserting the catheter through the RPA and LPA. Pressure and flow were measured simultaneously in order to perform WIA.

## 2.6 Data analysis

Pressure and flow (i.e. CO) signals during systole and diastole were verified to be in a stable periodic state and within the physiological range. Data were analysed using Matlab R2015a (MathWorks Inc., Natick, MA, US). Pressure and flow peak and mean values were recorded and averaged over 20 cycles. Flow splits are reported as % of the CO.

WIA (17) representing an important tool for the investigation of travelling waves, was conducted based on the method described by Parker (23), using pressure measured in the MPA and flow measured in the tubing between compliance chamber and the inlet of the pulmonary arterial model. Velocity in the MPA was calculated as input flow divided by cross-sectional area of the tube where flow was measured, see Figure 2. Pressure ( $P$ ) and velocity ( $U$ ) data were shifted with respect to each other until a linear slope is observed during early systole in the P-U loop (24). The signals were smoothed using a Savitzky-Golay filter (25) with a second order polynomial and window width of 51 data points. Ensemble averages of pressure and flow from 20 waves using the timing signal from the Harvard pump were then calculated. The P-U loop method was used for quantification of wave speed ( $c$ ), as knowledge of  $c$  is required to separate net wave intensity into forward and backward components. It is important to note that the magnitude of wave intensity depends on the sampling rate (23,26).

Calculation of net wave intensity from simultaneously acquired invasive P and U signals provides a measure of energy flux per unit area, as defined (Equation 3):

$$dI = dPdU \quad (3)$$

where  $dI$  the net wave intensity difference in one sampling time,  $dP$  is the pressure difference in one sampling time,  $dU$  is the velocity difference in one sampling time. Considering the relationship between P and U based on the water hammer equation (23), forward and backward components of pressure, velocity, and wave intensity changes are defined (Equation 4 and 5):

$$dP_{\pm} = 1/2(dP \pm \rho cdU), \quad dU_{\pm} = 1/2(dU \pm dP/\rho c) \quad (4)$$

$$dI_{\pm} = dP_{\pm}dU_{\pm} \quad (5)$$

where  $\rho$  is the density of the flowing medium (i.e. water). The energy of a wave of interest was calculated as the integral of  $dI$ , i.e. the area under the wave ( $A$ ).

## 2.7 Feasibility of MRI measurements

A 1.5T clinical MR scanner (Avanto, Siemens Healthcare, Erlangen, Germany) was used to assess the feasibility of using the MCS in the MRI setting for non-invasive measurements. The experimental setup was not modified, simultaneously measuring flow and pressure as described above, but all ferromagnetic equipment (i.e. the pump and all data acquisition devices) was placed in the MRI control room, while the compliance chamber, pulmonary arterial model, and reservoir were located on the bed of the MRI scanner. The pressure wire and flow probe are both MR compatible.

The pulmonary artery model with the surrounding acrylic case was submerged in a larger water tank to provide sufficient MR signal. Furthermore, contrast was improved by the addition of 10 ml Dotarem gadoteric acid intravenous contrast agent (Guerbet, Lanester, Brittany, France) at a concentration of 279.32 mg/ml which improves contrast by reducing spin lattice relaxation ( $T_1$ ). A conventional multi-slice scout sequence was employed to test the use of the MCS for non-invasive measurements with the following settings: echo time (TE) = 1.3 ms, repetition time (TR) = 283.3 ms, flip angle =  $77^\circ$ , field of view =  $256 \times 256$  pixels, and pixel spacing =  $2.1 \times 2.1$  mm.

## 3. Results

### 3.1 Pulmonary arterial model

A Young's modulus of 1.18 MPa was found for 10 layers of latex. The wall thickness resulting from 10 layers, needed for durability, was  $1.7 \pm 0.3$  mm.

### 3.2 Invasive measurements

Table 1 shows the flow distribution in the pulmonary arterial model. Flow distribution between RPA and LPA in the model was 54% and 46% respectively. Figure 3 displays typical pressure, flow waveforms in the MPA, together with the trigger signal (ECG equivalent) of the Harvard pump.

#### 3.2.1 Healthy scenario

Signals in Figure 3 are measured in the 'healthy scenario'. The following values represent mean and standard deviation of 10 beats, an example of the individual traces is shown in Figure 3. Mean pressure was  $15.2 \pm 0.1$  mmHg, with peak systolic pressure of  $22.4 \pm 0.2$  mmHg and minimum diastolic pressure of  $8.2 \pm 0.2$  mmHg. Mean flow rate was  $2.6 \pm 0.02$  l/min with peak systolic flow rate of  $3.3 \pm 0.04$  l/min and diastolic flow rate of  $1.9 \pm 0.03$  l/min. The repeatability of the signals was investigated by computing average pressure and flow and the resulting ensemble averages of 20 beats are shown in Figure 4. There was no substantial difference with ensemble averages of 10 beats, hence 10 beats were considered sufficient for further data analysis. WIA was carried out using the mean values and thus represents time-averaged wave intensity, as opposed to beat-to-beat wave intensity.

Figure 5 shows a typical P-U loop which was used to determine wave speed. Wave speed in the MPA was  $c = 10.7 \pm 0.1$  m/s. Velocity data was generally shifted forward about 10 data points, which corresponds to 40 ms for a sampling rate of 250 Hz.

Figure 6 shows time-averaged net wave intensity with forward and backward components. Net wave intensity shows three distinct waves: a forward compression wave (FCW), a backward compression wave (BCW), and a forward ejection wave (FEW). Table 2 lists peak time  $t_{peak}$ , peak wave intensity  $dI_{peak}$ , and wave area  $A$  of the three identified waves, along with values for time-average net wave intensity for the IPVR scenario.

### 3.2.2 IPVR scenario

Table 3 shows the mean and peak pressure with standard deviation based on 10 beats for the healthy and IPVR scenarios. Under these conditions, with a reservoir pressure head of 11.8 mmHg (16 cm H<sub>2</sub>O), PVR was 1.13 mmHg·min/l for the healthy scenario and 9.11 mmHg·min/l for the IPVR scenario. The pressure was significantly higher for IPVR than the healthy scenario (mPAP:  $33.8 \pm 0.2$  mmHg vs.  $14.7 \pm 0.1$  mmHg,  $p < 0.001$ ). The MCS was successfully tested with a mean pulmonary artery pressure up to 90 mmHg and with various flow rates and stroke volumes, indicating its suitability for exploring clinically relevant questions related to PAH.

### 3.3 Feasibility of MRI measurements

Figure 7 shows a single slice from an MR image of the pulmonary model and acrylic box submerged in a water tank. The MPA, RPA, and LPA are clearly visible, demonstrating the feasibility of acquiring MRI data with this model.

## 4. Discussion

This study aimed to replicate the pulmonary artery circulation to test clinically relevant scenarios and to study its compatibility with MRI. An elastic, anatomically representative pulmonary arterial model based on a patient image dataset was tested in a pulmonary MCS. The advantages of the pulmonary arterial model are demonstrated: the model was successfully manufactured with a 3D-printed mould and was suitable for withstanding a wide range of pulmonary pressures; the stability of the system was demonstrated by the low standard deviations in the pressure and flow measurements; and the feasibility of MRI measurements was shown by acquiring good quality MRI images. These properties allow the setup to potentially address a wide range of haemodynamic questions on the pulmonary side, including the investigation of pathologies (e.g. PAH, unilateral stenosis in the pulmonary artery, unusual flow split in TGA, and Eisenmenger's syndrome) and intervention strategies (e.g. physically deploying stents inside the phantom). Additionally, WIA can be carried out in a controllable in vitro environment.

Highly complex and physically robust patient-specific models can be produced with an anatomically shaped mould and commercially available latex rubber. Furthermore, the modular setup of the mould allows for easy modifications of the latex model. For example, a stenotic latex model can be obtained simply by replacing one of the 11 parts by a 3D-printed stenotic part and following the same manufacturing steps as before. This method is not limited to the pulmonary arteries, compliant aortic models of health and disease can be obtained following the same principles.

Latex has been previously used for its ease of manufacturing and compliant behaviour. A limitation of latex, however, is that it oxidises and the properties may change over a longer period of time. This might be reduced by adding additional preservatives and antioxidants to the liquid solution before brushing. Other materials might be used, for instance silicone. However,

its high stiffness would pose a major issue for removal of the mould after curing and the influence of a stiff material on the wave speed has to be considered. Even with the latex model wave speed was high, due to the amount of layers required for durability. Fewer layers would probably achieve a more physiological wave speed, however, preference was given to producing a durable model. Among other materials and production techniques, novel rapid prototyping techniques for direct printing of silicone and latex may be employed to eliminate the need of a mould and thereby increase the complexity of the elastomer model. The wall thickness resulting from 10 layers, needed for durability, was  $1.7 \pm 0.3$  mm, substantially higher than values found in vivo (27). The variability in thickness can be improved by a dip-coating approach with the use of an automated robotic arm (28).

The MCS presented here focuses on hydrodynamic measurements in the pulmonary arterial model. Hence, water alone was used as the flowing medium, which is in line with work on other MCS (1,29). This has been done because no major viscous effects were expected in the current setting and because the study was focusing on the feasibility of the setup and pulmonary measurements. A commonly used blood analogue is a solution of water and glycerine with a volume percentage of 33.5% glycerine (2,5,29), which could be easily employed in this setting.

The RPA – LPA flow distribution, governed by the downstream resistances, was similar to the normal in vivo flow distribution of 55% – 45% (30) and the RPA/LPA ratio of 1.18 corresponds to a ratio of  $1.1 \pm 0.2$  for the adult human pulmonary circulation at rest (31). The pressure for the IPVR scenario ( $33.8 \pm 0.2$  mmHg) was within the range of PAH and was significantly higher than the pressure for the healthy scenario.

The elastomer pulmonary model was utilised for WIA in a controllable, in vitro environment. However, the invasive nature of WIA in many arteries limits its use in vivo (26). The forward wave pattern contains an early systolic FCW and a late diastolic FEW, which is in line with

previously found patterns in human pulmonary artery. The backward wave pattern contains a late systolic BCW, whereas in vivo studies report both backward expansion waves (BEW) and BCW (16,32,33). It is hypothesised that a BEW is due to the considerable branching of the pulmonary artery and the result of an increase in total cross-sectional area (16,33), and a decrease in impedance, which is not included in our pulmonary model. Hollander *et al.* (21) observed a BEW in experiments in control dogs in vivo and a BCW under hypoxic conditions. They postulated that a closed-end reflection site may be present at the third or fourth generation of branches in the hypoxic state. Furthermore, Quail *et al.* (32) found significant differences between PAH patients and controls, where a BCW was present for PAH patients but absent for controls, and vice-versa for a BEW. Since the backward waves in vivo result from reflections from the distal circulation and in our model from reflections from the distal resistances, connecting tubes, and reservoir downstream of the arterial model, further work on the distal parts of our MCS are needed to accurately mimic in vivo behaviour.

Within the scope of the current work of designing and testing a pulmonary model, needle-pinch valves provided a convenient and reproducible mean of controlling resistance and have proven to have sufficient control over increasing pulmonary artery pressure, by approximately doubling PVR for 79% reduction of the minor axis length. However, a needle-pinch valve implements a non-linear resistor whose resistance increases progressively with reduction of minor axis length. A bundle of capillary tubes would better mimic PVR anatomically, i.e. similarity with the capillary bed, and a better resistance control could be achieved by varying its length since that is linearly related to the resistance (1).

#### **4.1 Limitations and future work**

Shifting of data, typically about 40 ms, based on the linear part of the P-U loop during systole was required mainly because of the different processing times for the pressure and flow



transducers. However, a small portion of the shift is also due to the wave travel time between the sites of the two transducers. The distance between the flow transducer outside the inlet of the arterial model and the pressure transducer in the MPA was typically 4 cm. At the measured wave speed this corresponds to a time delay of 4 ms. A better way of correction the time lag between the fibre optic wire and the ultrasound flow probe is automatic fitting using the highest correlation factor (33). This was not implemented in the current setup, as the current work focused on the feasibility of employing a latex model in a MCS. Therefore, due to the manual shifting, the P-U loop and wave speed in this work have to be considered with care. Another improvement could be replacing the fibre optic pressure wire by a combined Doppler flow and pressure wire for simultaneous pressure and velocity measurements in vivo, thereby reducing the need for shifting.

As a result of the anatomically shaped model with multiple outlets in various spatial orientations, it was difficult to incorporate large compliance chambers directly at the outlets of the model, thereby implementing the needed additional distal compliance without affecting the inflow waveform. A lumped compliance at the common outlet was tested with no effect on the pressure and flow waveforms at the inlet or elsewhere in the model. The compliance chamber between the pump and the inlet of the model successfully implemented proximal compliance and modulated the pressure in the desired range, however giving rise to diastolic flow. A proposed solution to resolve this limitation is to include 50ml syringes as compliance chambers at each of the seven outlets of the model. This could provide a sufficient amount of additional distal compliance, and will be explored in a future modification of the MCS. It must be noted that the versatility of the MCS should not be compromised in making such modifications, and that the dimensions of the MRI scanner should be taken into account, if using the system for non-invasive/visualisation measurements (i.e. 60 cm bore size in our setting).

In future experiments, additional models should be developed for clinically relevant pathologies. For example, a stenotic scenario can be simulated by introducing a narrowing of a vessel on the mould and thus on the latex model. Similarly, a mould can be made to include dilated vessels. These models should give distinct wave patterns that subsequently could be analysed using WIA. In addition, paediatric models could be developed with the challenge of retaining high complexity with small geometry, and consequently implement paediatric values.

As an alternative to invasive measurements, the MCS may also be used for non-invasive measurements. Firstly, a non-invasive WIA technique has recently been developed based on area or diameter rather than pressure (34). Studies with high temporal resolution phase-contrast magnetic resonance (PCMR) into pulmonary hypertension were able to find significant differences in wave intensity characteristics between hypertensive patients and controls (35).

Secondly, these specialised and highly complex models can be particularly useful for the comparison and verification of computational fluid dynamics (CFD) studies with the use of 4D cardiac magnetic resonance (CMR) flow measurements (36,37). The main advantages of this non-invasive technique is its ability to obtain time-dependent, 3D distribution of velocity in opaque phantoms. Therefore, MRI measurements of 4D flow are of particular interest and will be investigated in future experiments. Optimisation of the imaging resolution will be necessary to accurately capture wall thickness and fluid flows.

## Conclusion

A pulmonary arterial model was successfully produced with the use of a 3D-printed mould, based on a patient image dataset. Measurements of flow and pressure in two scenarios demonstrated the versatility of the MCS to investigate a wide range of haemodynamic questions. Future work will focus on further optimising the MCS and pulmonary model, and employing the model for 4D flow MRI measurements.

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## **Disclosure**

The authors declare no conflict of interest.

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## Tables

Location	Flow (l/min)	Percentage
Inlet	2.56 ± 0.01	100
LPA		(45.8)
Outlet 1	0.55 ± 0.01	22.6
Outlet 2	0.57 ± 0.002	23.2
RPA		(54.2)
Outlet 3	0.24 ± 0.004	9.7
Outlet 4	0.17 ± 0.001	7.1
Outlet 5	0.34 ± 0.003	13.9
Outlet 6	0.30 ± 0.002	12.2
Outlet 7	0.27 ± 0.01	11.2

Table 1: Flow values and percentage of total flow for the inlet and outlets. The inlet is defined as the cross-section just above the pulmonary valve on the main pulmonary artery (MPA) and the outlets are defined on the second or third generation of vessels on the right pulmonary artery (RPA) and left pulmonary artery (LPA) side. Data are mean ± SD.

	$t_{\text{peak}}$ (s)		$dI_{\text{peak}}$ (10 W/m <sup>2</sup> )		A (10 <sup>-3</sup> J/m <sup>2</sup> )	
	Healthy	IPVR	Healthy	IPVR	Healthy	IPVR
FCW	0.27	0.25	0.027	0.036	3.6	4.4
BCW	0.43	0.41	-0.008	-0.010	0.7	1.0
FEW	0.60	0.60	0.008	0.007	1.2	1.2

Table 2: Time of peak intensity ( $t_{\text{peak}}$ ), magnitude of peak intensity ( $dI_{\text{peak}}$ ), and area (A) of the forward compression wave (FCW), backward compression wave (BCW), and forward expansion wave (FEW). The values for the healthy scenario correspond to Figure 6. Health and IPVR are time-averaged net wave intensities in the main pulmonary artery (MPA).

	P (mmHg)	
	Mean	Peak
Healthy scenario	14.65 ± 0.14	20.88 ± 0.21
IPVR scenario	33.82 ± 0.15	39.45 ± 0.16
Difference	19.17 ± 0.16	18.57 ± 0.29

Table 3: Mean and peak pulmonary arterial pressure obtained in the MPA for the healthy scenario, the increased PVR scenario, and the difference between the two. Mean values ± SD are based on the average of 10 beats.

## Figures

Figure 1. Six steps representing the manufacturing model of a hollow pulmonary latex arterial model based on patient data: (1) CAD model from a CT scan of a 72 year-old male patient with no known pulmonary disease, (2) intermediate CAD model with simplified geometry, (3) finalised CAD model including extrudes and flanges for easy connections, (4) 3D-printed model consisting of 11 parts to act as a mould for latex brushing, (5) hollow latex model obtained after latex brushing, curing, and removal of the mould, and (6) finalised pulmonary model in an acrylic box with blue custom 3D-printed connectors for an external circulatory system.

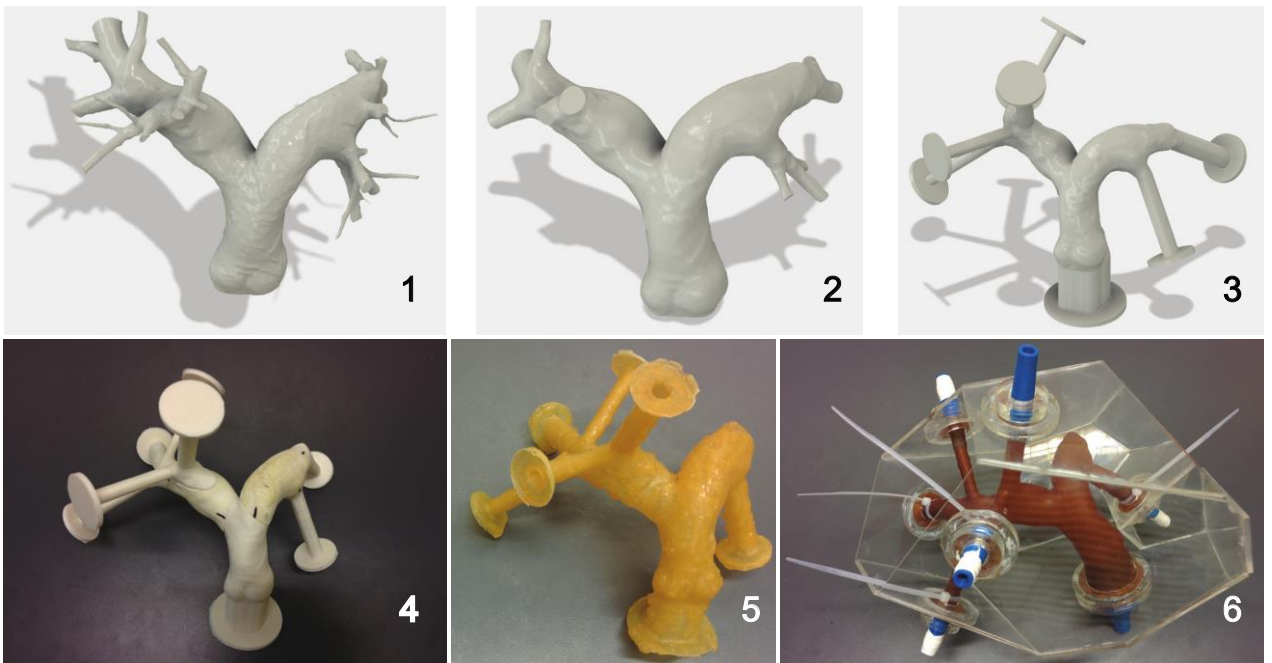


Figure 2. Schematic of the experimental setup including the reservoir, Harvard pump, compliance chamber, pulmonary arterial model including 7 outlets, flow meter, catheter, data acquisition devices, and computer.

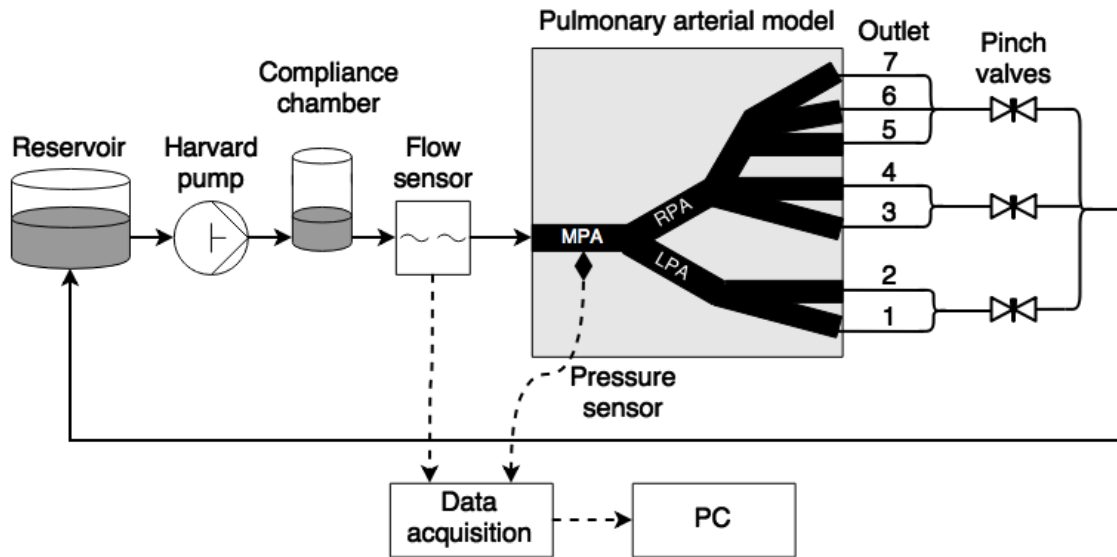


Figure 3. Example of typical pressure, flow, and trigger signals, as part of a longer acquisition. Pressure was measured in the MPA, flow at the inlet, and the trigger signal, i.e. square wave, that originated from the pump. For 10 consecutive beats, mean pressure was  $15.2 \pm 0.1$  mmHg with peak systolic pressure of  $22.4 \pm 0.2$  mmHg and minimum diastolic pressure of  $8.2 \pm 0.2$  mmHg, mean flow rate was  $2.6 \pm 0.02$  l/min with peak systolic flow rate of  $3.3 \pm 0.04$  l/min and diastolic flow rate of  $1.9 \pm 0.03$  l/min, and diastolic time fraction (DTF) is 50%.

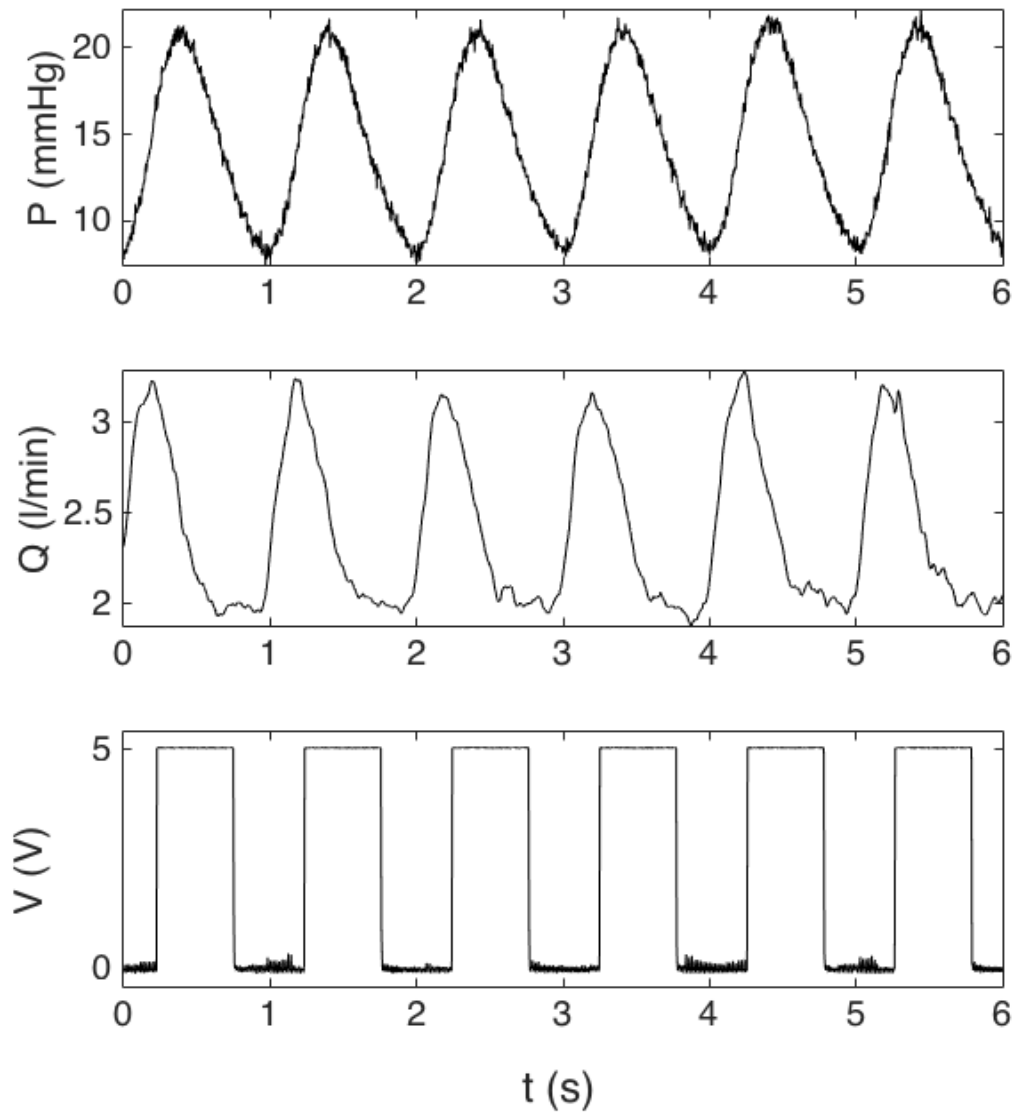


Figure 4. Ensemble averages for the aligned pressure (measured in the MPA) and velocity (measured at the inlet) for 20 beats. Each beat is shown by a coloured line and the solid black line and dotted black lines represent the ensemble average and 95% confidence intervals respectively.

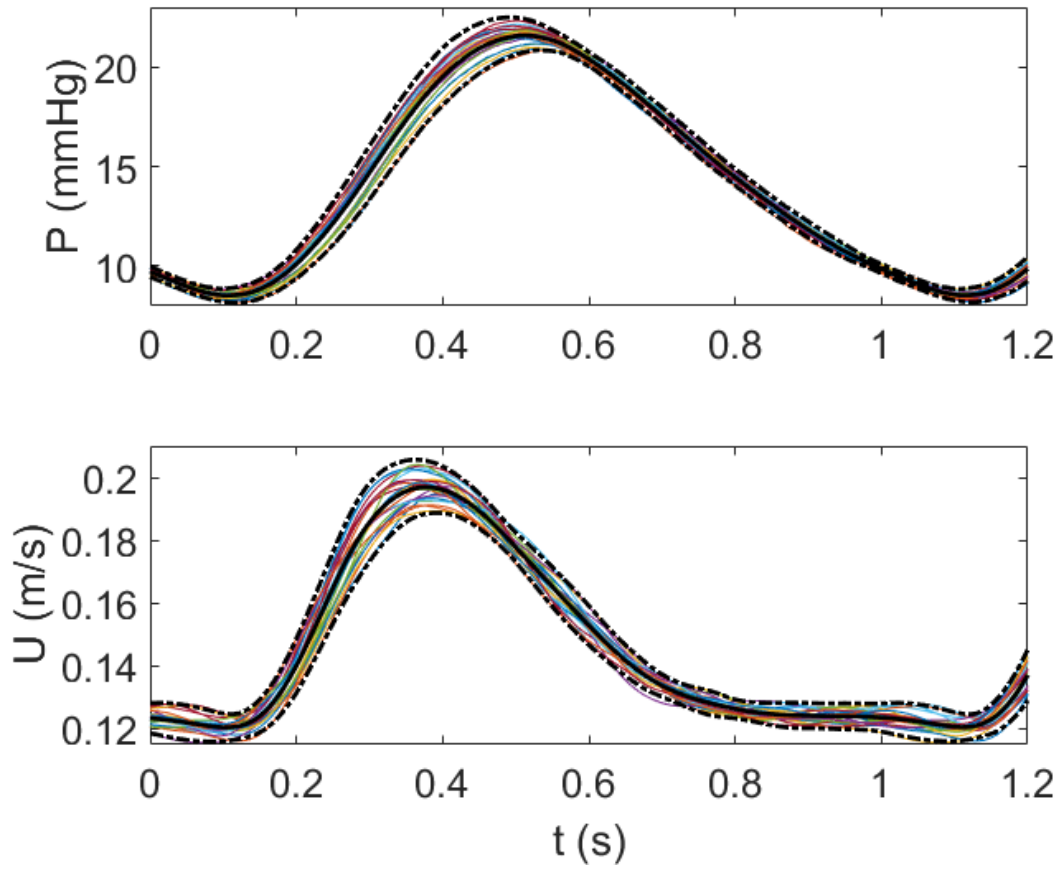


Figure 5. Pressure-velocity (P-U) loop of ensemble averaged flow velocity and pressure data. For wave intensity analysis, flow velocity data was shifted until a linear slope is observed in early systole as displayed here. Wave speed was calculated from the slope of the linear segment this graph on the basis of the water hammer equation and was  $10.7 \pm 0.1$  m/s, based on 10 measurements for this case.

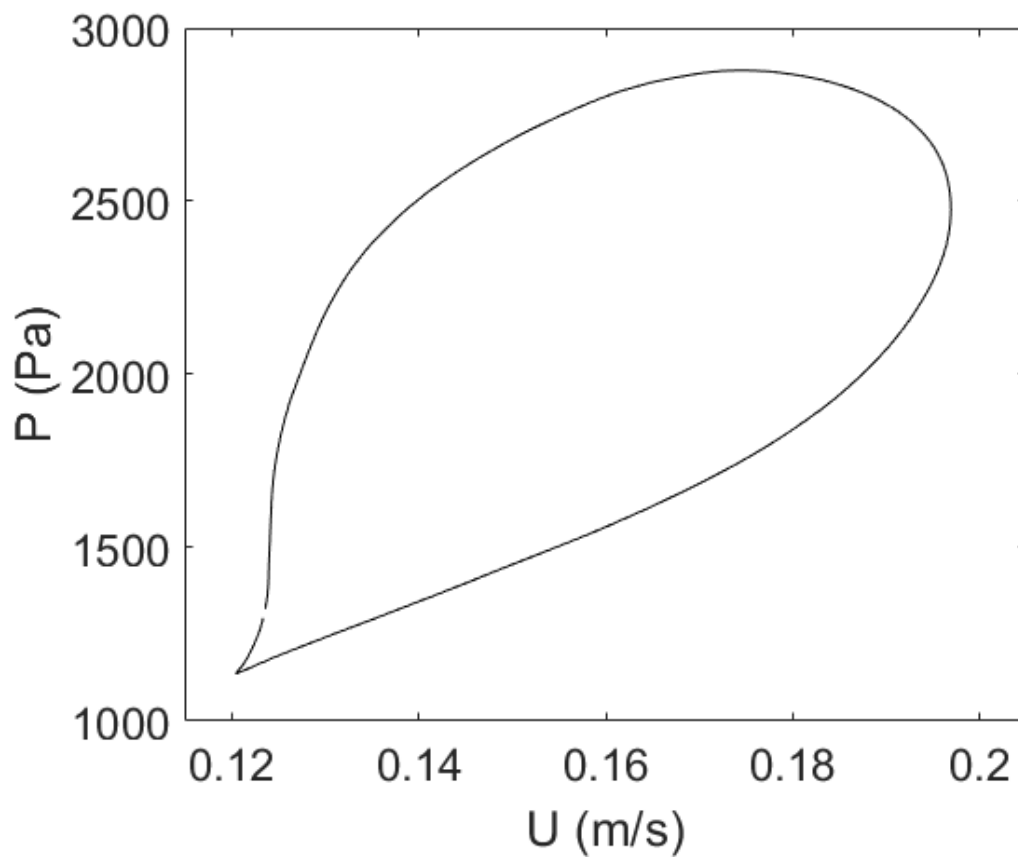


Figure 6. Example of wave intensity pattern obtained in the MCS, showing net ( $dl$ ), forward ( $dl_+$ ), and backward ( $dl_-$ ) wave intensity based on the ensemble averages for the healthy scenario. The wave intensity pattern contains three distinct waves: a forward compression wave (FCW), backward compression wave (BCW), and forward expansion wave (FEW).

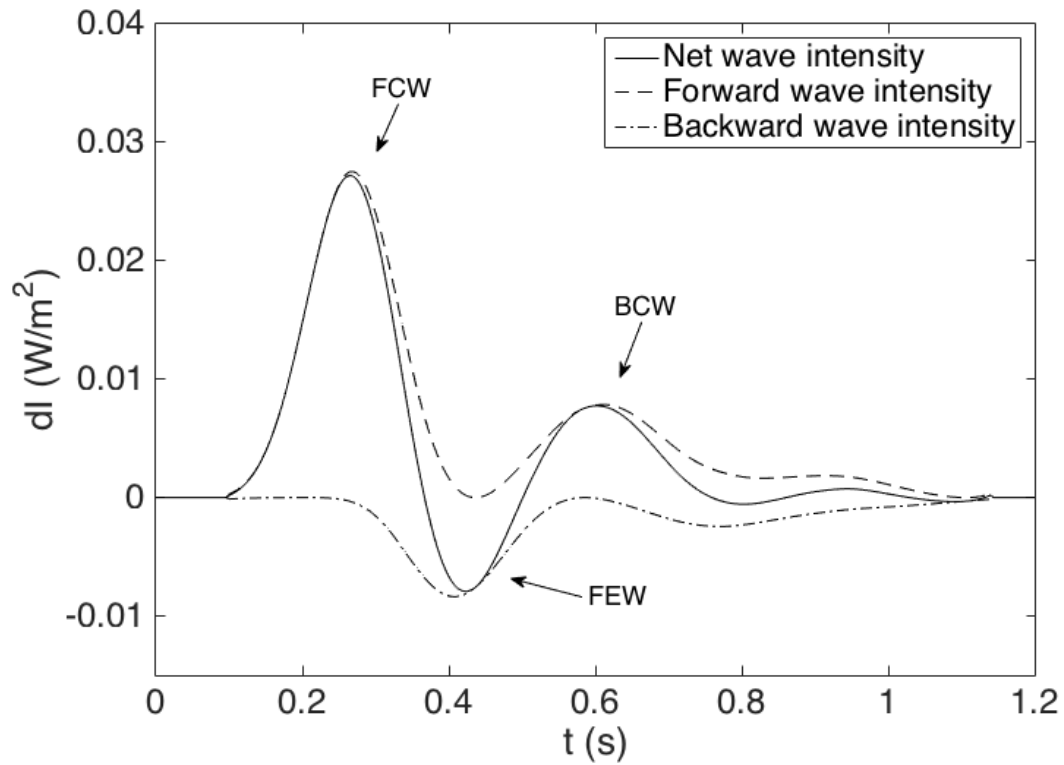




Figure 7. A single slice from an MR image of the pulmonary arterial model submerged in an acrylic tank of water. The image is obtained with a multi-slice scout sequence. The main pulmonary artery (MPA), right pulmonary artery (RPA), left pulmonary artery (LPA), and surrounding acrylic box are clearly visible. Scale is indicated.

