CHAPTER 3

Validation of an in-vitro model of the human systemic circulation for abdominal aortic aneurysm-studies

Submitted for publication

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Abstract

Objective: The aim of this study was to develop and to validate an in-vitro model of the human circulation. The in-vitro model had to mimic especially the pressure and flow waves as measured in the human abdominal aorta.

Methods: The model consisted of a pneumatic heart driver, an artificial heart, a ball valve, an air-chamber, a pressure cuff and a collecting system. Pressure curves were recorded and compared with pressure curves measured in the human aorta to validate the in-vitro model. Flow measurements were performed with a color-Duplex scan to validate the flow curve. Mean pressure and pulse pressure experiments were performed.

Results: The pressure and flow waves measured in the in-vitro model were similar to pressure and flow waves measured in the human aorta in vivo.

Conclusion: We developed an in-vitro model of the human systemic circulation. The model especially mimics blood flow and pressure characteristics of the human abdominal aorta. All different parameters of flow and pressure can be varied individually.
3.1 Introduction

An important complication of endovascular aneurysm repair (EVAR) is the incomplete seal of the aneurysm sac by the stent (endoleak) and the persistent pressurization of the sac without a detectable blood flow in the sac (endotension) [1, 2]. To study endoleaks and endotension, circulation models are preferable over animal experiments. Animal experiments are expensive, time-consuming and often an ethical dilemma exists.

An in-vitro model of the human circulation is appropriate to study endoleaks, endotension and other purposes in which hemodynamics play a role. In such a model adjustment of the cardiac output, the peripheral resistance and the compliance of the model should be possible.

Several studies are performed with in-vitro models of the human systemic circulation [3–7]. Validation of these models is required. However, validation of these models has never been published. It is quite important that a validated model will be used by different research groups. Investigators should be aware that it is appropriate to compare results obtained from different in-vitro models only if the fidelity of each system is known and preferably identical. The aim of this study was to design and validate an in-vitro model of the human systemic circulation that mimics the flow patterns in and pressure waves of a human aorta.

3.2 Methods

3.2.1 In-vitro model

Figure 3.1 depicts a schematic representation of the in-vitro model of the human systemic circulation. The in-vitro model included an artificial heart (A). The artificial heart consisted of two valves and one chamber of 70 ml. The chamber was divided into two parts by a flexible membrane. One part of the chamber was filled with starch solution to be transported; the other part was filled with pressurized air. The heart was driven by a pneumatic heart driver (LVAD-driver) (B). The heart frequency, the diastolic suction pressure, the systolic driving pressure and the proportion of time between systole and diastole of the artificial heart driver could be varied independently.

The arteries of the model were made of silicon tubing $\frac{1}{2} \times 3/32$ (12.7 × 2.38 mm) (Cobe cardiovascular, Sorin Biomedica U.K., Gloucester, England). A ball valve (C) was introduced to simulate the flow pattern of the human aorta. This valve helped to restrict a reverse flow during the diastole, because the valve closed during diastole like the aortic valve in vivo.

The “arteries” in the model were not compliant. Therefore, an air-chamber

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1 Obtained from emeritus Prof. W.J. Kolff, University of Utah, Salt Lake City, USA
Figure 3.1: Schematic representation of the in-vitro model of the human systemic circulation. The model consisted of an artificial heart with two valves (A), a LAVD-driver (B), a ball valve (C), an air-chamber (D) with a valve on top, a blood pressure cuff (E) for peripheral resistance, an open reservoir (F), a pressure measuring device (G), a flow transducer (H) and an aneurysm (I). The grey square indicates the part of the model that is identical to the in vivo situation and in which an aneurysm model can be incorporated.

(4 × 4 × 30cm) (D) was introduced to make the system more compliant, so continuous flow of blood through the in-vitro model was guaranteed. On top of the air-chamber a valve was installed. This valve was connected to a syringe to submit air to the air-chamber.

A blood pressure cuff (E) around a segment of rubber tubing was used to introduce peripheral resistance.

An open reservoir (F) was located distal to the blood pressure cuff. This reservoir had the same function as veins in a human body. The reservoir was the passageway for flow of blood into the heart. Other function was storing either small or large quantities of blood and making this blood available when the remainder of the circulation required it. The in-vitro model was filled with a starch solution with the same viscosity as human blood.

Pressure measurements were carried out by fluid filled pressure monitoring kits (G) (Pressure monitoring kit, Baxter, Uden, the Netherlands) as used in clinical practice in the operating room or in the intensive care unit.

An extracorporeal flow transducer (H) (Transflow 601 system; Skalar Instru-
ments, Delft, the Netherlands) was used for flow measurements.

### 3.2.2 Experiments

The adjustment of the in-vitro model during all experiments was: heart rate 70 beats/min, 339 ml air in the air-chamber, systolic driving pressure LAVD 165 mmHg, diastolic suction pressure LAVD 130 mmHg and blood pressure cuff 160 mmHg. During each experiment one parameter was changed. Hence the model was evaluated under various conditions (change of cardiac output and stroke volume, peripheral resistance and compliance of the circulation model).

Before carrying out some experiments to analyze the pressure and flow waves of the in-vitro circulation, compliance and peripheral resistance of the in-vitro model were calculated.

**Definition of the basic physical unit of compliance**

The air above the liquid level was removed. With the help of the syringe different quantified volumes of air were inflated into the air-chamber (range $0 - 350$ ml). By varying the level of starch solution in the air-chamber by submitting air to the chamber the compliance changed. Then the heart driver was switched on.

The compliance of the air-chamber was calculated by dividing the increase of volume in the air-chamber during heart contraction by the difference in systolic and diastolic pressure (pulse pressure). Ten measurements of the increase of volume in the air-chamber and pulse pressure were performed with thirteen different amounts of inflated air ($n = 130$).

**Definition of the basic physical unit of peripheral resistance**

The peripheral resistance was adjusted with a regular blood pressure cuff around a segment of the rubber tubing. The pressure in the cuff was read out on the measure gauge of the cuff. The unit of this measure gauge was mmHg. The peripheral resistance in $\text{dyne sec cm}^{-5}$ was calculated by dividing the decrease of pressure in the circulation over the cuff by the flow through the cuff. The pressure in the blood pressure cuff was variable (range $0 - 200$ mmHg). The decrease of pressure and the flow through the cuff were measured ten times with fourteen different pressures in the cuff, respectively ($n = 140$).

**Pressure curve measurements**

Pressure measurements were performed by pressure needles introduced in the circulation (Figure 3.1). The recorded pressure curves were compared with pressure curves measured in the human abdominal aorta as published in the literature [8].

**Flow curve measurements**

The flow wave in the in-vitro model was recorded with an ultrasound imaging system (Aloka SSD5500, Aloka, Tokyo, Japan).
Mean pressure measurements
Mean pressure measurements were performed to demonstrate the possibility of changing the mean pressure in the in-vitro model by changing the physiological factors of mean pressure. The two physiological determinants of the mean arterial pressure are the cardiac output and the total peripheral resistance [9]. First systolic driving pressure of the LAVD-driver was changed to enhance the cardiac output. The mean arterial pressure was measured five times distal to the air-chamber with ten different cardiac output values, respectively ($n = 50$). The peripheral resistance was kept constant.

Then the cardiac output was changed by increasing the frequency of the LAVD-driver. The mean arterial pressure was determined five times with five different cardiac output values ($n = 25$).

Peripheral resistance is the second determinant. In the last mean pressure experiment the peripheral resistance was changed and the cardiac output was kept constant. For eleven different peripheral resistances the mean arterial pressure was determined five times ($n = 55$).

Pulse pressure measurements
Two physical determinants of pulse pressure are arterial compliance and stroke volume [10]. Pulse pressure measurements were performed to demonstrate the possibility of changing the pulse pressure in the in-vitro model by changing these physical factors of pulse pressure.

First, with different compliances the pulse pressure was measured distal to the air-chamber. The pulse pressure was determined five times for ten compliance-values. ($n = 50$).

The other physical determinant of pulse pressure is the stroke volume. The systolic driving pressure of the LAVD-driver was varied to change the stroke volume. For ten stroke volumes the pulse pressure was determined five times ($n = 50$).

3.3 Results

Definition of the basic physical unit of compliance
Figure 3.2A depicts the relation between the air volume above the liquid level in the air-chamber and the compliance of the air-chamber. When air was supplied into the air-chamber the compliance of the in-vitro model increased and when air was removed from the air-chamber the compliance of the model decreased. The maximum compliance of the in-vitro model was $0.36 \text{ ml/mmHg}$.

Definition of the basic physical unit of peripheral resistance
Figure 3.2B depicts the relation between the pressure in the cuff and the peripheral resistance of the in-vitro model.
3.3 Results

**Figure 3.2:** A) Plot of the air volume above liquid level in the air-chamber against the compliance of the air-chamber. The mean and the range of ten measurements with the same amount of inflated air are depicted. B) Plot of pressure in the cuff against the peripheral resistance of the in-vitro model. The mean and the range of ten measurements with the same pressure in the pressure cuff are depicted.

*Pressure curve measurements*

Figure 3.3 depicts the pressure curve of the in-vitro model.

*Flow curve measurements*

Figure 3.4 shows the flow curve of the in-vitro model. The flow curve is biphasic and corresponds with velocity waveform as published by Mills et al [8].
Figure 3.4: Colour doppler and flow profile of the in-vitro model. The measurements were carried out distal to the air-chamber.

Mean pressure measurements
During the first experiment the systolic driving pressure of the LAVD-driver was changed to adjust the cardiac output. Figure 3.5A depicts the relation between the cardiac output and the mean pressure. An increase in the cardiac output caused an increase in mean pressure.

Figure 3.5B depicts also the relation between the cardiac output and the mean pressure. During this experiment the small increase in cardiac output was obtained by increasing the heart rate. An increase in cardiac output caused an increase in mean pressure.

Figure 3.6 shows the relation between the peripheral resistance and the mean pressure. An increase of the peripheral resistance enhanced the mean pressure.

Pulse pressure measurements
Figure 3.7 depicts the relation between the compliance and the pulse pressure. As compliance rose, the pulse pressure dropped.

Figure 3.8 shows the relation between arterial pressure and the volume increase in the in-vitro model. The volume increase during heart action depends on the compliance. When the compliance in the model was low, like in old individuals, the increase in the arterial volume produced by each heart contraction was much less than when the compliance in the model was high, like in young individuals.
Figure 3.5: A) Plot of cardiac output against the mean arterial pressure in the in-vitro model. The mean and range of five measurements with the same cardiac output are depicted. B) Plot of the cardiac output against the mean arterial pressure in the in-vitro model. The mean and range of five measurements with the same cardiac output are depicted.

The relation between the stroke volume and the pulse pressure is depicted in Figure 3.9. Increase of pulse pressure caused an increase of the stroke volume.

3.4 Discussion

We designed and validated an in-vitro model of the human systemic circulation to mimic the pressure and flow curve in a human abdominal aorta. The model was especially developed for abdominal aortic aneurysm studies. This in-vitro model is also appropriate for education and other type of studies (for example, flow imaging studies). The effect of stroke volume, cardiac output, compliance and peripheral resistance on the pressure can be illustrated with use of an in-vitro model.

Mills et al. recorded blood pressure and velocity waveforms in a series of patients at cardiac catheterization [8]. We compared the pressure curve with the pressure curve measured in the abdominal aorta by Mills et al. We concluded that the pressure curve in the in-vitro model was similar to the curve in the abdominal aorta of a human. Even the dicrotic nodule in the pressure curve of the model, due to the ball valve, was present.

The flow curve of the in-vitro model was biphasic. Mills et al. measured a flow
velocity of about 58 cm/s in the abdominal aorta. We measured a flow velocity of 59.4 cm/s in the in-vitro model.

The mean and pulse pressure experiments were performed to demonstrate that the determinants of pulse and mean pressure could be adjusted independently within physiological range. Change in cardiac output or in peripheral resistance changed the mean pressure. Variation of compliance or stroke volume influenced the pulse pressure of the in-vitro model.

The decrease in compliance of arteries is a manifestation of the increased rigidity (atherosclerosis) of the systemic circulation. The increase in the diameter of the aorta produced by each cardiac contraction is much less in elderly persons than in young persons. This phenomenon was demonstrated in the in-vitro model (Figure 3.8). When the compliance in the model was low, as in older individuals, the increase in the arterial volume produced by each cardiac contraction was much less than when the compliance in the model was high, like in young individuals (windkessel functionality).

Our in-vitro model was based on a previous described in-vitro model of our group [3] No air-chamber was incorporated in the old in-vitro model. The compliance of our previous model could not be adjusted. This means that stiffening of the arteries could not be mimicked.

Figure 3.6: Plot of the peripheral resistance against the mean pressure of the in-vitro model. The mean and range of five measurements with the same peripheral resistance are depicted.
3.4 Discussion

Figure 3.7: Plot of the compliance against the pulse pressure of the in-vitro model. Every point in this plot represents the mean value of five experiments with the same compliance. The range of the five measurements is depicted.

Mehta et al. described an in-vitro model in which the rubber tubing created compliance [4]. However, the compliance of this system was not quantified and could not be changed without changing the rubber tubing of the whole system. Pulsatile pressure was generated in this model by a pulsatile pump, but it is not clear if this wave was identical to the pressure wave measured in a human aorta.

Flora et al. constructed a very big in-vitro model [5]. This model is not appropriate to perform experiments with CT or MRI. Our model was made of plastic components. It is possible to position this in-vitro model in the CT or MRI scan.

The in-vitro model described by Gawenda et al. included also a cuff device to alter peripheral resistance, an air-chamber (windkessel) and a collecting system [6]. They assert that the pressure curve of the in-vitro model was comparable to that of a middle-sized animal (like dogs) or human being. It is not clear if they mean that the pressure curve of the in-vitro model is identical to the pressure curve in the human aorta or to the curve in another part of the human body for example the radial artery. They did not publish a pressure curve or validation data. Their in-vitro model did not include a ball valve. It is not clear how typical flow pattern including a dicrotic nodge was mimicked. Furthermore, the shape of the flow curve has not been published or described.

In this paper we described and validated an in-vitro model of the human circulation. The in-vitro model was especially developed for endovascular aneurysm repair studies, but is also appropriate for other flow studies. It is quite important that a validated model will be used by different research groups. Investigators should be aware that it is appropriate to compare results obtained from different in-vitro models only if the fidelity of each system is known and preferably identi-
Figure 3.8: Plot of the mean pressure, measured distal to the air-chamber, against the increase in volume (%).

The pressure curve in the model was identical to the pressure curve in a human abdominal aorta, as published in literature. The flow pattern in the in-vitro model was biphasic.

Parameters of pulse and mean pressure could be adjusted independently. Therefore, we believe that this model is appropriate to simulate various different cardiovascular steady states.
**Figure 3.9:** Plot of the stroke volume against the pulse pressure of the in-vitro model. Every point in the plot represents the mean value of five measurements with the same stroke volume. The range of these five measurements is depicted.
Acknowledgement

We thank Mr. Ir. J.R.C. Jansen for his remarks with respect to physical aspects of the in-vitro model, Mr. R.C. van Wissen for his assistance in ultrasound scanning, Mr. M. Boonekamp sr. and his colleagues for their contribution to the construction of the in-vitro model and Mr. O.H.J. Koning, MD, for his review of the manuscript.
References


